

Vaxzevria: Periodic safety update report assessment

29th December 2022 to 28th December 2023

This document consists of:

1. The PRAC assessment report of the Vaxzevria periodic safety update report (PSUR) covering the period 29 December 2022 to 28 December 2023, and;
2. The Vaxzevria PSUR itself.

The PSUR is a pharmacovigilance document intended to provide an evaluation of the risk-benefit balance of the medicinal product during the reference period mentioned above.

The objective of the PSUR is to present a comprehensive and critical analysis of the risk-benefit balance of the product, taking into account new or emerging safety information in the context of cumulative information on risk and benefits. The marketing authorisation holder is legally required to submit PSURs at defined time points after the authorisation of a medicinal product.

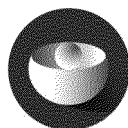
EMA's safety committee, the PRAC, assesses information in the PSUR to determine if there are new risks identified for a medicine and/or if its risk-benefit balance has changed. The outcome of this assessment is summarised in the PRAC assessment report of the PSUR.

The PSUR and the PRAC assessment report of the PSUR include information about **suspected** side effects, i.e. medical events that have been observed following the use of the vaccine, but which are not necessarily related to or caused by the vaccine itself. Information on suspected side effects should not be interpreted as meaning that the vaccine or the active substance causes the observed event or is unsafe to use.

Only a detailed evaluation and scientific assessment of all available data, as described in the PRAC assessment report of the PSUR, can determine the impact of new data on the benefits and risks of a medicine.

Further information on the [safety of COVID-19 vaccines](#) and on [PSUR submission and assessment](#) is available on the EMA website.

This document may contain redactions for commercially confidential information (CCI) and protected personal data (PPD) in accordance with applicable legislation and guidance.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA/PRAC/293708/2024
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC PSUR assessment report

Procedure no.: EMEA/H/C/PSUSA/00010912/202312

Active substance(s): COVID-19 Vaccine (ChAdOx1-S [recombinant])
(Vaxzevria)

Period covered by the PSUR: 29/12/2022 To: 28/12/2023

Centrally authorised Medicinal product(s):	Marketing Authorisation Holder
For presentations: See Annex A	
Vaxzevria	AstraZeneca AB

Status of this report and steps taken for the assessment			
Current step	Description	Planned date	Actual Date
☐	Start of procedure:	14 March 2024	14 March 2024
☐	PRAC Rapporteur's preliminary assessment report (AR)	13 May 2024	13 May 2024
☐	MS/PRAC members and MAH comments	12 June 2024	12 June 2024
☐	PRAC Rapporteur's updated assessment report following comments	27 June 2024	21 June 2024
☐	PRAC Rapporteur's second updated assessment report following comments	27 June 2024	21 June and 03 July 2024
☒	PRAC recommendation	11 July 2024	



-

Procedure resources	
PRAC Rapporteur	Name: Jean-Michel Dogné
Contact person - PRAC Rapporteur	
Assessor – PRAC Rapporteur	
EMA Procedure Lead	
EMA Procedure Assistant	

Table of contents

1. Background information on the procedure..... 4

2. Assessment conclusions and actions..... 4

3. Updated Recommendations..... 6

4. PSUR frequency and other changes to the EURD list 8

1. Background information on the procedure

This is the assessment of PSUR(s) submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) for COVID-19 Vaccine (ChAdOx1-S [recombinant]) (Vaxzevria).

2. Assessment conclusions and actions

This is the **fifth Periodic Benefit-Risk Evaluation Report (PBRER)** for **Vaxzevria**. It summarises safety and efficacy/effectiveness data for the period **from 29 December 2022 to 28 December 2023**, and places it in the context of the cumulative data and the overall benefit risk profile.

Vaxzevria is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of SARS CoV-2. Following administration, the S glycoprotein of SARS-CoV-2 is expressed locally stimulating neutralizing antibody and cellular immune responses.

Vaxzevria is indicated for active immunization of individuals 18 years old and older for the prevention of COVID-19. The primary vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 4 and 12 weeks after the first dose. A booster dose (third dose) of 0.5 ml may be given to individuals who completed the primary vaccination course with Vaxzevria or another authorised COVID-19 vaccine at least 3-months after completing the primary vaccination course. The approval and dosing interval of booster dose for Vaxzevria may vary according to the countries of authorisation.

Vaxzevria is supplied as a vial containing either 8 doses or 10 doses per vial, 0.5 mL per dose for intramuscular (IM) injection.

Vaxzevria was first authorised for emergency use in the United Kingdom on 29 December 2021. The vaccine received conditional marketing authorization in the EU on 29 January 2021, which was switched to a standard marketing authorisation on 31 October 2022. Vaxzevria has been granted either full marketing authorisation, conditional marketing authorisation or emergency use authorisation in multiple countries worldwide and managed by AstraZeneca and its partners – Serum Institute of India (SII), R-pharm and Fiocruz. On 5 March 2024, the MAH requested to withdraw for commercial reasons the marketing authorisation (EU/1/21/1529/002) for Vaxzevria (EMA/H/C/005675). The marketing authorisation for Vaxzevria was withdrawn on 7 May 2024 (adopted by the European Commission on 27 March 2024).

Actions taken for safety reasons and changes to Reference Safety Information

During the period under review:

- There were no actions taken for safety reasons.
- The EU-SmPC Section 4.8 was updated to include 'Venous thromboembolism' (not known) in the list of ADRs and a warning was included in the Section 4.4 (PRAC recommendation for PSUSA//00010912/202212).
- Frequencies of ADRs and percentage numbers were revised in Section 4.8 of the CDS based on the final study data from the pooled University of Oxford sponsored studies COV001, COV002, COV003 and COV005, US study D8110C00001 and the Booster Study D7220C00001

Exposure

The estimated cumulative exposure of clinical trial subjects is approximately 35,942 healthy volunteers who have received Vaxzevria (AZD1222) and 1,523 who have received AZD2816.

The estimated cumulative exposure from post approval experience is over 2.99 billion doses distributed globally and over 2.36 billion doses administered worldwide. In the EU, there were approximately 69 million doses administered (i.e. ~39 million Dose 1, ~30 million Dose 2, and ~32,000 Booster dose).

The MAH clarified that the last batch that was available in the EU expired on 31 August 2022 and the last one available outside the EU expired on 30 December 2023.

Signals

During the period under review, two validated signals were closed and considered as non-important identified risk by the MAH:

- *Decreased appetite*: was already listed in section 4.8 of the EU-SmPC
- *Potential Vaccination Failure/Lack of Efficacy against Emerging Variants (including Omicron XBB)*: warning included in section 4.4 of the CDS but not in the EU-PI (currently under evaluation in variation II/0095)

New safety information

During the reporting period, no new safety concerns were identified by the MAH.

However, new information became available regarding Acute disseminated encephalomyelitis (ADEM), following 3 studies published shortly after the DLP of this PSUR. A large multi-country observational cohort study across 8 countries and including 23,093,399 doses of ChAdOx1 suggests an increased risk of ADEM following first dose of Vaxzevria based on an observed to expected analysis (i.e., O/E ratio of 2.23 [95 % CI: 1.15, 3.60]). The signal was further confirmed by a SCCS using an Australian vaccine datalink. The authors observed associations between ChAdOx1 vaccination and ADEM (all dose RI: 3.74 [95 % CI 1.02,13.70]), translating to a small absolute risk of ADEM (0.78 per million doses). A SCCS analysis conducted in England also reported an increased risk of ADEM after the first dose of ChAdOx1-S vaccine with 12 events in the 42 days following vaccination (RI = 3.13, 95% CI [1.56–6.25]). No other vaccine or dose gave a significant increased risk. The vaccine attributable risk was estimated at 0.39 per million doses.

Overall, the PRAC considers that there is sufficient evidence to conclude there is a reasonable possibility that Vaxzevria is causally related to ADEM. Acute disseminated encephalomyelitis (ADEM) is thus considered as a new ADR of Vaxzevria and warrants an update of the product information.

Furthermore, a cumulative review of cases of Erythema Multiforme (EM) was provided by the MAH upon request of the PRAC Rapporteur in the previous PSUR AR. Four probable and several possible cases of EM were reported in close temporal association with Vaxzevria and without apparent plausible alternative explanation for the event. Based on the review of cases of EM and the plausible mechanisms of action discussed in the previous AR, the PRAC considers that a causal association between EM and Vaxzevria should be considered at least a reasonable possibility. Erythema Multiforme is thus considered as a new ADR of Vaxzevria and warrants an update of the product information.

The PRAC considers that the safety concerns for Vaxzevria are:

- Important Identified Risks: Thrombosis with thrombocytopenia syndrome; Thrombocytopenia, including immune thrombocytopenia; Guillain-Barré syndrome; Venous thromboembolism (VTE)

- Important Potential Risks: Immune-mediated neurological conditions; Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)
- Missing Information: Use during pregnancy and while breastfeeding; Use in immunocompromised patients; Use in frail patients with co-morbidities¹; Use in patients with autoimmune or inflammatory disorders; Interactions with other vaccines; Long-term safety

Several Health Authority Requests were under close monitoring during the reporting period. Following the assessment of these issues, the PRAC concludes that the safety topics of interest for Vaxzevria are SCARs.

New benefit information

Immunogenicity and effectiveness data support a positive effect of prime vaccination and homologous boost vaccination with Vaxzevria against variants, including Omicron. However, no detectable level of nAb against variant XBB.1.5 is observed following administration of 3 doses of Vaxzevria. There are no RWE data on protection conferred by three doses of Vaxzevria on disease caused by variant XBB.1.

Furthermore, upon enquiry by the EMA, the MAH clarified that they do not intend to update their vaccine to any of the recommended variants of concerns (VOC), including XBB and any following.

After the DLP, in February 2024, EMA's Emergency Task Force (ETF) issued a statement on the use of recently updated COVID-19 vaccines: [...] As SARS-CoV-2 circulates and evolves, new SARS-CoV-2 variants continue to emerge with the ability to evade immunity induced by prior infection or vaccination. Consequently, COVID-19 vaccines require regular strain updates, a situation very similar to the regularly updated influenza vaccines. [...].

ETF concluded that EU Member States are recommending that people in the EU/EEA at increased risk for severe COVID-19 disease should be offered vaccination. To provide optimal protection against circulating strains, ETF recommends that the most recently updated COVID-19 vaccines should be used. The ETF recognizes that, in the future, new COVID-19 vaccines may initially be authorised with a composition that does not match circulating VOCs but reflects the composition of the vaccines used in pre-licensure clinical trials. Whenever this occurs, similarly to influenza, the vaccines are expected to be updated before deployment to reflect recent and/or circulating SARS-CoV-2 variants. The ETF will continue to evaluate SARS-CoV-2 epidemiological data and provide updated vaccine composition recommendations as appropriate.

Moreover, on 30 April 2024, ETF recommended updating COVID-19 vaccines to target the new JN.1 variant for the 2024/2025 vaccination campaign. All marketing authorisation holders are expected to update the composition of their authorised vaccines in accordance with this recommendation.

Finally, the MAH requested to withdraw the marketing authorisation (EU/1/21/1529/002) for Vaxzevria (EMA/H/C/005675) on 5 March 2024. The marketing authorisation for Vaxzevria was withdrawn on 7 May 2024 (adopted by the European Commission on 27 March 2024). No valid marketing authorisation is therefore available in the EU/EEA at this time.

3. Updated Recommendations

Based on the PRAC review of data presented in the context of this PSUR, the PRAC is of the view that the product information should be updated.

¹ e.g., chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders

This recommendation is without prejudice to the Marketing Authorisation withdrawal adopted by EC on 27 March 2024, with an effective withdrawal date of 7th May 2024.

Scientific conclusions and grounds for recommending the update of the product information on the basis of the data submitted in the context of this PSUR

In view of available data on acute disseminated encephalomyelitis (ADEM) from the literature and spontaneous reports and in view of a plausible mechanism of action, the PRAC considers a causal relationship between COVID-19 Vaccine (ChAdOx1-S [recombinant]) (Vaxzevria) and acute disseminated encephalomyelitis is at least a reasonable possibility. The PRAC concluded that the product information of products containing COVID-19 Vaccine (ChAdOx1-S [recombinant]) (Vaxzevria) should be amended accordingly.

Moreover, based on available data on erythema multiforme from the literature and spontaneous reports including in some cases a close temporal relationship, and in view of a plausible mechanism of action, the PRAC considers a causal relationship between COVID-19 Vaccine (ChAdOx1-S [recombinant]) (Vaxzevria) and erythema multiforme is at least a reasonable possibility. The PRAC concluded that the product information of products containing COVID-19 Vaccine (ChAdOx1-S [recombinant]) (Vaxzevria) should be amended accordingly.

Precise scope:

Update of section(s) 4.8 and 4.4 of the SmPC to add the adverse reactions erythema multiforme and acute disseminated encephalomyelitis (ADEM) with a frequency not known, and a warning/precaution regarding ADEM. The Package leaflet is updated accordingly.

The following changes to the product information of medicinal products containing COVID-19 Vaccine (ChAdOx1-S [recombinant]) (Vaxzevria) are recommended (new text **underlined and in bold**, deleted text ~~strike-through~~):

Summary of Product Characteristics

- Section 4.4

A warning should be amended as follows:

Neurological events

Guillain-Barré syndrome (GBS), ~~and~~ transverse myelitis (TM) **and acute disseminated encephalomyelitis (ADEM)** have been reported very rarely following vaccination with Vaxzevria. Healthcare professionals should be alert of GBS, ~~and~~ TM **and ADEM** signs and symptoms to ensure correct diagnosis, in order to initiate adequate supportive care and treatment, and to rule out other causes.

- Section 4.8

The following adverse reaction(s) should be added under the SOC Nervous system disorders with a frequency **not known: Acute disseminated encephalomyelitis**

The following adverse reaction(s) should be added under the SOC Skin and subcutaneous tissue disorders with a frequency **not known: Erythema multiforme**

Package Leaflet

4. Possible side effects

- Frequency **not known: widespread inflammation of the brain and spinal cord (acute disseminated encephalomyelitis)**

- Frequency **not known: a skin reaction that causes red spots or patches on the skin that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)**

4. PSUR frequency and other changes to the EURD list

Based on the European Commission Decision issued on 27 March 2024 this product is currently withdrawn from the European market. No further PSUR submission is requested.

Annex: updated PRAC Rapporteur assessment comments on PSUR

Medicinal product no longer authorised

1. PSUR Data

1.1. Introduction

This Periodic Benefit Risk Evaluation Report (PBRER) for COVID-19 Vaccine (ChAdOx1-S [recombinant]) (AZD1222) (VAXZEVRIA) covers the period **between 29 December 2022 and 28 December 2023**.

The VAXZEVRIA International Birth Date (IBD) is **29 December 2020**.

VAXZEVRIA is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of the Severe Acute Respiratory Coronavirus 2 (SARS CoV-2). Following administration, the S glycoprotein of SARS CoV 2 is expressed locally stimulating neutralizing antibody and cellular immune responses.

VAXZEVRIA is indicated for active immunisation of individuals ≥ 18 years for the prevention of Coronavirus Disease 2019 (COVID-19). The use of VAXZEVRIA should take into account the available efficacy, effectiveness and immunogenicity data.

VAXZEVRIA is supplied as a vial containing either 8 doses or 10 doses per vial, 0.5 mL per dose for intramuscular (IM) injection. VAXZEVRIA primary vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 4 and 12 weeks after the first dose. It is recommended that individuals who receive a first dose of VAXZEVRIA complete the primary vaccination course with VAXZEVRIA. The core data sheet (CDS) indicates that a booster dose (third dose) of 0.5 ml may be given to individuals who completed the primary vaccination course with VAXZEVRIA or another authorised COVID 19 vaccine. The third dose should be administered at least 3 months after completing the primary vaccination course. The status of approval and the recommendation in national prescribing information (PI) documents relating to the booster dose vary.

The MAH does not propose any update of the product information as part of the submission of this PBRER.

1.2. Worldwide marketing authorisation status

VAXZEVRIA was first authorised in United Kingdom (UK) on 29 December 2020 and in the EU on 29 January 2021. It is either approved as Marketing Authorisation (MA), Conditional Marketing Authorisation (CMA) or Emergency Use Authorisation (EUA) in multiple countries worldwide and managed by AstraZeneca and its partners – Serum Institute of India (SII), R-Pharm and Fiocruz.

Rapporteur assessment comment:

On 5 March 2024, the MAH requested to withdraw the marketing authorisation (EU/1/21/1529/002) for Vaxzevria (EMA/H/C/005675). The marketing authorisation for Vaxzevria was withdrawn on 7 May 2024 (approved by the European Commission on 27 March 2024).

The MAH indicated that : *"This withdrawal is for commercial reasons and is not based on the grounds provided in Articles 116 and 117 of Directive 2001/83/EC; this withdrawal is not a result of safety or efficacy concerns.*

Newer variant COVID-19 vaccines have been developed and authorised for both primary series and booster vaccination and, Vaxzevria which was developed against the ancestral SARS-CoV-2 virus strain, is not used within the European Union. No future commercial demand for the vaccine is expected. The last batch released into the EU expired 31 August 2022.

Considering that Vaxzevria is not being used, information directed to the public or health care

1.3. Overview of exposure and safety data

1.3.1. Actions taken in the reporting interval for safety reasons

No significant actions related to safety were taken or proposed during the reporting period.

1.3.2. Changes to reference safety information

The reference safety information is the Core Data Sheet (CDS).

The VAXZEVRIA CDS in effect at the beginning of the reporting period was dated 08 November 2022 (version 21.0). During this reporting period, the VAXZEVRIA CDS was updated three times to include the changes summarised in Table 1.

Table 1 - Summary of safety-related changes to the VAXZEVRIA CDS during the reporting period

CDS version date	CDS Section Number – CDS Section Title Detail of the safety-related change	PBRER Section cross-reference, where applicable
Version 22.0 21 February 2023	CDS Section 4.8 Undesirable Effects • Addition of Decrease appetite as an adverse drug reaction with frequency uncommon. • Revision of numbers and frequencies in Table 1 adverse drug reactions. • Information in Overall summary of the safety profile updated to reflect data from the final pooled analysis DC03.	Decreased appetite: Section Error! Reference source not found.
Version 23.0 30 August 2023	CDS Section 4.4 Special Warnings and Special Precautions for Use • to include information about circulating variants at the time Vaxzevria was developed and clinical efficacy studies were conducted. • and to consider the characteristics of the circulating variants including regional or geographical differences for the use of Vaxzevria.	Section Error! Reference source not found.

CDS version date	CDS Section Number – CDS Section Title Detail of the safety-related change	PBRER Section cross-reference, where applicable
-------------------------	---	--

Version 24.0	CDS Section 4.8 Undesirable Effects	Not applicable
--------------	--	----------------

01 November 2023	Booster dose (third dose) Revision to the number of participants who had previously received a 2-dose primary vaccination course with Vaxzevria.	
------------------	--	--

Summary of the safety data from D8110C00001

- To the number of participants aged ≥ 18 years who received at least one dose and
- To the number of participants in the placebo group.

For the purpose of this PBRER, the CDS dated 01 November 2023 (version 24.0), is the reference for both the benefit and risk sections.

Rapporteur assessment comment:

The section 4.8 of the EU-SmPC has been updated regarding ADR 'Decreased appetite' and data on booster dose.

No information about circulating variants is included in the EU-PI. This is currently under evaluation within the variation II/0095.

1.3.3. Estimated exposure and use patterns

1.3.3.1. Cumulative subject exposure in clinical trials

Overall cumulative subject exposure is provided in Table 2, based on actual exposure data from completed clinical trials. There are no ongoing clinical trials enrolling participants and no further clinical development is planned for VAXZEVRIA.

Table 2 - Cumulative subject exposure from clinical trials

Treatment	Number of subjects
AZD1222	35942
AZD2816 ^a	1523
MenACWY	10960
Rabies	200
Placebo	11972

^a: AZD2816 is a discontinued vaccine developed from AZD1222 targeting Beta variant of SARS-CoV-2. AZD2816 is used in Study D7220C00001 which is further described below

1.3.3.2. Cumulative and interval patient exposure from marketing experience

The post-marketing patient exposure data in this report is presented by number of doses distributed and doses administered. All exposure is intended for the same indication and route of administration.

During this reporting period, the global post-marketing patient exposure (by doses distributed) to VAXZEVRIA was estimated to be over 5.9 million doses (0.20% of cumulative).

The cumulative global post-marketing patient exposure (by doses distributed) to VAXZEVRIA, since launch to 30 December 2023, have been estimated to be over 2.99 billion doses.

The MAH has obtained exposure data based on doses administered to vaccinees in EU, Afghanistan, Argentina, Australia, Bangladesh, Brazil, Canada, Chile, Colombia, Ecuador, Ghana, Guatemala, India, Iran, Iraq, Japan, Lebanon, Malaysia, Mexico, Nepal, New Zealand, Peru, Philippines, Saint Lucia, South Korea, Taiwan, Thailand, UK and Uruguay. This information is summarised in Table 3 below and was obtained from Government bodies or country specific websites. Please note that administration in other markets where VAXZEVRIA is authorised has not yet been made available to AstraZeneca.

The cumulative global post-marketing patient exposure (by doses administered) to VAXZEVRIA, since launch to 30 December 2023, have been estimated to be over 2.36 billion doses.

Most of the countries stopped publishing the exposure numbers and in many countries the product was not dispatched or administered since August 2022. However, exposure numbers reflecting under reporting interval are based on data published in health authority database. Thus, the derived interval exposure calculated, may not be a true reflection of the doses administered during the reporting interval.

Table 3 - VAXZEVRIA interval and cumulative exposure based on doses administered, by Region/Country

Region	Interval			Cumulative			Percentage (%)
	Dose 1	Dose 2	Dose3/ Dose 4/ Booster	Dose 1	Dose 2	Dose3/ Dose 4/ Booster	Cumulative
European Union*	-14816	-14795	21999	38921043	29815982	53950	2.910
United Kingdom	0	0	0	24725401	24141350	59155	2.070
Afghanistan	0			975338			0.041
Australia	0	0	0	6710682	6644072	479167	0.585
Philippines	1796112			23931246			1.012
India	4206681			1749417978			74.009
Canada	-2684	-968	41	2233943	576120	1829	0.119
Argentina	2442	3454	6872	10184070	9947533	6650638	1.133
Bangladesh	76	2058	36891	20769467	19505767	16005534	2.381
Colombia	269035	375720	415620	6030298	4261806	2455414	0.539
Ecuador	17	12	174	1764566	1470117	5039182	0.350
Iran	0	0	0	5601073	5045996	3779468	0.610
Japan	11	43	0	58700	59203	0	0.005
Brazil	76768	164566	1764497	62346597	56605568	34627963	6.497
Chile	-16	-6	-76	410029	139637	2656524	0.136
Guatemala	640	836	719	2038728	1613090	838201	0.190
Ghana	0			10545038			0.446
Lebanon	7328			730198			0.031
Iraq	0			717233			0.030
Mexico	0			49783383			2.106
Malaysia	-56	65	188	2047926	2027769	1631991	0.241
Nepal	0	0	0	5506364	4789110	4703764	0.635
Peru	2666	3253	79730	2247245	2113704	3827508	0.346
Saint Lucia	0	0	0	37850	34810	0	0.003
Taiwan	368			15298079			0.647
Thailand	2112	2011	10024	14100757	28684215	5933269	2.061
New Zealand	4	2	7	3321	3648	2083	0.000
South Korea	-3			20348870			0.861
Uruguay	463	425	180	47150	44879	359	0.041
Grand Total	9220690			2363802948			100

See PBRER for detailed data cut-off

The MAH provided estimated exposure data for other countries such as African countries, if available as requested by the PRAC in previous PBRER assessment report (EMA/H/C/PSUSA/00010912/202212). The exposure data is available for Ghana until 30 November 2023 and is included within Table 3. For the rest of the African countries, data is unavailable.

Rapporteur assessment comment:

During the reporting period, Vaxzevria was only distributed in India (i.e., ~5,9 million doses distributed by Serum Institute of India). The cumulative exposure has been estimated to be over 2.99 billion doses distributed.

Cumulatively, over 2.36 billion doses of Vaxzevria have been administered worldwide, including about 68,8 million in the EU.

The MAH has informed the EMA by email exchange that the last batch that was available in the EU expired on 31 August 2022 and the last one available outside the EU expired on 30 December 2023.

No valid batch was available on the EU market during the reporting period.

The exact number of doses distributed during the reporting period remains unclear. Vaxzevria was not administered in many countries since August 2022.

1.3.4. Data in summary tabulations

Cumulative summary tabulations of serious adverse events from clinical trials

A cumulative summary tabulation of serious adverse events (SAEs) from AstraZeneca-sponsored interventional clinical trials that have been reported during the Vaxzevria clinical development programme, from the Development International Birth Date (DIBD) to the data lock point (28 December 2023), organised by SOC, is presented in Appendix 2 of PBRER.

Cumulative and interval summary tabulations from post-marketing data sources

Cumulative and interval summary tabulations of adverse reactions (ie, AEs considered as “a reasonable possibility of a causal relationship between the medicinal product and the event”) that have been reported from marketed experience with Vaxzevria, from the IBD to the data lock point, organised by SOC, are presented in Appendix 2 of PBRER.

Compared to the previous interval, there is a decrease in the case and event counts for the current reporting interval. This is due to decreased uptake in many regions, compared to the previous intervals and most of the reports received during the current reporting interval were also related to vaccinations in the earlier reporting interval.

Rapporteur assessment comment:

No new important safety information is identified from the data in summary tabulations.

1.3.5. Findings from clinical trials and other sources

1.3.5.1. Completed and ongoing clinical trials

Completed clinical trials

There were 10 (D7220C00001, COV001, COV002, COV003 including booster sub-study, COV004, COV005, COV006, COV008, D8110C00001, and D8110C00010) completed clinical trials during the

reporting period. There were no additional clinically important emerging efficacy or safety findings obtained from the clinical trials completed during the reporting period.

D7220C00001 (A Phase II/III Partially Double-Blinded, Randomised, Multinational, Active-Controlled Study in Both Previously Vaccinated and Unvaccinated Adults to Determine the Safety and Immunogenicity of AZD2816, a Vaccine for the Prevention of COVID-19 Caused by Variant Strains of SARS-CoV-2): Phase II/III

This was an AstraZeneca-sponsored, multi-country Phase II/III study to evaluate the safety and immunogenicity of AZD2816, an AstraZeneca's candidate ChAdOx1 vector vaccine against SARS-CoV-2 variant strain B.1.351, as single-dose vaccination in previously vaccinated adult participants (AZD1222 or an mRNA COVID-19 vaccine) and as a 2-dose primary vaccination in previously unvaccinated adult participants (homologous AZD2816 vaccination and heterologous vaccination with AZD1222 as first dose). The participant population included adults ≥ 18 years of age. In both the single-dose booster treatment regimen and the 2-dose primary vaccination treatment regimen, participants received study intervention consisting of IM administration of either AZD1222 (5×10^{10} vp) or AZD2816 (5×10^{10} vp). Participants receiving a 2-dose primary vaccination were dosed at intervals of 4 weeks (for AZD1222 and AZD2816) or 12 weeks (AZD2816 only). All study participants were followed up for 180 Days after the administration of their last vaccination dose to collect safety related information.

A total of 1394 participants were randomised in the single-dose booster arms in previously vaccinated treatment regimen. Non-inferiority of booster doses of AZD1222 and AZD2816 was demonstrated for the primary and all key secondary endpoints. The humoral immune response to a booster dose of AZD1222 was non-inferior to the response elicited by primary vaccination with AZD1222 (AZD1222 cohort Geometric Mean Titer [GMT] ratio: 1.02 [95% CI 0.90, 1.14]; mRNA cohort GMT ratio: 3.47 [95% CI 3.09, 3.89]). Strong humoral responses to SARS-CoV-2 were observed by 28 Days after booster doses of either AZD1222 or AZD2816 in seronegative participants previously vaccinated with AZD1222 or an mRNA vaccine. The safety (through Day 29), extended safety (through 6 months), and reactogenicity (through Day 8) of booster doses of AZD1222 or AZD2816 in participants previously vaccinated with either AZD1222 or an mRNA vaccine was consistent with the known safety profile of AZD1222 administered as a 2-dose primary series. No emergent safety issues were identified. There were no clinically meaningful differences between the safety profiles of booster doses of AZD1222 and AZD2816.

A total of 1449 previously unvaccinated participants were randomised and 1441 received at least one dose of AZD2816 or AZD1222 as primary series vaccination. The non-inferiority of AZD2816 was demonstrated for the co-primary and first key secondary endpoints. The GMT ratio for the comparison of the AZD2816 treatment group (4-week interval) against the Beta variant versus the AZD1222 treatment group against the Wuhan-Hu-1 strain was 1.19 (95% CI 1.08, 1.32) and the seroresponse difference was 1.7 (95% CI -3.1, 6.5). The GMT ratio for the comparison of the AZD2816 treatment group (4 week interval) against the Beta variant versus the AZD1222 treatment group against the Beta variant was 3.21 (95% CI 3.06, 3.36). The safety (through 29 Days post-dose), extended safety (through 6 months), and reactogenicity (through Day 8 post-dose) of AZD1222 and/or AZD2816 in previously unvaccinated participants was consistent with the known safety profile of AZD1222 administered as a 2-dose primary series. No emergent safety issues were identified. There were no clinically meaningful differences between the safety profiles across the treatment groups.

COV001 (A phase I/II study to determine efficacy, safety and immunogenicity of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19 in UK healthy adult volunteers): Phase I/II

COV001 was an Oxford-sponsored, single-blinded, multi-centre randomised, controlled Phase I/II trial assessing the safety, efficacy, and immunogenicity of ChAdOx1 nCoV-19 (VAXZEVR1A) in 1067 healthy

adults 18 to 55 years of age in the UK. Trial participants were healthy and at increased risk for being exposed to the SARS-CoV-2 virus. Participants received either a single IM dose or a 2-dose IM regimen of the low dose (LD) ($\sim 2.5 \times 10^{10}$ vp) and/or the standard dose (SD) ($\sim 5 \times 10^{10}$ vp) of AZD1222 or the comparator, meningococcal vaccine (MenACWY). The participants were followed for 12 months from the last vaccination.

AZD1222, when administered as a 2-dose SD regimen, had a VE estimate of 77.68% and a lower bound of the 95% CI of 22.29%. These results should be interpreted cautiously due to the small population size and few COVID-19 cases. AZD1222 generated a strong humoral response.

Analyses of solicited AEs post-vaccine administration showed that AZD1222 was reactogenic and that reactogenicity reduced after the second dose compared with the first dose. Most AEs were mild or moderate, and no clinically meaningful imbalances between AZD1222 and control in SAEs were observed. Most of the events considered as related to AZD1222 by the investigator were AEs that commonly observed following vaccine administration. Overall, AZD1222 had an acceptable safety profile.

COV002 (A phase II/III study to determine the efficacy, safety and immunogenicity of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19): Phase II/III

COV002 was an Oxford-sponsored, single-blinded, multi-centre, randomised, controlled Phase II/III trial assessing the safety, efficacy and immunogenicity of ChAdOx1 nCoV-19 (VAXZEVRIA) in 10,717 participants in the UK. Trial participants were ≥ 18 years of age. Participants were enrolled by age groups of 18 to 55 years, 56 to 69 years, and ≥ 70 years. Recruitment for this study focused on health care professionals and other adults with high potential for exposure to COVID-19. Participants received a single IM dose or a 2-dose IM regimen of the LD ($\sim 2.5 \times 10^{10}$ vp) and/or the SD ($\sim 5 \times 10^{10}$ vp) of VAXZEVRIA or the comparator, quadrivalent capsular group A, C, W, and Y meningococcal protein-polysaccharide conjugate vaccine (MenACWY), depending on the study group. The participants were followed for 12 months from the last vaccination.

The primary efficacy analysis resulted in a VE estimate of 74.34%, with a lower bound of the 95% CI of 62.39%. AZD1222 provided complete protection against COVID-19 hospital admission, severe disease, and death during the blinded period, with no cases observed. Overall, AZD1222 generated a strong humoral immune response.

Solicited local and systemic AEs were reported by 81.6% and 79.8% of evaluated participants, respectively, in the AZD1222 group and 63.2% and 71.3% of evaluated participants, respectively, in the control group. Most solicited local and systemic AEs and unsolicited AEs following any dose of AZD1222 were mild or moderate in severity, and most related AEs were mild or moderate in severity.

Reactogenicity was reduced after the second dose compared with the first dose across all solicited AEs in the AZD1222 group. Most of the commonly reported unsolicited AEs were consistent with solicited AEs commonly observed following vaccination (eg, headache, fatigue, pyrexia) and were reported at a higher frequency in the AZD1222 group compared with the control group. No clinically meaningful imbalances in the incidence of SAEs were noted. Overall, VAXZEVRIA had an acceptable safety profile.

COV003 (A Randomised, Controlled, Phase III Study to Determine the Safety, Efficacy, and Immunogenicity of the Non-Replicating ChAdOx1 nCoV-19 Vaccine): Phase III

COV003 was an Oxford-sponsored, single-blinded, multi-centre, randomised, controlled Phase III trial assessing the safety, efficacy, and immunogenicity of ChAdOx1 nCoV-19 Vaccine (VAXZEVRIA) in 10,416 participants in Brazil. Trial participants were ≥ 18 years of age, who were healthy or have medically stable chronic diseases and were at increased risk for being exposed to the SARS COV- 2 virus.

Participants were randomised to receive either a 2-dose regimen of the SD ($\sim 5 \times 10^{10}$ vp) of VAXZEVRIA or MenACWY as the first dose and saline placebo as the second dose by means of an IM injection. In the

main study, the participants were followed up for 12 months from the last vaccination. Approximately 7% of participants in the main safety analysis set were aged ≥ 65 years, which is relatively similar to the proportion of the overall Brazilian population aged ≥ 65 years (9.6% in 2020 World Bank 2022).

A subsequent optional booster third and fourth dose of ChAdOx1 nCov-19 vaccine was offered to a subgroup of participants who previously received ChAdOx1 nCov-19 within the trial. Participants in this booster sub-study were followed for 6 months from the booster vaccination. In the safety analysis population, the median age prior to dose 4 of AZD1222 was 36.8 years (range: 20.5–78.3), 94.8% were aged 18–64 years, 55.8% were male, 64.0% were White, mean BMI was 26.6 kg/m² (SD: 3.95), 29.1% had at least one protocol-defined comorbid condition, and 32.6% were seropositive prior to dose 4.

A total of 10,416 participants were randomised and received at least one dose of study intervention. The primary efficacy analysis resulted in a VE estimate of 57.61%, with a lower bound of the 95% CI of 40.73%. Overall, AZD1222 generated a strong humoral immune response in this study.

Solicited local and systemic AEs were reported by 81.7% and 69.0% of evaluated participants, respectively, in the AZD1222 group and 59.2% and 65.0% of evaluated participants, respectively, in the control group. Most solicited local and systemic AEs and unsolicited AEs following any dose of AZD1222 were mild or moderate in severity, and most related AEs were mild or moderate in severity. Most of the common unsolicited AEs were AEs commonly observed following vaccine administration. Reactogenicity was reduced after the second dose compared with the first dose in the AZD1222 group. No clinically meaningful imbalances in the incidence of SAEs were noted. Overall, VAXZEVRIA had an acceptable safety profile.

In the subsequent booster sub-study, a total of 172 participants were enrolled and 58 had solicited AEs collected. The humoral immune response elicited by Dose 3 of AZD1222 was noninferior to that after Dose 2 (ie, after a primary series of AZD1222) for all assays used (including anti-Spike antibodies and nAbs) and for all SARS-CoV-2 strains tested (including the Wuhan, Alpha, Beta, Gamma, Delta, and Omicron BA.1 [anti-Spike assay]/BA.5 [nAb assay] strains). The humoral immune response elicited by Dose 4 was noninferior to that after Dose 3 for all assays used and for all SARS-CoV-2 strains tested, although the magnitude of the response elicited by Dose 4 was smaller than that elicited by Dose 3 due to high pre-Dose 4 titres. Finally, the humoral immune response elicited by Dose 4 also noninferior to that after Dose 2 for all assays used and for all SARS-CoV-2 strains tested.

Of the 58 participants who had received 4 doses of AZD1222 and who were evaluated for solicited AEs within 7 Days after Dose 4, solicited local and systemic AEs were reported by 60.3% and 43.1% of evaluated participants, respectively. Most solicited local and systemic AEs following any dose of AZD1222 were mild or moderate in severity. Of the 172 participants who received 4 doses of AZD1222, most of the unsolicited AEs related to study intervention were AEs commonly observed following vaccine administration, all were mild or moderate in severity, and none occurred in more than one participant. No SAEs were reported, and no participants had fatal AEs. Overall, the safety data after Dose 3 and Dose 4 of AZD1222 in adult participants did not raise any new safety concerns and the safety profile remained consistent with that observed after 2 doses (ie, primary series) of AZD1222.

COV004 (A phase Ib/II single-blinded, randomised, controlled study to determine safety, immunogenicity and efficacy of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19 in adults in Kenya): Phase Ib/II

Results from the COV004 were reported in a manuscript and summarized below, as no Clinical Study Report was produced for this clinical trial. COV004 was an Oxford-sponsored, phase Ib/II trial single-blinded, randomised, controlled study of the SD ($\sim 5 \times 10^{10}$ virus particles (vp) of ChAdOx1 nCoV-19 (VAXZEVRIA) in comparison to the rabies control vaccine in Kenya. The primary endpoints of the trial were vaccine safety and immunogenicity of VAXZEVRIA vaccine as compared to the rabies control

vaccine, with VE against COVID-19 evaluated as a secondary endpoint. A total of 400 healthy adults ≥ 18 years of age with ChAdOx1 nCoV-19 (n=200) or rabies vaccine (n=200) were randomized and received at least one vaccination. Baseline participant characteristics were similar across vaccine groups, although males comprised 81% (n=325) of the study participants. The most commonly reported local AEs were tenderness (98 in ChAdOx1 nCoV-19 and 36 in rabies; relative risk [RR] 2.72, 95% CI 1.84 to 4.11), pain at injection site (74 in ChAdOx1 nCoV-19 and 32 in rabies; RR 2.31, 95% CI 1.51 to 3.62), and induration (5 in ChAdOx1 nCoV-19 and 1 in rabies group; RR 5.0, 95% CI 0.56 to 236.49). Headache was the most common systemic reaction with both vaccines occurring in 52 (26%) of 200 participants in ChAdOx1 nCoV-19 group and 25 (13%) of 200 participants in rabies group (RR 2.10, 95% CI 1.21). Myalgia was the second most common AE occurred in 35 (18%) of 200 participants in the ChAdOx1 nCoV-19 group and 10 (5%) of 200 participants in the rabies vaccine group (RR 1.47, 95% CI 0.73 to 3.04). The least common systemic adverse reaction was fever which occurred in one participant in each vaccine group. No participant reported a severity grade of 3 or 4 for all solicited local and systemic adverse reactions, except for one participant in the ChAdOx1 nCoV-19 group who had a grade 4 fever. In total, 79 unique unsolicited adverse reactions (60 in ChAdOx1 nCoV-19 and 53 in rabies vaccine groups) were reported throughout the study. Three serious adverse events, of which one resulted in death, were reported throughout the trial, all considered unrelated to study vaccination. The geometric mean anti-spike IgG titres 28 Days after second dose vaccination were higher in the ChAdOx1 group (2773 Enzyme-Linked Immunosorbent Assay [ELISA] units [EU], 95% CI 2447, 3142) than in the rabies vaccine group (61 EU, 95% CI 45, 81) and persisted over the 12 months FU. Vaccine efficacy against clinically apparent infection could not be determined given the lack of symptomatic infections. Vaccine efficacy against asymptomatic SARS-CoV-2 infection was 38.4% (95% CI -26.8% to 70.1%; p=0.188). In conclusion, the safety and immunogenicity of ChAdOx1 nCoV-19 was consistent with the known profile of the vaccine (Hamaluba M et al 2023)

COV005 (An adaptive phase I/II randomised placebo-controlled trial to determine safety, immunogenicity and efficacy of non-replicating ChAdOx1 SARSCoV-2 vaccine in South African (SA) adults living without HIV; and safety and immunogenicity in adults living with HIV): Phase I/II

COV005 was a double-blind, multi-centre, randomised, placebo-controlled Phase I/II trial in adults living with and without HIV in SA to assess the safety, efficacy, and immunogenicity of ChAdOx1 SARSCoV-2 vaccine (VAXZEVRIA). 2021 HIV-uninfected trial participants aged 18-65 years received a 2-dose IM regimen of the SD (5-7.5 $\times$ 10¹⁰vp) of VAXZEVRIA or saline placebo. The total duration of the study was 12 months from the day of enrolment for all participants.

The primary efficacy analysis resulted in a VE estimate of 37.04% (95% CI -277.20 to 89.49; p=0.612). The low efficacy against symptomatic COVID-19 observed in the study was due to the B.1.351 variant emerged in SA. AZD1222 generated a strong humoral response to SARS-CoV-2 ancestral strain.

Solicited local and systemic AEs were reported by 52.6% and 56.9% of participants, respectively, in the AZD1222 group and 22.8% and 44.3% of participants, respectively, in the control group. Most solicited local and systemic AEs and unsolicited AEs following any dose of AZD1222 were mild or moderate in severity, and most AEs considered related to study treatment were mild or moderate in severity. Most of the commonly reported unsolicited AEs were consistent with solicited AEs commonly observed following vaccination (eg, headache, influenza-like illness, vaccination-site erythema). Reactogenicity was reduced after the second dose compared with the first dose across all solicited AEs in the AZD1222 group. There were no clinically meaningful imbalances in the incidence of SAEs between the AZD1222 and control groups. Overall, VAXZEVRIA had an acceptable safety profile and was well tolerated in healthy adult participants.

Efficacy, safety, and immunogenicity results from pooled analyses including data from

COV001, COV002, COV003 and COV005 studies:

The evaluation of the efficacy, immunogenicity and safety of VAXZEVRIA for prevention of COVID-19 was based on the pooled data from 4 clinical studies COV001 (UK), COV002 (UK), COV003 (Brazil), and COV005 (SA).

The primary efficacy analysis demonstrated effective protection against COVID-19 with a VE of 66.73% (95% CI 57.41 to 74.01; $p < 0.001$) from 15 Days after the second dose in seronegative participants receiving two standard doses (SDSD) or 1 LD and 1 standard dose (LDSD) of VAXZEVRIA. The pooled analyses demonstrated that VAXZEVRIA provided complete protection against COVID-19 hospital admission ≥ 22 Days after the first SD dose in the seronegative analysis set. For the SDSD regimen, it was demonstrated that vaccine protection begins from 22 Days after the first dose and extends at least until 12 weeks, allowing the second dose to be given in a flexible window between 4 to 12 weeks. VAXZEVRIA elicited a strong humoral immune response, as measured by different serological assays following the first dose and the second dose of VAXZEVRIA regardless the presence of co-morbid conditions at baseline, country, and age. The vaccine was well tolerated in pooled safety analyses. The incidence of SAEs in both the AZD1222 and control groups was low, with no difference in either frequency or type between the treatment groups. There was not a significant change in the safety profile during the reporting period.

The safety profile of AZD1222 was generally similar in participants 18 to 64 and ≥ 65 years of age, although older adults reported fewer solicited AEs of grade 3 severity compared with younger adults.

AstraZeneca has modified the list of Adverse Drug Reactions (ADRs) in the CDS based on the final pooled analysis results. See Section 4 and 16.2.5.1 for more information.

COV006 (A single-blind, randomised, phase II study to determine safety and immunogenicity of the Coronavirus Disease (COVID-19) vaccine ChAdOx1 in UK healthy children and adolescents [aged 6-17]): Phase II

COV006 was an Oxford-sponsored, Phase II, single-blinded, active-controlled, randomized study in healthy children and adolescents aged 6-17 years in the UK of 2 doses 4 or 12 weeks apart of ChAdOx1 nCoV-19 (VAXZEVRIA) or active control (licensed Meningococcal Group B vaccine - MenB) administered IM (Li et al 2022). The study assessed the safety, tolerability and immunogenicity of a SD dose ($\sim 5 \times 10^{10}$ vp) of ChAdOx1 nCoV-19. The total duration of the study was 12 months from the day of enrolment for all participants.

Overall, 262 participants were randomised and 261 participants received study intervention. The disposition of participants was generally balanced across all study arms, with the majority of participants receiving both doses of study intervention (250 [95.4%] participants).

Across all AZD1222 study arms, neutralizing antibodies and Spike protein (S)- and receptor-binding domain (RBD)-binding antibodies increased after the first dose, increasing further after the second dose. Antibody levels peaked at 28 Days post second dose in all study arms, with higher antibody levels observed in the D112/12-17 years study arm than in the D28/12-17 years study arm, and the highest antibody levels observed in the D112/6-11 years study arm. At 28 Days post second dose, in the D28/12-17 years, D112/12-17 years, and D112/6-11 years AZD1222 study arms, seroresponse was recorded in 86.0%, 92.1%, and 100% of participants, respectively, for neutralizing, and in 100% of participants for S-binding and RBD-binding antibodies. At this time point, across AZD1222 study arms, antibody levels were comparable with or numerically greater than the levels for adults post second dose from pooled AZD1222 studies. Across all AZD1222 study arms, interferon (IFN)- γ ELISpot responses to SARS-CoV-2 Spike protein increased post first dose; responses did not increase further post second dose.

Overall, 100% of participants experienced solicited AEs after any dose of study intervention. The

incidence of solicited AEs was similar across all study arms. Local and systemic solicited AEs were reported in fewer participants after the second dose of study intervention than after the first dose. Across all study arms, the majority of participants had mild (Grade 1) or moderate (Grade 2) local or systemic solicited AEs, with pain and tenderness being the most common local solicited AEs and fatigue and headache being the most common systemic solicited AEs. Unsolicited AEs after any dose of study intervention were reported in a similar proportion of participants in the D28/12-17 years and D112/12-17 years AZD1222 study arms (25/58 [43.1%] and 20/62 [32.3%] participants, respectively) and corresponding MenB study arms (5/16 [31.3%] and 5/14 [35.7%] participants, respectively), and in a numerically higher proportion of participants in the AZD1222/D112/6-11 years study arm than in the corresponding MenB study arm (49/90 [54.4%] and 6/21 [28.6%] participants, respectively). The majority of unsolicited AEs in any study arm were mild (Grade 1) or moderate (Grade 2) in severity. No participant died during the study. Five participants in the AZD1222 study arms had SAEs, none of which were considered related to study intervention by the Investigator. In summary, AZD1222 administered in 2 intramuscular injections was well-tolerated in children and adolescents 6-17 years of age, at dosing intervals of 28 Days or 112 Days. No safety concerns were raised in this study.

COV008 (A Phase I study to determine safety, tolerability and immunogenicity of intranasal administration of the COVID vaccine ChAdOx1 nCoV-19 in healthy UK adults): Phase I

COV008 was a Phase I open-label study investigating intranasal (IN) administration of ChAdOx1 nCoV-19, sponsored by the University of Oxford, has completed and a manuscript published. The aim of the study was to evaluate the safety and immunogenicity of intranasally-administered ChAdOx1 nCoV-19 both in vaccine-naïve participants and in participants who had previously received intramuscularly administered SARS-CoV-2 vaccines. A total of 42 healthy volunteers under the age of 55 years participated in this study. Solicited local and systemic reactions in all groups were predominantly mild (grade 1), following both first and second IN vaccinations. The most frequent solicited adverse reactions were sore throat (52%), nasal discharge (45%), headache (48%) and fatigue (48%). There was no obvious relationship between the frequency or severity of solicited AEs and dose level, first versus second IN vaccination, or previous receipt of IM COVID-19 vaccines. Occasional moderate (grade 2) reactions were reported. No SAEs were reported during the study. Three (3) non-serious AEs of note were reported: grade 3 (severe) chest pain without identified cause; grade 3 diplopia due to decompensation of a pre-existing esodeviation (an adverse event of special interest (AESI) but assessed as unlikely to be related to IN vaccination); and grade 1 (mild) transient anosmia 10 Days after vaccination, for which the investigators' assessment was that the most likely cause was intercurrent upper respiratory tract infection, although relatedness to IN vaccination could not be excluded. Antigen-specific mucosal antibody responses to IN vaccination were detectable in a minority of participants, rarely exceeding levels seen after SARS-CoV-2 infection. Systemic responses to IN vaccination were typically weaker than after intramuscular vaccination with ChAdOx1 nCoV-19 (Madhavan M et al 2022).

D8110C00001 (A Phase III Randomised, Double-blind, Placebo-controlled Multicentre Study in Adults to Determine the Safety, Efficacy, and Immunogenicity of VAXZEVRIA, a Non-replicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19): Phase III

D8110C00001 was an AstraZeneca-sponsored, Phase III randomised, double-blind, placebo controlled, multi-centre study assessing the safety, efficacy, and immunogenicity of VAXZEVRIA compared to saline placebo for the prevention of COVID-19. Participants were adults ≥ 18 years of age who were healthy or have medically stable chronic diseases and were at increased risk for SARS-CoV-2 acquisition and COVID-19. All participants were planned remain on study for 2 years following administration of first dose of study intervention (Day 730).

A total of 32379 participants were randomised and received at least one dose of study intervention (21583 in the AZD1222 group; 10796 in the placebo group). A total of 30720 participants (94.7%) had

received 2 doses of study intervention, with 20769 participants receiving AZD1222. Most participants in both treatment groups (16099 participants [74.4%] AZD1222; 7213 participants [66.7%] placebo) completed the study through 2 years. By the end of the study, most participants in both treatment groups had received a non-study COVID-19 booster vaccination (14665 participants [67.8%] AZD1222; 6109 participants [56.5%] placebo).

In the primary efficacy analysis using 203 adjudicated cases, AZD1222 showed a VE estimate of 74.0% against SARS-CoV-2 Reverse Transcriptase (RT)-PCR-positive symptomatic illness, with a lower bound of the 95.0% CI of 65.34%. The VE estimate of 100.0% (95% CI 71.62 to NE) was observed for prevention of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness (due to no cases in the AZD1222 group). Efficacy assessment following first dose demonstrated a VE estimate of 54.5% (95% CI 46.48 to 61.26) against symptomatic illness and a VE estimate of 85.0% (95% CI 58.97 to 94.50) against severe or critical illness.

Overall, AZD1222 generated a strong humoral response, including when stratified by age, race, and ethnicity. Spike (S)-binding and receptor binding domain (RBD)-binding antibodies peaked at 14 Days post-second dose of AZD1222 and were maintained above the levels achieved by the first dose through at least Day 90. Neutralizing antibody responses were elevated above baseline at 14 Days post-first dose of AZD1222 with responses peaking at 28 Days post-second dose.

Overall, vaccination with AZD1222 had an acceptable safety profile up to 2 years post-dose and was well tolerated in healthy adult participants, as well as in high-risk adult populations of older adults and adults with comorbidities, who have an increased risk of death and severe disease associated with COVID-19. Unsolicited AEs were consistent with AEs commonly observed following vaccination. The majority of solicited (local and systemic) AEs and unsolicited AEs following vaccination with AZD1222 were mild or moderate in severity and completely resolved within 2 to 3 Days. Reactogenicity, as evaluated by the incidence of solicited AEs for 7 Days after each dose, was lower following the second dose. The incidences of SAEs were low, and there were no clinically meaningful imbalances between the AZD1222 and placebo groups. None of the fatal events in either treatment group were considered related to study intervention by the investigator. A review of the pregnancy cases did not raise any safety concerns.

D8111C00010 (A Phase IV Open-Label, Non-Randomized, Multi-Cohort, Multi-centre Study in Previously Unvaccinated Immunocompromised Adults to Determine the Immunogenicity and Safety of AZD1222 Vaccine for the Prevention of COVID-19): Phase IV

This was an AstraZeneca-sponsored, Phase IV open-label, non-randomized, multi-cohort, multicentre study to evaluate the immunogenicity and safety of AZD1222 for the prevention of COVID-19 in previously unvaccinated immunocompromised adults ≥ 18 years. Due to recruitment challenges from increasing COVID-19 vaccination rates globally, particularly in the immunocompromised population, the study could not recruit the required 360 unvaccinated/naïve participants and was terminated prematurely.

A total of 34 participants were enrolled, of these 23 were immunocompetent and 11 were immunocompromised. The two cohorts were not balanced in terms of age and gender.

The results showed that immunological responses to vaccination were lower in the immunocompromised cohort than in the immunocompetent cohort after each vaccination dose. However, in both cohorts, dose titers were increased after each vaccination compared to the previously measured titers showing the intended effect of the vaccination.

Solicited local and systemic AEs were slightly more frequent in the immunocompetent cohort compared to the immunocompromised cohort. The frequency of local and systemic AEs was higher after Dose 1 compared to after Dose 2 in both cohorts, even though the decrease was more pronounced in the

immunocompetent cohort than in the immunocompromised cohort. Unsolicited AEs were more frequently reported in the immunocompromised cohort than in the immunocompetent cohort. No SAEs or AEs leading to discontinuation of vaccination were considered related to AZD1222 by the Investigator. Overall, the safety profile of AZD1222 was acceptable in both cohorts.

Ongoing clinical trials

There was one ongoing clinical trial sponsored by University of Oxford during the reporting period (COV009). There was no clinically important information that arose from ongoing clinical trials during the reporting period. The clinical trial described below has completed subjects' recruitment and follow-up, but neither a final Clinical Study Reports (CSRs) nor a manuscript presenting the study results had yet been published by the end of the reporting period and therefore the study is not considered as completed.

COV009 (Post-approval follow-up for the COV001 and 002 trials, to determine the long-term safety and character of immunological response to the ChAdOx1 nCoV-19 coronavirus vaccine): Long-term follow-up

COV009 was an Oxford-sponsored, FU study of participants previously enrolled on the phase I/II (COV001) and phase II/III (COV002) trials to determine the long-term safety and character of immunological responses to the ChAdOx1 nCoV-19 vaccine. Up to 1,077 participants were eligible for enrolment for the COV001 cohort and up to 10,812 participants for the COV002 cohort. No treatment will be given during this Study. Study duration is 12 months.

Rapporteur assessment comment:

The MAH detailed in this section that there were 10 completed clinical trials during the reporting period (D7220C00001, COV001, COV002, COV003 including booster sub-study, COV004, COV005, COV006, COV008, D8110C00001, and D8110C00010). There were no additional clinically important emerging efficacy or safety findings obtained from the clinical trials completed during the reporting period. There was one ongoing clinical trial sponsored by University of Oxford during the reporting period (COV009).

Based on the pooled data from 4 clinical studies COV001 (UK), COV002 (UK), COV003 (Brazil), and COV005 (SA) following was noted: the safety profile of AZD1222 was generally similar in participants 18 to 64 and ≥ 65 years of age, although older adults reported fewer solicited AEs of grade 3 severity compared with younger adults. The MAH has modified the list of Adverse Drug Reactions (ADRs) in the CDS based on the final pooled analysis results. See Section 1.3.2. and 2.2. for more information.

1.3.5.2. Vaccination errors

MAH's summary and conclusion (see Section 9.2 of the PBRER for further details).

Most frequently reported vaccination errors along with other AEs included Inappropriate schedule of product administration, Incorrect route of product administration, Product administered to patient of inappropriate age, Wrong product administered, Interchange of vaccine products, Medication error, Product dose omission issue, Incorrect dose administered, Incomplete course of vaccination, and Expired product administered. Most of the AEs reported for these vaccination errors were related to the reactogenicity events such as Pyrexia, Headache, Chills, Fatigue, Pain, Pain in extremity, Myalgia, Arthralgia, and Malaise. There was no clustering of AEs or AESI's with any of the vaccination error types.

Review of these fatal cases did not identify safety issues in relation to type of vaccination errors.

A review of all the vaccination error AE reports received during this interval and cumulative period did not demonstrate any medication error-emergent safety pattern associated with VAXZEVRIA. No new relevant

patterns of vaccination errors or new safety concerns were identified during the reporting period.

Reports related to VAXZEVRIA vaccination errors will continue to be monitored by AstraZeneca through standard surveillance activities.

Rapporteur assessment comment:

A total of 1645 case reports (1231 initial and 414 follow-up), including 1748 vaccination error AEs, have been identified during the reporting period, which represents 7.45% cases of the cumulative (22075 case reports). Notably, there were 6 case reports with fatal outcome during reporting interval: Overdose (n=3), Inappropriate schedule of product administration (n=2) and Interchange of vaccine products (n=1) were most frequently reported vaccination error events in these reports.

Taking into consideration the review of the risk of vaccination errors, no further action is considered warranted at this stage.

1.3.5.3. Literature

AstraZeneca has reviewed the published non-clinical scientific literature relevant to AZD1222. No publications were identified that included any relevant new safety information or information with potential impact on the benefit or risk evaluations during the reporting period.

AstraZeneca conducts comprehensive reviews of peer-reviewed published scientific literature and unpublished manuscripts routinely on an ongoing basis. The search strategy includes VAXZEVRIA and other COVID-19 vaccines in order to identify potential class related findings.

Relevant literature articles containing new and significant safety findings relevant to VAXZEVRIA published during the review period were retrieved. Important identified and Potential risks or Missing information have been included in section. Articles containing new and significant safety findings are summarized below.

Jia et al 2023 examines reported instances of Sweet syndrome (SS) emergence subsequent to COVID-19 vaccines such as VAXZEVRIA, Jcovden, BNT162b2, Spikevax and BBIBP-CorV. A total of 16 patients (8 females, 7 males, 1 unknown) with a median age set as 60, reveals a varied spectrum of onset intervals for SS post-vaccination, reported after 8 hours to 1 month. From the 16 vaccinee, 5 received VAXZEVRIA. Most of the events were related to Dose 1 of vaccination. The most common clinical manifestations were mentioned as, skin reactions like red plaques, papules, edema, and pustules. Neurological symptoms, such as myoclonus and tendon hyperreflexia, were observed in one patient. As reported by the authors, majority of the patient reported elevated neutrophil levels, elevated C-reactive protein (CRP), and elevated erythrocyte sedimentation rate (ESR), and during the assessment of skin biopsy, the main manifestation reported was dermal neutrophilic infiltration, papillary edema, and vascular neutrophilic infiltration, however one patient reported myelodysplastic syndrome (MDS) during bone marrow biopsy. Authors agreed upon the pathophysiological mechanism of vaccine-induced SS is not cleared, however, a potential mechanism as hypersensitivity phenomenon, which was supported by frequent occurrence after infection and less involvement of the remaining organs in response to glucocorticoid therapy, however other theory mentioned in the article, suggested the characteristics of fever and increased ESR from the perspective of cytokine involvement. The authors concluded that SS, despite reported as a very rare AE caused by vaccine, needs to be distinguished from other AEs, since it is generally associated with haematological malignancies.

AstraZeneca comment

During the study, authors came across with few numbers of cases related to SS, mostly related to

BNT162b2 (6 reports out of 16), following by VAXZEVRIA (5 reports). However, as known, the low incidence of SS, moreover the even reduced incidence of vaccine-induced SS requires a higher number of patients to provide a reliable data, considering the exclusion of several reports due to limited information provided by the time of the research. Still, during the inclusion criteria and discussion, a complete upper respiratory infections analysis was not incorporate to consider other possible causes of the syndrome, neither gastrointestinal infection. Hence, causality in the reported cases could not be inferred.

Gasparotto M et al 2023 reported a case series of suspected rheumatic diseases (RDs) following anti-COVID-19 vaccination. These patients were evaluated at first-aid rheumatologic consultancy and at rheumatologic outpatient and inpatient clinic at Padova University Hospital between May and September 2021 presenting with a rheumatic disease (RD) within 30 Days after an anti-COVID-19 vaccine dose. Patients were regularly re-evaluated by telemedicine or face-to-face visit. The case series included 30 cases of RD following vaccination: 24 (80.0%) new onsets and 6 (20.0%) flares. Most of patients (n=23; 76.6%) received the BNT162b2 vaccine and 7 had received VAXZEVRIA (24.4%). The mean time to RD onset/flare was 12±9 Days. Slightly higher incidence of RD was reported in females (53.3%). In general, RD occurred mostly after the second dose (56.7%) and after a mean of 12±9 Days from vaccine administration. The most common manifestations were inflammatory arthritis (40.0%), rheumatic polymyalgia (33.3%) and adult-onset Still's disease (13.3%). All reports 6 reports with an exacerbation of their underlying RD, were after BNT162b2 vaccine. Seven reports of RD following VAXZEVRIA, 3 of them were reported after dose 1 and 4 of them after dose 2. At the last FU visit (9.6±2.2 months), 83.3% of patients showed complete response to first- or second-line therapy, 13.3% a partial response and one patient (3.3%) was still experiencing an active disease. Authors also discussed potential mechanism of action such as innate immunity through the activation of the same endoscopic and cytoplasmic nucleic acid receptors, however it was concluded that an exact mechanism required further investigations to define whether in susceptible patients could induce the development of autoinflammatory rather than autoimmunity conditions. Overall, the authors reported that the RDs following COVID-19 vaccinations were generally mild, with a benign course with prompt response to therapy.

AstraZeneca comment

The publication identified fewer number of cases of rheumatic disease following COVID-19 vaccination, particularly involving VAXZEVRIA compared to BNT162b2 vaccine (76.6%). Furthermore, limited information on the case reports were noted, such as etiological work-up, diagnosis details, medical history or family history for those with new onset of rheumatic disease. Hence causality in the reported cases could not be inferred. Overall, this article does not provide sufficient evidence of an increased risk of rheumatic disease in vaccinees who received VAXZEVRIA.

Nafilyan et al 2023 assessed the impact of COVID-19 vaccination and positive SARS-CoV-2 tests on the risk of cardiac and all-cause mortality in young people (12 to 29 years) using a self controlled case series (SCCS) design.

AstraZeneca comment:

Authors recognize some restrictions in their analysis, however during our assessment; a number of additional limitations were noted:

- The authors have grouped all non-mRNA vaccines together, including all other recorded vaccine manufacturers and nonrecorded vaccination manufacturers. According to MHRA, three COVID-19 vaccines - the monovalent COVID-19 Vaccine Pfizer/BioNTech, VAXZEVRIA and monovalent COVID-19 Vaccine Moderna - were used in the primary and booster vaccination campaigns up to the end of August 2022 (<https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting>). Based on this we could assume the

vast majority of the non-mRNA vaccines were VAXZEVRIA. However, including other, and nonrecorded vaccine manufacturers in this category may lead to mRNA vaccines being misclassified as non-mRNA vaccines.

- Even though the study used a large sample including the whole population of England, there were multiple sub-analyses per outcome strata without clarity on how multiplicity was handled and low event count per strata affecting precision. Fifteen cardiac deaths occurred in women after first dose of non-mRNA vaccination and CIs were wide (IRR:3.52 [CI: 1.71 – 7.26]). The authors report: "Between 8 December 2020 and 25 May 2022, there were 4,012,520 females aged 12 to 29 who received at least one dose of a COVID-19 vaccine between these dates, of which 177,042 received a first dose of a non mRNA or unknown vaccine vector. There were 25 cardiac registered deaths of females within 12 weeks of receiving the first dose of a COVID-19 vaccination, of which 15 had received a first dose of a non mRNA or unknown vaccine vector."
- The study used a risk period of 12 weeks, for which the authors provided no reasoning. This is longer than the recommended RW for cardiac adverse events of special interests (for example, 1-28 Days for myocardial infarction or 1-42 Days for Myocarditis/Pericarditis where Day 0 is the day of vaccination (FDA Guideline), (Kuntz et al 2018). Including a twice as long FU than recommended may lead to deaths occurring after the true RW being attributed to vaccination, when it is not biologically plausible. In fact, sensitivity analyses with varying lengths of risk periods all COVID-19 vaccines remained below or not significantly different to 1, particularly in the range <12 weeks. In contrast, analyses of deaths after a positive SARS-CoV-2 test for those unvaccinated at time of testing showed the risk of all-cause death was greater for shorter risk period definitions, particularly for hospital deaths. Last, the results in this study are conflicting with another SCCS study from the US where the risk period was set at 28 Days (see below).
- There is lack of detail regarding the cause of death registrations included, the authors included deaths with a cardiac diagnosis mentioned on the death certificate, rather than including the main cause of death. This may have led to misclassification. Moreover, cardiac deaths included only ICD codes I130 to I152, the authors give no reason for including only these codes.
- The authors did not take COVID-19 infection into consideration in the analysis of COVID-19 vaccination and death, even though the study periods overlapped. It is possible that individuals change behaviour after COVID-19 vaccination, increasing social contacts, and as a consequence, being at an increased risk of COVID-19 infection after vaccination. Moreover, as a large proportion of the study population are expected to be healthcare workers based on the vaccination roll out, they would be at high risk of COVID-19 infection. Specifically, the interaction between vaccination and infection was not explored. The distribution of events over calendar time post positive test result clearly shows a modal value close to day 0 which means a high proportion of deaths can be attributable to the infection. Observations post dose are not dissimilar but, the model value has shifted to 20 weeks for dose 1 and further for dose two making any inference of direct relationship more challenging. An understanding of any synergistic effect is needed for a more comprehensive understanding of risk. Of note, in the US SCCS study cited by the authors (Ladapo et al 2022), where post-vaccination positive tests for SARS-CoV-2 were excluded, no increased risk of cardiac deaths post non-mRNA vaccination was observed as compared to post mRNA vaccination – particularly among males (see below for more details).
- The authors provided no explanation for the biological basis underlying their key result of a possible sex difference in the rates of deaths following non-mRNA vaccination, with significant risk thereof in young females. Moreover, these results are inconsistent with studies published to date. For example, in the SCCS study from the US Ladapo et al 2022 where the risk period was set at 28 Days, there was an increased risk of cardiac deaths in males receiving mRNA vaccines (RI 1.11, CI: 1.05-1.18) while males who received non-mRNA vaccines had lower risk (IR 0.75, CI: 0.58-0.98). Notably, similar pattern was

observed among females, and among the subgroups evaluated, males aged 18-39 had the highest risk (RI 1.97, CI: 1.16 - 3.35). Although the two studies may not be directly comparable with respect to non-mRNA vaccines, given that VAXZEVRIA was not used in the US, results from mRNA analyses provide valuable insights with expected reproducibility across different geographies.

- The roll-out VAXZEVRIA in this age group was limited to health care workers and people who were clinically extremely vulnerable. Therefore, these results cannot be generalised to the population as a whole. The data available for analyses in this study lacked the means to characterise potentially impactful differences across the study sub-groups, specifically those who received non-mRNA vaccines as compared to those who received mRNA vaccines. Given the design inherent limitation of lacking the capacity to construct direct, matched comparisons between the two groups, the indirect contrast set forth by the authors should have been provided with a word of caution – that is the lack of incomparability between the two groups as a result of major shifts in COVID-19 vaccination policy during the study period.

In this study, the authors reported no significant increase in cardiac or all-cause mortality in the 12 weeks following COVID-19 vaccination compared to more than 12 weeks after any dose. However, they reported an increase in cardiac death in women aged 12-29 years after a first dose of non-mRNA vaccines. In summary, several limitations were identified after reviewing the study design and methods, including low precision; methodological uncertainties including the choice of RW in main analyses; conflicting results with published literature; lack of characterisation of/comparability between study sub-groups; and combining VAXZEVRIA with unknown and “other” vaccinations. These methodological concerns limit the inferences that can be drawn from this study.

Rapporteur assessment comment:

The MAH's review of literature does not suggest any new safety issue. The publication by *Nafilyan et al 2023* regarding cardiac and all-cause mortality following COVID-19 vaccination has been assessed as part of the LEG 115 on myocarditis.

1.3.6. Lack of efficacy in controlled clinical trials

MAH conclusion (see Section 13 of the PBRER for further details).

In conclusion, nAbs were not detected against Omicron XBB with a third booster dose in a study performed before XBB emergence; however, following a fourth dose, hybrid immunity driven nAb responses to XBB were observed in approximately 50% of a small sample of study participants. It is unknown how the level of immune response against different variants correlates with clinical outcome. Real world VE data for VAXZEVRIA against the Omicron variant is limited with no available data for Omicron XBB. While there were no nAbs against XBB following a third booster dose, VE was maintained over time against severe disease from Omicron as T cell epitopes are somewhat conserved across variants including XBB descendants which would explain the protection against severe disease offered by vaccines developed against the ancestral SARS-CoV-2 strain.

Rapporteur assessment comment:

The MAH concluded that nAbs were not detected against Omicron XBB with a third booster dose in a study performed before XBB emergence. A fourth dose (which is outside the current approved posology) induced low levels of nAB against XBB.1.5 but only in half of the vaccinees, which may be effect of hybrid immunity.

Immune response against omicron variants and real world effectiveness data are discussed in detail as part of the variation procedure EMEA/H/C/005675/II/0095 (ongoing clock-stop; restart on 26/05/2024).

1.3.7. Late-breaking information

No potentially important safety or efficacy/effectiveness findings arose after the DLP. Of note, due to the evolving new COVID variants and vaccines landscape there was decreased administration of VAXZEVRIA, and the safety data is limited during this reporting period.

Rapporteur assessment comment:

After the DLP of this PBRER, on 5 March 2024, the MAH requested to withdraw the marketing authorisation (EU/1/21/1529/002) for Vaxzevria (EMA/H/C/005675). The marketing authorisation for Vaxzevria was withdrawn on 7 May 2024 (approved by the European Commission on 27 March 2024). (please refer to Section 1.2. of this AR for further information).

2. Signal and risk evaluation

2.1. Summary of safety concerns

Table 4 presents a summary of the safety concerns included in the Core RMP for VAXZEVRIA (Version 8.0, dated 10 November 2022) and the EU RMP for VAXZEVRIA (Version 6, dated 10 February 2023) that were in effect at the beginning of the reporting period.

Table 4 - Summary of safety concerns at the beginning of the reporting period [from Appendix R3 of the PBRER]

Risk Category	Core Risk Management Plan (V8 dated 10 November 2022)	EU Risk Management Plan (V6 dated 10 February 2023)
Important identified risk	Thrombosis in combination with Thrombocytopenia	Thrombosis with thrombocytopenia syndrome
		Thrombocytopenia, including immune thrombocytopenia
		Guillain-Barré Syndrome
Important potential risk	Cerebrovascular venous sinus thrombosis without thrombocytopenia	Thrombosis
	Immune mediated neurological conditions	Immune mediated neurological conditions
		Vaccine-associated enhanced disease (VAED), including vaccine associated enhanced respiratory disease (VAERD)*
Missing information	Use of AZD1222 in pregnancy and breastfeeding women	Use during pregnancy and while breastfeeding
	Use of AZD1222 in subjects with severe immunodeficiency	Use in immunocompromised patients
	Use of AZD1222 in subjects with severe and/or uncontrolled underlying disease	Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)
		Use in patients with autoimmune or inflammatory disorders
		Interactions with other vaccines*
		Long-term safety

EU European Union; VAED Vaccine-Associated Enhanced Disease; VAERD Vaccine Associated Enhanced Respiratory Disease

*Safety concerns VAED/VAERD and Interactions with other vaccines are reclassified from the list of safety concerns in the core RMP V8.

As an outcome of the previous PBRER assessment report, the MAH was requested to update the safety concerns of the PSUR and RMP as follows:

- To Re-classify the important potential risk of 'Thrombosis' as an important identified risk at the next regulatory opportunity
- To maintain 'Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)' in the important potential risks
- To maintain 'Interactions with other vaccines' and 'Long-term safety' in the missing information.

MAH's response:

The important potential risks 'Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)', and the missing information topics 'Interactions with other

vaccines' and 'Long-term safety' have been maintained in the EU RMP. The new information on these topics presented within the PBRER Appendix R3.

The following change were included within the EU RMP version 8.0 succession 2.0 which was submitted with variation EMEA/H/C/005675/II/0097 (review ongoing at PBRER submission):

"Thrombosis" is reclassified and removed from the list of safety concerns and "Venous thromboembolism (VTE) without thrombocytopenia" is added as an important identified risk.

Rapporteur assessment comment:

The variation II/097 is closed and received final opinion on 07.03.2024. The currently approved RMP v8 includes Venous thromboembolism (VTE) as an important identified risk.

2.2. Signal evaluation

During the reporting period, two validated signals were closed and considered as identified risk categorised as non-important :

- One signal of "Decreased appetite" and
- One signal of "Potential Vaccination Failure/Lack of Efficacy against Emerging Variants (including Omicron XBB)"

Signal term	Date detected	Status (new, ongoing or closed)	Data closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
Decreased appetite	Dec 2022	Closed	Jan 2023	AZ clinical trial (Pooled data analysis)	GSP or SSaMT Leader consider signal requires evaluation	Qualitative data analysis (Individual Case Safety Report or Case Series) Literature Quantitative Signal	Change to Reference Safety Information and Product Labelling: CDS Section 4.8 (Undesirable effects) was updated to include Decreased appetite as an ADR (frequency: uncommon)
Potential Vaccination Failure/Lack of Efficacy against Emerging Variants (including Omicron XBB)	Jun 2023	Closed	Jun 2023	Updates from immunogenicity study and developments from the ICMRA COVID-19 Omicron variant workshop	GSP or SSaMT Leader consider signal requires evaluation	Clinical Trial and Real-world evidence data	AstraZeneca evaluated the benefit-risk profile of VAXZEVRIA against currently circulating variants of concern (Omicron BA.4/5 and XBB; prior to designation of EG.5). Based on available data and structured benefit-risk assessment, CDS was updated to ensure that the healthcare professionals are aware that there are no clinical efficacy/VE data available with emerging variants and to remind them to consider the characteristics of circulating SARS- VAXZEVRIA CoV-2 viral variants, including regional or geographical differences when using

ADR Adverse Drug Reaction; AZ AstraZeneca; CDS Core Data Sheet; COVID-19 Coronavirus Disease Of 2019; GSP Global Safety Physician; ICMRA International Coalition of Medicines Regulatory Authorities; SARS-CoV-2 Severe Acute Respiratory Coronavirus; SSaMT Safety Strategy and Management Team; VE: Vaccine Efficacy.

Rapporteur assessment comment:

The signal of '**Decreased appetite**' was triggered by the final pooled analysis of COV studies which was assessed within the type II variation EMEA/H/C/005675/II/0089 procedure (final opinion issue on 20/07/2023). 'Decreased appetite' was already included as an ADR (frequency uncommon) in the EU-PI (see Section 16.2.5.1 of the PBRER for further information).

The signal of '**Potential Vaccination Failure/Lack of Efficacy against Emerging Variants (including Omicron XBB)**' was triggered by updates from immunogenicity study and developments from the International Coalition of Medicines Regulatory Authorities (ICMRA) COVID-19 Omicron variant workshop. The MAH reviewed clinical trial and RWE studies including the booster doses of Vaxzevria and evaluated the benefit-risk profile of VAXZEVRIA against currently circulating variants of concern (Omicron BA.4/5 and XBB; prior to designation of EG.5). The MAH has updated the CDS to include a warning/reminder to the treating physician on potential vaccination failure/lack of efficacy against the circulating variants including regional or geographical differences.

This information is not included in the EU-PI. The benefit-risk balance of Vaxzevria is currently under evaluation within the variation procedure EMEA/H/C/005675/II/0095 (ongoing clock-stop; restart on 26/05/2024) (see Section 1.3.6. for further information regarding VE against new variants).

2.3. Evaluation of risks and safety topics under monitoring

2.3.1. Important Identified Risk – Thrombosis in combination with thrombocytopenia/Thrombosis with thrombocytopenia syndrome

MAH's conclusion (see Section 16.3.2.1 of the PBRER for further details).

Based on currently available data, no new safety information concerning TTS was identified. The current risk minimisation measures described in the product information are considered adequate.

No new or emerging concern regarding TTS has been identified with booster doses of AZD1222. Based on the review of available safety data, there is no indication suggesting that the safety profile of an AZD1222 booster after a primary series with another vaccine would be different with respect to TTS from that of a first vaccine dose of AZD1222.

The topic 'thrombosis in combination with thrombocytopenia/ TTS will continue to be closely monitored as part of AstraZeneca's ongoing surveillance activities.

Rapporteur assessment comment:

During the period under review, no new significant safety information concerning TTS was identified. Taking into consideration the review of this important identified risk, **no further action is considered warranted at this stage.**

2.3.2. Important Identified Risk (EU-specific) – Thrombocytopenia, including immune thrombocytopenia

MAH's conclusion (see Appendix R3 - Section 2.2.1 of the PBRER for further details).

Overall, the review for case reports of Thrombocytopenia including Immune Thrombocytopenia did not raise any new relevant safety information for VAXZEVRIA.

Rapporteur assessment comment:

A total of 427 reports of Thrombocytopenia were retrieved through the search during reporting interval: 310 (72.8%) reports with co-reported thromboembolic events and 117 (27.2%) reports without co-reported thromboembolic events. None of the cases met WHO-UMC criteria for Certain (including immune thrombocytopenia) causality. Notably, there were 6 reports with fatal outcome.

Taking into consideration the review of the risk thrombocytopenia, including immune thrombocytopenia, **no further action is considered warranted at this stage.**

2.3.3. Important Identified Risk (EU-specific) – Guillain-Barré Syndrome

MAH's conclusion (see Section 15.2.6 of the PBRER for further details).

During the period covered by this report, a total of 163 case reports (98 initial reports and 65 FU reports) were identified. Cumulatively, a total of 1976 cases were reported.

Out of the 163 interval cases, 33 cases fulfilled BCC 1 level criteria, 21 fulfilled BCC 2 level criteria and 5 BCC 3 level criteria. When these 60 are assessed according to WHO-UMC causality criteria, 2 cases were classified as "Unassessable/unclassifiable", 5 as "Unlikely", and 53 as "Possible" causality to VAXZEVRIA.

The review of GBS cases post COVID-19 booster dosing did not show any significant safety concern.

There is high variability in the data for the observed versus expected analysis of cumulative cases reported, making an assessment on causal association not possible. The majority of the stratifications and analysis suggest that the observed cases are less than expected for all three risk windows (14-30-42 Days). However, some analysis for global reports, UK and the EU-UK-Brazil-Australia suggest observed cases are more or significantly more than expected. It is important to note that the mainstream of reported cases correlate with the period of peak pandemic activity, suggesting a potential role of COVID-19 infection in causing GBS. Seasonal fluctuations in the incidence of GBS with a higher incidence in winter compared to summer is also a consideration.

Based on the review of available evidence from literature and from reports in the safety database on the topic of GBS, AstraZeneca considers that there is not sufficient evidence to confirm any particular clinical features associated with vaccination or establish a causal association with VAXZEVRIA.

In conclusion, from the data identified during the reporting period, and also taking into account the cumulative experience, no new information on GBS warrant any changes in the CDS or RMP. The topic of GBS will continue to be closely monitored as part of AstraZeneca's ongoing surveillance efforts for the important potential risk of immune mediated neurological conditions.

Rapporteur assessment comment:

As previously extensively discussed in previous SSR and PBRER procedures, the PRAC Rapporteur considers that a causal association between Guillain-Barré and Vaxzevria should be considered at least a reasonable possibility (disagreement with the MAH's opinion). Of note, a publication after the DLP by *Faksova et al 2024*, the largest global vaccine safety study to date², confirmed the safety signal of GBS (O/E of 2.49, 95 % CI: 2.15, 2.87 following a first dose). Currently, GBS is appropriately described in the EU-PI (sections 4.4 and 4.8) and in the EU-RMP (important identified risk). Information becoming available during the period under review did not raise any new safety concern regarding GBS.

Taking into consideration the review of the risks of GBS **no further action is considered warranted at**

² <https://brightoncollaboration.org/press-release-qvdm-largest-global-vaccine-safety-study/#::~text=The%20GCoVS%20Project%20was%20made,vaccines%20across%20diverse%20global%20populations.>

this stage.

2.3.4. Important potential risk (EU-specific) – Thrombosis

MAH's conclusion (see Appendix R3 - Section 2.1.1 of the PBRER for further details).

From the data identified during the reporting period, and also taking into account the cumulative experience, no causal relationship between arterial thrombosis and VAXZEVRIA could be established. However, few literature articles showed increased risk for VTE in association with VAXZEVRIA. Thus, IPR of "Thrombosis" is reclassified and removed from the list of safety concern and replaced with "Venous thromboembolism (VTE) without thrombocytopenia" as an important identified risk.

Rapporteur assessment comment:

In the AR of the previous PBRER (EMA/H/C/PSUSA/00010912/202212), the MAH was requested to re-classify the important potential risk of 'Thrombosis' as an important identified risk at the next regulatory opportunity. 'Thrombosis' was reclassified and removed from the list of safety concerns and 'Venous thromboembolism (VTE)' was added as an important identified risk in EU-RMP version 8.0 succession 2.0, which was submitted with variation EMA/H/C/005675/II/0097 (review ongoing).

The MAH did not provide a (cumulative) review of cases of VTE in association with Vaxzevria in the current PBRER.

As discussed previously, the PRAC Rapporteur considers that a causal association between VTE and Vaxzevria should be considered at least a reasonable possibility. Currently, VTE is appropriately described in the EU-PI (sections 4.4 and 4.8) and in the EU-RMP (important identified risk).

No further action is considered warranted at this stage.

2.3.5. Important potential risk – CVST without thrombocytopenia

MAH's conclusion (see Section 16.3.1.1 of the PBRER for further details).

AstraZeneca continued to review the safety information for CVST without thrombocytopenia from sources including clinical trials, post-marketing reports, and the published literature for the reporting period.

There were no case reports indicating recurrence (after the first and second dose of the vaccine). There are 620 and 32 cases for the cumulative and reporting period respectively.

From the data identified during the reporting period and also taking into account the cumulative experience, AstraZeneca considers that there is currently insufficient evidence of a reasonable possibility of causal relationship between VAXZEVRIA and CVST without thrombocytopenia. CVST without thrombocytopenia is included in section 4.4 (section 4.4 Warnings and Precautions) of the CDS to inform prescribers that these events may require different treatment approaches than TTS. Healthcare professionals should consult applicable guidance. No changes to the CDS or product leaflets are warranted at this time.

AstraZeneca will continue to monitor safety information for CVST without thrombocytopenia as an important potential risk and take further actions as deemed appropriate.

Rapporteur assessment comment:

As already discussed in previous MSSR and PBRER procedures, the PRAC Rapporteur disagrees with the MAH's conclusion on causality. A causal association between CVST without thrombocytopenia and

Vaxzevria should be considered at least a reasonable possibility. Of note, a publication after the DLP by *Faksova et al 2024*, confirmed the safety signal of CVST following the first dose of Vaxzevria (O/E of 3.23, 95 % CI: 2.51, 4.09). Cerebrovascular venous and sinus thrombosis is appropriately described in the EU-PI (sections 4.4 and 4.8).

During the period under review, no new significant safety information concerning CVST without thrombocytopenia was identified. **No further action is considered warranted at this stage.**

2.3.6. Important potential risk –Immune-mediated neurological conditions / Nervous system disorders, including immune-mediated neurological conditions during the reporting period

MAH's conclusion (see Section 16.3.1.2 of the PBRER for further details).

During the period covered by this report, a total of 682 cases from literature, interventional studies, non-interventional studies and spontaneous sources were reported within the concept of immune-mediated neurological disorders. Cumulatively, a total of 8964 cases were reported.

The MAH reviewed cases from a prospective case series (Francis et al 2023) and a retrospective chart review (Samim et al 2023). Overall, there was limited data on individual case characteristics for a comprehensive causal assessment or possible risk factors/alternate explanation were identified. Quantitative trends of MOGAD cases were similar to BG frequency with lack of consistency of frequency trends with subsequent VAXZEVRIA doses or in subsequent months. No significant concerns for MOG positivity frequencies or underlying core clinical demyelinating event distribution were observed.

As per the Section 4.4 of the current CDS regarding neurological events, demyelinating disorders are very rare events reported following vaccination with VAXZEVRIA. A causal relationship has not been established. It is the MAH's opinion that no further changes to the VAXZEVRIA CDS or RMP, are warranted based on the review of currently available information. Immune-mediated neurological conditions will continue to be closely monitored as part of AstraZeneca's ongoing surveillance efforts for the important potential risk of immune-mediated neurological conditions.

Rapporteur assessment comment:

No new significant safety information immune-mediated neurological conditions was identified. No further action is considered warranted at this stage.

2.3.6.1. Encephalitis, including fatal

MAH's conclusion (see Section 16.3.1.2.1 of the PBRER for further details).

During the reporting period, there are 70 case reports of encephalitis (i.e., 24 were initial case reports and 46 were FU reports), in vaccinees who received VAXZEVRIA, out of which 2 cases were reported with fatal outcome. Cumulatively, there are 442 cases of encephalitis received, including 22 cases with fatal outcome.

Overall, the clinical pattern of case presentation and numbers of reports are broadly consistent with what might be expected from the natural epidemiology of encephalitis, and there was no specific biological mechanism for development of encephalitis post vaccination with VAXZEVRIA.

From the data identified during the reporting period and taking into account the cumulative experience, there is currently insufficient evidence of a causal association between encephalitis and VAXZEVRIA.

VAXZEVRIA CDS Section 4.4 includes warnings on Neurological events. In addition, encephalitis (immune mediated neurological condition/ nervous system disorders, including immune mediated neurological conditions.) is considered as an Important potential risk in the Core and EU RMPs for VAXZEVRIA. No further updates to the VAXZEVRIA CDS or RMP are warranted at this time. As such, the topic will continue to be closely monitored as part of AstraZeneca's ongoing surveillance for the important potential risk of immune-mediated neurological conditions.

Rapporteur assessment comment:

No new significant safety information about encephalitis was identified. Taking into consideration the review of encephalitis, no further action is considered warranted at this stage.

2.3.6.2. Transverse Myelitis

MAH's conclusion (Section 16.3.1.2.2 of the PBRER for further details).

During the reporting period, there are 62 case reports describing 64 events of transverse myelitis (i.e., 31 were initial case reports and 33 were FU reports), in vaccinees who received VAXZEVRIA. Out of these cases, 4 cases were reported with fatal outcome. Cumulatively, there are 419 cases of transverse myelitis received, including 7 cases with fatal outcome.

The information from this periodic review found insufficient evidence for a new or emerging signal regarding TM and VAXZEVRIA. No changes to the CDS or RMP are recommended for TM at this time. As such, the topic will continue to be closely monitored as part of AstraZeneca's ongoing surveillance efforts for the important potential risk of immune mediated neurological conditions.

Rapporteur assessment comment:

As previously in-depth discussed in previous SSR and PBRER procedures, the PRAC Rapporteur considers that a causal association between transverse myelitis and Vaxzevria should be considered at least a reasonable possibility (disagreement with the MAH's opinion). Of note, a publication after the DLP by *Faksova et al 2024*, confirmed the safety signal of TM (O/E of 1.91; 95 % CI: 1.22, 2.84 – following a first dose). Currently, transverse myelitis is appropriately described in the EU-PI (sections 4.4 and 4.8). Information becoming available during the period under review did not raise any new safety concern regarding transverse myelitis.

Taking into consideration the review of the risks of transverse myelitis no further action is considered warranted at this stage.

2.3.6.3. Acute disseminated encephalomyelitis (ADEM)

MAH's summary and conclusion (see Section 16.3.1.2.3 of the PBRER for further details).

During the reporting period, there are 22 case reports describing acute disseminated encephalomyelitis (ADEM) (i.e., 11 were initial case reports and 11 were FU reports), in vaccinees who received VAXZEVRIA. Cumulatively, there are 91 unique cases of ADEM reported.

Of the 22 cases of ADEM reported in the period of this report, most of the cases occurred in the age group between 23 and 61 years with no significant difference between the genders. All the cases were MC and serious, 4 cases had a fatal outcome. Most of the cases event occurred with Dose 1 of vaccination (20/22) and in two cases after Dose 2. Fourteen cases that met the Brighton Collaboration level 1-3 were assessed as per WHO-UMC causality assessment criteria. These cases were considered as "Possible"

based on the temporal relationship only, with limited information precluding a comprehensive causal assessment.

The O/E analysis of all ADEM cases suggested that overall, the observed numbers were significantly less than the expected numbers in the 42-day risk windows. The observed numbers were greater than expected in a few subgroup stratifications and may be explained by reporting bias for increased reporting of cases with a shorter risk window for the passive event reporting of rare diseases. Review of cases in these subgroups where observed numbers were above expected showed that most cases had insufficient information to make any causality assessment. AstraZeneca does not consider the trend analysis to be suggestive of increased risk due to VAXZEVRIA.

On review of the literatures received in the reporting period of the PBRER, there is insufficient evidence of a causal association or any conclusive mechanism leading to the development of ADEM.

The information from this updated review found insufficient evidence for a new or emerging signal regarding ADEM and VAXZEVRIA. No changes to the CDS or RMP are recommended. The topic 'ADEM' will continue to be closely monitored as part of AstraZeneca's ongoing surveillance activities for the important potential risk of immune-mediated neurological conditions.

Rapporteur assessment comment:

Cumulatively, 91 cases of ADEM were reported after Vaxzevria, including 22 cases during the interval period. Among those 22 cases, 14 cases fulfilled BCC L1-3 criteria and were assessed as possible as per the WHO-UMC causality assessment criteria. This is in line with the previous cumulative review of spontaneous data which identified 4 possible cases fulfilling BCCL1 and 25 possible cases fulfilling BCC L-23 among 83 cumulative cases.

During the reporting period, new epidemiological data became available:

- *Nabizadeh et al 2023* (already discussed in the previous PBRER AR) conducted a comprehensive systematic search using three databases. Twenty studies were included in the systematic review with a total of 54 cases, of which 35 were reported after Vaxzevria vaccination. Cases occurred more frequently after the first dose. The authors highlighted the challenging differential diagnosis spectrum of ADEM and conclude that it is not clear that ADEM could be a potential complication of COVID-19 vaccination but suggest that neurologists should be aware of serious neurological consequences that may arise after COVID-19 immunization, in particular for the ChAdOx1;
- *Samim et al 2023* performed retrospective chart review (India, from 01 Feb 2021 to 30 Jun 2022). Out of 51 cases of neurological disorders in temporal association with COVID-19 vaccination, CNS demyelination was described in 39 cases, including 4 cases of ADEM.

The PRAC rapporteur **identified 3 additional articles published shortly after the DLP:**

- *Faksova et al 2024³* performed an observational cohort study comparing observed with expected rates of 13 selected AESI across neurological, haematological, and cardiac outcomes. The Global COVID Vaccine Safety (GCoVS) Project, established in 2021 under the multinational Global Vaccine Data Network (GVDN), aimed to evaluate the risk of AESI following COVID-19 vaccination from 10 sites across 8 countries (*i.e.*, Argentina, Australia, Canada, Denmark, Finland, France, New Zealand and Scotland).

Expected rates were obtained by participating sites using pre-COVID-19 vaccination healthcare data

³ Faksova K, Walsh D, Jiang Y, Griffin J, Phillips A, Gentile A, Kwong JC, Macartney K, Naus M, Grange Z, Escolano S, Sepulveda G, Shetty A, Pillsbury A, Sullivan C, Naveed Z, Janjua NZ, Giglio N, Perälä J, Nasreen S, Gidding H, Hovi P, Vo T, Cui F, Deng L, Cullen L, Artama M, Lu H, Clothier HJ, Batty K, Paynter J, Petousis-Harris H, Buttery J, Black S, Hviid A. COVID-19 vaccines and adverse events of special interest: A multinational Global Vaccine Data Network (GVDN) cohort study of 99 million vaccinated individuals. *Vaccine*. 2024 Apr 2;42(9):2200-2211. doi: 10.1016/j.vaccine.2024.01.100. Epub 2024 Feb 12. PMID: 38350768.

stratified by age and sex. Observed rates were reported from the same healthcare datasets since COVID-19 vaccination program rollout. Risks were assessed using observed versus expected (OE) ratios with 95 % confidence intervals (42-days risk period).

Participants included 99,068,901 vaccinated individuals. In total, 183,559,462 doses of BNT162b2, 36,178,442 doses of mRNA-1273, and 23,093,399 doses of ChAdOx1 were administered across participating sites in the study period.

ADEM showed an OE ratio of 2.23 (95 % CI: 1.15, 3.60) following the first dose of Vaxzevria, but not after the second and third doses (OE ratio of 1.63 [0.70-3.21] and 0 respectively). Sensitivity analysis by country confirms the imbalance with an OE ratio of 5.30 [1.72-12.36] for the study site Australia: NSW.

Of note, a signal is also detected for mRNA-1273 vaccine with an OE ratio of 3.78 [1.52-7.78].

- *Morgan et al 2024⁴* performed a SCCS and utilized an Australian vaccine datalink, Vaccine Safety Health-Link (VSHL). VSHL was selected for this analysis as while VSHL data are utilised for GVDN association studies, they were not included in the GVDN observed expected analyses. The authors observed associations between ChAdOx1 adenovirus vector COVID-19 vaccination and ADEM (all dose RI: 3.74 [95 %CI 1.02,13.70]) and TM (dose 1 RI: 2.49 [95 %CI: 1.07,5.79]) incident admissions in the 1-42 days following vaccination. Dose-specific analysis suggests that dose 1 may be associated with ADEM and TM more broadly. A sensitivity analysis of the narrow 5-28 day risk window increased the dose 1 ADEM signal, but diminished the all-dose ADEM signal. No increased risk was observed following mRNA BNT162b2 vaccine administration and there were insufficient cases following mRNA-1273 to adequately assess the association. These findings translate to a small absolute risk of ADEM (0.78 per million doses) and TM (1.82 per million doses) following vaccination. TM is listed as an ADR in the EU SmPC.
- *Stowe et al 2024⁵* performed a SCCS using the Secondary Uses Service (SUS) database in England. There was evidence of an increased risk of ADEM after the first dose of ChAdOx1-S vaccine with 12 events in the 42 days following vaccination (RI = 3.13, 95% CI [1.56–6.25]). No other vaccine or dose gave a significant increased risk. When doses 1 and 2 were combined the increased risk was just significant (1.96 [95%CI 1.01–3.82]). Although the diagnosis coding in this study was not validated, the sensitivity analysis using the ADEM ICD-10 diagnosis code only in the primary field resulted in a slightly higher estimate RI 4.08 (1.93–8.59) compared to using a diagnosis in the first three diagnosis fields (RI 3.13 (1.56–6.25)), but this difference was not significantly higher. The vaccine attributable risk was estimated at 0.39 per million doses.

In conclusion, the signal of ADEM with Vaxzevria which was previously raised by spontaneous reporting data is now confirmed by two more robust and powerful studies. The multi-country cohort study shows an increased number of observed cases of ADEM compared to expected within a large and diverse sample size. Despite the limitations (i.e., heterogeneity in data collection/quality, bias related to differences in healthcare infrastructure and surveillance system, population confounding factors,...), the O/E analysis performed in the context of the GCoV project offers several advantages including a good estimation of exposure from immunisation registries covering the same population and geographic region as the data sets used to calculate background rates. The signal confirmation is also supported by the recent SCCS analysis conducted in Australia and England.

Taking into consideration the review of the risk of ADEM, including data from spontaneous reporting and data from epidemiological studies, the PRAC Rapporteur considers that a causal association between ADEM and Vaxzevria should be considered at least a reasonable

⁴ Morgan HJ, Clothier HJ, Sepulveda Kattan G, Boyd JH, Buttery JP. Acute disseminated encephalomyelitis and transverse myelitis following COVID-19 vaccination - A self-controlled case series analysis. *Vaccine*. 2024 Apr 2;42(9):2212-2219. doi: 10.1016/j.vaccine.2024.01.099. Epub 2024 Feb 12. PMID: 38350771.

⁵ Stowe J, Lopez-Bernal J, Andrews N. The risk of acute disseminated encephalomyelitis (ADEM) following covid-19 vaccination in England: A self-controlled case-series analysis. *Hum Vaccin Immunother*. 2024 Dec 31;20(1):2311969. doi: 10.1080/21645515.2024.2311969. Epub 2024 Feb 1. PMID: 38299507; PMCID: PMC10841003.

possibility.

2.3.7. Important potential risk – Vaccine-Associated Enhanced Disease (VAED) / Vaccine-Associated Enhanced Respiratory Disease (VAERD)

MAH's summary and conclusion (see Appendix R3 - Section 2.1.2 of the PBRER for further details).

Summary

On review of 369 cases of VAED/VAERD received during the reporting period, a majority (290 out of 369, 78.6%) of them were reported as serious, of which 237 cases were medically confirmed, and 51 out of 369 (13.8%) cases reported fatal outcomes. These cases had insufficient information on dose latency, medical history, concomitant medications, baseline medical condition prior to vaccination, clinical course, diagnostic and etiologic workup, and storage and transport conditions of the vaccine, which precluded a proper causal assessment.

No hypothesized mechanism/pathways have been identified to date. No new safety information on this topic was identified through the review of the literature.

Conclusion

From the data identified during the reporting period, and also taking into account the cumulative experience, no causal relationship between VAED/VAERD and VAXZEVRIA could be established. VAED/VAERD is included as an important potential risk in the EU Risk Management Plan and the topic will continue to be kept under close surveillance by AstraZeneca.

Rapporteur assessment comment:

Taking into consideration the review of the previous request for monitoring [to maintain VAED, including VAERD in the important potential risks and to discuss relevant data from the literature], no further action is considered warranted at this stage.

2.3.8. Other potential risks not categorised as important – AESI

MAH's conclusion (see Appendix 8 of the PBRER for further details).

The AESIs for the COVID-19 VACCINE ASTRAZENECA and associated PTs are listed in Appendix 7 of the PSUR. AESIs have been included for review in Section 16.3.3 and Appendix 8 of the PSUR (O/E Analyses).

AESI for which the O/E analysis resulted in a ratio >1 are presented in Table 5.

Table 5 - Observed versus expected analyses for AESI and Safety Concerns in the COVID-19 VACCINE ASTRAZENECA RMP –cumulative to 28 December 2022 with rate ratio above one (built by the Assessor from Appendix 8)

Medical Concept	Observed cases	Expected cases	Risk Window (days)	Background rate/100,000 person-years	Rate ratio (CI 95%)
Anaphylaxis type reactions b	1478	576.83	2	22.6	2.56 (2.43 - 2.7)
Anaphylaxis type reactions b (including unknown TTO)	2280	576.83	2	22.6	3.95 (3.79 - 4.12)
Angioedema – Hypersensitivity c	10545	2552.36	2	100	4.13 (4.05 - 4.21)
Angioedema – Hypersensitivityc (including unknown TTO)	15589	2552.36	2	100	6.11 (6.01 - 6.2)
Acute disseminated encephalomyelitis	46	26.8	14	0.15	1.72 (1.26 - 2.29)

Acute disseminated encephalomyelitis (including unknown TTO)	67	26.8	14	0.15	2.5 (1.94 - 3.17)
Acute disseminated encephalomyelitis (including unknown TTO)	76	57.43	30	0.15	1.32 (1.04 - 1.66)
GBS Overall (including unknown TTO)	992	807.57	14	4.52	1.23 (1.15 - 1.31)

Rapporteur assessment comment:

The following AESI had a Observed significantly > Expected : Anaphylaxis type reactions, Angioedema – Hypersensitivity, GBS and Acute disseminated encephalomyelitis. These events, with the except of ADEM, are included in Section 4.8 of the EU-SmPC. ADEM is discussed in 2.3.7.3 of this AR.

Taking into consideration the review of the AESIs, **no further action is considered warranted at this stage.**

2.3.9. Missing information

MAH's conclusion (see Section 16.3.5 and Appendix R3 - Section 2.3 of the PBRER for further details)

No new information relevant to the previously recognised missing information of has been identified during the reporting period.

Detailed information regarding missing information is provided in:

- Section 16.3.5.1: Use of VAXZEVRIA in pregnant and breastfeeding women / Use during pregnancy and while breastfeeding
- Section 16.3.5.2: Use of VAXZEVRIA in subjects with severe immunodeficiency / Use in immunocompromised patients
- Section 16.3.5.3: Use of VAXZEVRIA in subjects with severe and/or uncontrolled underlying disease / Use in frail patients with co-morbidities
- Appendix R3 - Section 2.3.1 : Use in patients with autoimmune or inflammatory disorders (EU-specific)
- Appendix R3 - Section 2.3.2: Interactions with other vaccines (EU-specific)
- Appendix R3 - Section 2.3.3: Long-term safety (EU-specific)

Rapporteur assessment comment:

Taking into consideration the review of the Missing information, no further action is considered warranted at this stage.

2.3.10. Other safety issue – Fatal events

MAH's conclusion (see Section 6.3.2 of the PBRER for further details).

From the review of data available during the reporting period for all fatal case reports (including sudden death) and also taking into account the cumulative experience along with the O/E analysis of fatal cases, there is no new safety information identified on this topic in association with VAXZEVRIA.

Rapporteur assessment comment:

Cumulatively, the MAH retrieved 7180 fatal cases. Out of these 7180 cases, 403 cases were reported with PT sudden death. Cumulative O/E analyses were conducted for fatal cases, and were stratified by age group and gender where administration data was available. O/E was significantly below 1 for all subgroups.

Among the cases reporting fatal outcome, no specific pattern regarding underlying conditions or cause of death could be identified. No new safety concerns were identified.

Taking into consideration the review of the risk 'fatal events', **no further action is considered warranted at this stage.**

2.3.11. Other safety issue – Lack of efficacy from post-marketing

MAH's conclusion (see Section 6.3.1 of the PBRER for further details).

Review of all the lack of efficacy reports did not demonstrate any specific trend or safety information associated with use of VAXZEVRIA. There was a decrease in the number of case reports for lack of efficacy during this interval (342) compared to the previous PBRER (2716) covering the period 29 June 2022 to 28 December 2022.

Cumulatively, of the 25594 lack of efficacy reports, there have been 169 fatal cases. Of the 25594 reports, 86.4% (22107) were reported from Austria. This is due to a local reporting system where cases from the epidemiological reporting system for COVID-19 are linked with the vaccination passport and submitted to EudraVigilance/AstraZeneca in bulk.

Rapporteur assessment comment:

No new important safety information was identified on lack of efficacy/effectiveness in post-marketing experience. **No further action is considered warranted at this stage.**

2.3.12. Health Authority Request – Pemphigus and Pemphigoid

MAH's conclusion (see Section 15.2.1 of the PBRER for further details).

AstraZeneca performed a cumulative evaluation of available data on pemphigus and pemphigoid from sources including pre-clinical, clinical studies, post-marketing case reports, observed versus expected analysis and published literature.

There were no reports of pemphigus and pemphigoid in the Oxford Studies (COV001, COV002, COV003, and COV005) and from US Study (D8110C00001), one case (PT: Ocular pemphigoid) was reported in the placebo group and one non-serious Pemphigus (Pemphigus Vulgaris) was reported with AZD1222 arm (not related to treatment medication as per investigator).

Within AstraZeneca Global Safety Database, 23 events of interest (7 pemphigus, 16 pemphigoid) were identified. The distribution of cases by age, gender, reporting country, were similar to the BG rates in non-COVID-19 vaccinated population. The trends of fatality and relapse rates were less than the expected trends based on BG data in non-COVID-19 vaccinated population.

Overall, majority of the cases had insufficient information for a comprehensive causality assessment. No specific pattern or index case was identified upon a careful assessment of these cases.

Upon review of literature retrieved, no abnormal epidemiologic trends of pemphigus/pemphigoid post COVID-19 vaccination. In summary, a review of the clinical, post-marketing cases, literature data did not identify any safety concerns in association of pemphigus and pemphigoid and VAXZEVRIA.

Based on the review of the currently available cumulative data, AstraZeneca considers that there is insufficient evidence to suggest a causal association between pemphigus/pemphigoid and VAXZEVRIA. It is AstraZeneca's opinion that no changes to the CDS or RMP on this topic are warranted at this time. AstraZeneca will continue to monitor pemphigus and pemphigoid as part of routine surveillance activities for VAXZEVRIA.

Rapporteur assessment comment:

The signal of pemphigus and pemphigoid (EPITT 19858) was closed in April 2023. The PRAC concluded that the available evidence was insufficient to establish a causal relationship between Vaxzevria and pemphigus or pemphigoid and that these topics should continue to be monitored in the next PSUR.

During the period under review, 7 cases (4 initial, 3 follow-up) of pemphigus and 16 cases (12 initial, 4 follow-up) of pemphigoid were identified.

Data available during the current reporting period did not raise any new safety signal. Taking into consideration the review of the previous request for monitoring pemphigus and pemphigoid, **no further action is considered warranted at this stage.**

2.3.13. Health Authority Request –Myositis-specifically Dermatomyositis

MAH's conclusion (see Section 15.2.2 of the PBRER for further details).

During the reporting interval, 9 new cases were retrieved within AstraZeneca Global Safety Database. Most of these cases were literature case reports. The cases were assessed and classified according to the EULAR/ACR IIM criteria. None of these cases probable/ definite based on the available information. Overall, majority of the cases had insufficient information for a comprehensive causality assessment. No specific trend or pattern was identified.

Upon review of literature retrieved, no abnormal epidemiologic trends of dermatomyositis post COVID-19 vaccination. In summary, a review of the clinical, post-marketing cases, literature data did not identify any safety concerns in association of dermatomyositis and VAXZEVRIA. Based on the review of the cumulative data, the MAH has concluded that there is insufficient evidence to suggest a causal association between dermatomyositis and VAXZEVRIA. No changes to the CDS or RMP are recommended for myositis specifically for dermatomyositis and the topic will continue to be monitored as part of ASTRAZENECA's ongoing safety surveillance activities for VAXZEVRIA.

Rapporteur assessment comment:

A signal of myositis (EPITT 19882) which was initially triggered by EMA on December 2022 was assessed in the previous PBRER assessment report. It was concluded at that time that there is no sufficient evidence to confirm a causal association between Vaxzevria and myositis. However, it was requested to continue the monitoring of dermatomyositis.

During the reporting period, no new significant safety information about dermatomyositis was identified. Taking into consideration the review of dermatomyositis, **no further action is considered warranted at this stage.**

2.3.14. Health Authority Request –SCARs in particular erythema multiforme

Request from previous PBRER

SCAR cases: The MAH is requested to review and discuss all available literature cases (i.e. cases that might have been discussed in the previous PSUR together with any new literature cases)

Erythema multiforme cases: The MAH is requested to present:

- a cumulative review of erythema multiforme (at PT level) based on data from all available sources;
- a causality assessment of the cases (using the WHO-UMC causality assessment) and discuss the cases assessed as WHO Possible, Probable or Certain;
- relevant literature data;
- a discussion on the need for updating product information and/or risk management plan, and submit proposal as required.

MAH's discussion and conclusion on literature cases of SCARs (see Section 15.2.3 of the PBRER for further details).

AstraZeneca performed a cumulative review to identified 29 literature case reports (including 19 presented in the previous reporting interval). Upon review of the cases, none of them were considered as probable as per the WHO-UMC causality assessment. Overall, majority of the cases (17/21, 81%) had insufficient information for a comprehensive causality assessment, 2 cases were confounded by underlying medical condition and in 2 cases event occurred beyond the risk window. No specific trend or pattern was identified upon a careful assessment of these cases.

Based on the review of the currently available cumulative data, AstraZeneca considers that there is insufficient evidence to suggest a causal association between SCARs and VAXZEVRIA. It will continue to be monitored as part of routine surveillance activities for VAXZEVRIA.

MAH's summary of Erythema Multiforme

In the assessment report received from the PRAC (EMA/H/C/PSUSA/00010912/202112) for the VAXZEVRIA PBRER (review period: 29 June 2022 to 28 December 2022), the PRAC requested a review of Erythema multiforme in this PBRER. Cumulatively, a total of 430 SCARs cases concerning 414 events were reported in AstraZeneca's global Safety database. Cases were assessed by age, sex, type of event and outcome. A female (63.3%) prevalence versus male (32.6%) was expressed. The median age was 55 years. The majority (44.7%) of events were reported after Dose 1. In 1 case, Erythema Multiforme occurred after Dose 1 and subsequently reappeared after Dose 2 of the vaccination. The recurrence case was assessed against the WHO-UMC causality criteria as 'Probable', due to temporal relationship, and considering recurrence, and the fact that it is not likely that any other confounder was present during both occurrences and absent in between.

All Erythema Multiforme case reports (N=128) were serious and none of the cases was reported with fatal outcome, 61 (46.2%) events had favourable outcome (either 'resolving' 'recovered' or 'recovered with sequelae'). The time to onset (TTO) was available in 97 (75.7%) case reports and ranged from 0 Days to 229 (median: 7 Days) of which 83 (85.5%) case reports were within range of 0-28 Days. Amongst 128 cases, 2 (1.6%) cases met WHO-UMC causality criteria for 'Probable/Likely' (PT: Erythema Multiforme) and 86 (67%) were considered as 'Possible', of which 25 (19.5%) were identified with relevant risk/confounding factors. The remaining cases had limited information to perform a comprehensive causality assessment.

MAH's conclusion on Erythema Multiforme

Based on the review of cumulative information from clinical, post-marketing and literature articles, AstraZeneca has concluded that there is insufficient evidence to suggest a causal association between Erythema Multiforme and VAXZEVRIA. No changes to the CDS or RMP are recommended for Erythema Multiforme. Erythema Multiforme will continue to be monitored as part of AstraZeneca's routine safety surveillance activities for VAXZEVRIA.

Rapporteur assessment comment:

Severe cutaneous adverse reactions (SCARs)

A detailed assessment of SCARs cases (cumulative review, causality assessment, O/E analysis, discussion on mechanism) was made in the previous PBRER procedure (EMA/H/C/PSUSA/00010912/202212).

As requested previously, the MAH presented and discussed cases of SCARs from its global patient safety database and literature. Cumulatively, the MAH retrieved 21 literature case reports of SCARs from its global safety database with following PTs: Acute generalized exanthematous pustulosis (1), Dermatitis bullous (5), Erythema multiforme (6), Stevens-Johnson syndrome (6), Toxic epidermal necrolysis (TEN) (4). One case of TEN had a fatal outcome. This case was confounded by medical history of diabetes and hypertension.

The MAH's conclusion that all above cases either had limited information or were confounded by co-suspected medication or medical history is not endorsed. In accordance with the PRAC guidance for the assessment of SCARs cases, the PRAC Rapp considered the following cases of importance and reassessed their WHO-UMC causality as at least possible (with sufficient information):

Furthermore, in the literature article of Wantavomprasert et al. (2021) 2 additional cases (1 case of AGEP and 1 case of SJS) were reported which were not retrieved by the MAH.

Overall, in the majority of the literature cases of SCAR there was a close temporal association with Vaxzevria and no apparent plausible alternative explanation for the event. Considering the previous assessment of SCARs and the literature cases discussed in this PBRER, **the PRAC Rapp considers that SCARs remain a safety topic of interest.**

Erythema multiforme (EM)

As requested, the MAH provided a cumulative review of EM cases from all sources, including causality assessment.

Overall, the review of EM cases (n=128 cases and events) shows all cases, for which the dose number was specified, were reported after the first and second dose and that the majority of the events occurred within 14 days (70.1%) and 28 days (85.6%) post vaccination. All 128 cases were serious and 61.7% of the cases were medically confirmed. Median TTO was 7 days and mean duration of the event was 29.3 days. The most co-reported PTs were Pyrexia, Rash, Myalgia, Headache and Arthralgia. The WHO-UMC case causality was assessed as probable-likely in 2 cases (1.6%) and as possible in the majority (67.2%) of the cases, however, all possible cases were confounded or had limited information.

The MAH presented one case () with recurrence of event with both doses and assessed this case as possible with limited information (no info on medical history and concomitant medications; clinical course of EM with dose 1 unclear) based on the WHO-UMC criteria.

Additionally the MAH has presented 7 literature cases with causality unassessable (n=4) and possible with limited information (n=3). For two of these cases () and () the references (Goodarzi et al 2021; Charfi et al 2022) provided by the MAH could not be linked to the presented cases. The causality of literature cases () and () was assessed as possible with limited

information by the MAH. The PRAC Rapp considers the causality for these cases as probable considering the TTO (6 and 10 days), available laboratory data and screening to rule out other possible infections. Additionally, the PRAC Rapp noted another case of EM-like morphology in the publication of Mehta et al. (2022).

In conclusion, 4 probable and several possible cases of EM were reported in close temporal association with Vaxzevria and without apparent plausible alternative explanation for the event. Furthermore, as discussed in the previous PBRER AR (EMA/H/C/PSUSA/00010912/202212), there is a plausible mechanism for how the vaccine may cause EM. **Taking into consideration the review of cases of Erythema Multiforme, the PRAC Rapporteur considers that a causal association between EM and Vaxzevria should be considered at least a reasonable possibility. Erythema Multiforme (EM) is thus considered as a new ADR of Vaxzevria.**

2.3.15. Health Authority Request –Menstrual disorder (literature review)

MAH's comment on literature (see Section 15.2.4 of the PBRER for further details).

Study 1: Ljung et al 2023 performed a nationwide, register-based cohort study conducted in Sweden aimed to evaluate the risk of menstrual disturbance and bleeding following SARS-CoV-2 vaccination in women who are premenopausal or postmenopausal.

AstraZeneca Comments: This is a post-marketing surveillance study, authors used data from various national and regional registers, including vaccination registers to assess the risk of menstrual disturbance and bleeding following SARS-CoV-2 vaccination in women, before and after menopause. Some limitations noted included the possible underestimation on number of cases, considering the healthcare contacts for outcome ascertainment may introduce bias, some events which didn't result in medical attention could not get captured by the system. There is lack of information related to body mass index, smoking history, each patient medical history, previous infections, hormone disorder, concomitant medication, which could be considered as well as potential confounders.

Study 2: Duijster et al 2023 performed a comprehensive study conducted in the Netherlands, the impact of COVID-19 vaccination on menstrual abnormalities was investigated using both spontaneous reporting and a prospective cohort event monitoring (CEM) study. The analysis covered data from 01 February 2021 to 29 March 2022, and included 4 vaccines: Comirnaty, VAXZEVRIA, Spikevax and Jcovden.

AstraZeneca Comments:

Using CEM and spontaneous data, authors suggested a likely causal relationship between menstrual abnormalities and COVID-19 vaccines, including VAXZEVRIA, giving the highest concern to Comirnaty and Jcovden vaccinees. Associations were identified between menstrual abnormalities other possible factors associated with menstrual abnormalities, including age, body mass index (BMI), comorbidities, and hormonal contraceptive use, reporting a significantly increased ORs for those women who indicated presence of underlying psychological disorders, especially for intermenstrual blood loss (OR 3.01; 95% CI 1.50–5.50), followed by irregular blood loss (OR 2.41; 95% CI 1.28–4.17) and amenorrhoea/oligomenorrhoea (OR 2.08; 95% CI 1.14–3.50). Some limitations were noted, as mentioned by authors, the extensive media coverage on potential AEs of COVID-19 vaccination could have influenced the reporting patterns in both: spontaneous reporting system and the CEM study, in addition a detailed clinical information about menstrual abnormalities in most case report was lacking, including the use of hormonal contraceptives which was underreported in both data sources, as well, considering a limited documentation in regards the BG incidence of menstrual abnormalities in the Dutch population, which can challenge the estimating magnitude of excess menstrual abnormalities in vaccinated women.

MAH's conclusion

Based on the review of the updated literature review, no new significant information to suggest an association between menstrual disorders and VAXZEVRIA was observed. Therefore, AstraZeneca does not consider any changes to the CDS or RMP on this topic to be warranted at this time. AstraZeneca will continue to monitor menstrual disorders as part of routine surveillance activities for VAXZEVRIA.

Rapporteur assessment comment:

Taking into consideration the review of the previous request for monitoring literature of menstrual disorders, **no further action is considered warranted at this stage.**

2.3.16. Health Authority Request –Hearing loss

MAH's conclusion (see Section 15.2.5 of the PBRER for further details).

AstraZeneca received the request from TGA to provide an updated signal analysis on hearing loss cases including age stratified and age specific observed versus expected analyses, in the next PSUR to further evaluation of this signal.

Based on currently available data, AstraZeneca has concluded that there is insufficient evidence to suggest a causal association between hearing loss and VAXZEVRIA. This review did not find evidence of a new or emerging signal for hearing loss to suggest a need to update the VAXZEVRIA product information or RMP. Hearing loss will be monitored through routine pharmacovigilance and ongoing surveillance activities.

Rapporteur assessment comment:

During the previous PSUSA procedure (EMA/H/C/PSUSA/00010912/202212), the PRAC Rapp had already assessed the updated hearing loss data and no regulatory action was deemed necessary. It was agreed with MAH to continue the monitoring as of ongoing surveillance activities and to discuss the topic only in case that new safety information arises.

In response to request from TGA, the MAH provided an updated review of 1866 cumulative hearing loss cases (1993 events) from EU, UK, AU, and BZ. O/E was significantly below 1 for all subgroups.

Taking into consideration the review of the TGA request for monitoring Hearing loss, **no further action is considered warranted at this stage.**

2.3.17. Health Authority Request –Myocarditis

On 06 July 2023, as part of the assessment report on the LEG request 115 (EMA/PRAC/283257/2023) on myocarditis the following safety data was requested to be submitted in the next PSUR:

- The MAH is requested to provide a review of the literature for new publications on epidemiologic studies of interest related to myocarditis.
- The MAH is requested to verify the O/E analysis and correct the errors, especially in the analyses by individual regions.
 - in the stratification of UK/Male/20-29 years, the number of expected cases in the RW of 14 days is lower than in the RW of 7 days.
 - in the EEA analysis, the number of expected cases by age group for all cases and BCC level 1-3 cases are not the same.

MAH's conclusion (see Response to PRAC Requests for the VAXZEVRIA PBRER [29.12.2022-28.12.2023] for further details).

Based on currently available data, it is AstraZeneca's opinion that there is insufficient evidence to suggest a causal association between myocarditis and VAXZEVRIA. This review did not find evidence of a new or emerging signal for myocarditis to suggest a need to update the VAXZEVRIA product information or risk management plan. Myocarditis is an AESI for VAXZEVRIA and will continue to be kept under close surveillance by AstraZeneca.

Rapporteur assessment comment:

As requested (LEG request 115) the MAH updated the literature review and verified the O/E analysis, providing updated numbers.

During the reporting period, no new significant safety information about myocarditis was identified. Taking into consideration the review of myocarditis, **no further action is considered warranted at this stage.**

2.4. Characterisation of risks

At the end of the reporting period, the VAXZEVRIA safety specification presented in the global core-RMP (Version 9.0, dated 03 March 2023) and in the EU-RMP (Version 8, succession 2 submitted on 24 November 2023) included the following important identified and important potential risks, and missing information (see Table 6).

Table 6- Characterisations of the safety concerns (core-RMP v9.0 [03 March 2023]; EU-RMP v8 [submitted 24 Nov 2023])

Safety concerns	Characterisation (DLP 28 June 2023)
Important Identified Risks	
Thrombosis in combination with thrombocytopenia^{core} / Thrombosis with thrombocytopenia syndrome^{EU}	<i>Frequency</i> • Post-market: 2811 cumulative cases • Clinical-trials: no cases <i>Potential mechanism:</i> The exact mechanism of thrombosis concurrent with thrombocytopenia following immunisation with VAXZEVRIA is unknown. Several hypothetical biologic mechanisms have been proposed to explain the pathophysiology of thromboembolic events with thrombocytopenia following vaccination (Greinacher et al 2021 (NEJM)). Among them a study by Baker et al 2021, proposes an interaction between the ChAdOx1 vaccine vector used in VAXZEVRIA and PF4; however, it is unknown if the adenoviral ChAdOx1 interaction with PF4 is actually platelet activating or thrombogenic (causal of blood clots). Greinacher et al 2021 (NEJM) suggested that ChAdOx1 itself or proteins contained within the vaccine can bind to PF4 to form immune complexes which may drive a B-cell response causing high-titer anti-PF4 antibodies resulting in TTS. However, none of these hypotheses have been confirmed. <i>Risk factors:</i> There are no known risk factors.
Thrombocytopenia, including immune thrombocytopenia^{EU}	<i>Frequency</i> • Post-market: 4975 cumulative cases¹

Safety concerns	Characterisation (DLP 28 June 2023)
	Clinical-trials: in study D8110C00001, thrombocytopenia was reported in 2 participants (<0.1%) in the VAXZEVRIA group, and immune thrombocytopenia was reported in 1 participant (<0.1%) in the placebo group. In the long-term safety analysis at 6-months, 1 additional event of thrombocytopenia was reported in a participant in the VAXZEVRIA group. None of these events were serious and none of these participants in either of the treatment groups reported concurrent thromboembolic event. <i>Potential mechanism:</i> The exact mechanism of thrombocytopenia, including immune thrombocytopenia following immunisation with VAXZEVRIA is unknown. <i>Risk factors:</i> There are no known risk factors for the development of thrombocytopenia following vaccination. In general, individuals with a history of thrombocytopenic disorder, such as immune thrombocytopenia, the risk of developing low platelet levels should be considered before administering the vaccine and platelet monitoring is recommended after vaccination as described in Section 4.4 of the SmPC.
Guillain-Barré Syndrome^{EU}	<i>Frequency</i> - Post-market: 1976 cumulative cases - Clinical-trials: 1 case of a demyelinating event (SAE initially reported as GBS, subsequently diagnosed as Chronic inflammatory demyelinating polyradiculoneuropathy) <i>Potential mechanism:</i> Exact mechanism of GBS following immunization with VAXZEVRIA is unknown. Although the underlying aetiology and pathophysiology of GBS are not completely understood, it is believed that immune stimulation plays a central role in its pathogenesis (Sejvar et al 2011). <i>Risk factors:</i> There are no known risk factors for the development of GBS following vaccination. In general, infection with the bacteria <i>Campylobacter jejuni</i> is one of the most common risk factors for GBS. People also can develop GBS after having the flu or other infections such as cytomegalovirus and Epstein-Barr virus. On very rare occasions, people develop GBS in the days or weeks after getting a vaccination (CDC 2019).
Venous thromboembolism (VTE)	<i>Frequency:</i> VTE has been observed rarely following vaccination with Vaxzevria in clinical trials, however, there was no increase in VTE events among individuals who received AZD1222 compared to placebo/comparator. In the post marketing setting very rare events of VTE (DVT/PE) without thrombocytopenia have been observed; few literature articles showed increased risk for venous thromboembolism in association with Vaxzevria. VTE is an adverse drug reaction described in the SmPC. <i>Potential mechanism:</i> The exact mechanism of VTE following immunisation with Vaxzevria is unknown. In general, the pathophysiology of VTE includes a blood flow stasis, hypercoagulability, endothelial dysfunction and injury.

Safety concerns

Characterisation (DLP 28 June 2023)

Severe COVID-19 is associated with increased risk of venous thromboembolism events.

Risk factors: There are no known risk factors identified for the development of VTE following vaccination.

Important Potential Risks

CVST without thrombocytopenia^{core}

Frequency

- Post-market: **620 cumulative cases**
- Clinical-trials: **no cases**

Potential mechanism: The exact mechanism of CVST without thrombocytopenia following administration with VAXZEVRIA is unknown.

Risk factors: There are no known risk factors for the development of CVST without thrombocytopenia following vaccination

Immune-mediated neurological conditions^{core/EU}

Frequency

- Post-market: **8964 cumulative cases**, including 682 interval cases. During the reporting period, the most commonly reported PTs were: Neuralgia (143), Guillain-Barre syndrome (140), Sensory disturbance (78), Neuropathy peripheral (63), Myelitis transverse (46), Demyelination (30), Polyneuropathy (29), Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) (28), Multiple sclerosis (MS) (27), Sensory loss (25), Small fibre neuropathy (25), Optic neuritis (23), ADEM (22), Encephalitis (20), Myelitis (16), CIDP (14), Neuromyelitis optica spectrum disorder (NMOSD) (14), Multiple sclerosis relapse (9), Myelopathy (9), Peripheral sensory neuropathy (9), Demyelinating polyneuropathy (7), Encephalitis autoimmune (7), Encephalomyelitis (6)
- Clinical-trials: In the US study, neurologic or neuroinflammatory AESIs were reported **in 0.6%** (121/21,587 participants) in the VAXZEVRIA group and 0.4% (48/10,792 participants) in the placebo group. There were 5 non-serious AEs of facial paralysis and 1 SAE of a demyelinating event in the VAXZEVRIA group (event initially reported as GBS, which was subsequently diagnosed as an SAE of Chronic inflammatory demyelinating polyradiculoneuropathy).
In the pooled Oxford studies, neurologic or neuroinflammatory AESIs were reported **in 0.7%** (81/12,282 participants) in the VAXZEVRIA group and 0.8% (90/11,963 participants) in the control group. The most frequently reported events were non-serious AEs of facial paralysis (4 vs 3). There were 3 SAEs of demyelinating events (2 cases in the VAXZEVRIA group [1 case of transverse myelitis, and 1 case of multiple sclerosis in a participant with pre-existing, but previously unrecognised, multiple sclerosis], and 1 case of myelitis in the control group.)

Potential mechanism: Several hypothetical biological mechanisms have been proposed to explain the pathophysiology of neurologic adverse reactions following immunisation; most involve the concept of autoimmunity and the

Safety concerns

Characterisation (DLP 28 June 2023)

possibility that the vaccine's immunostimulatory effect results in an aberrant immunologic response (Stratton KR et al 1994).

Risk factors: There are no known risk factors for the development of immune-mediated neurological conditions following vaccination.

Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)^{EU}

Frequency

- Post-market: **2729 cumulative cases, including 369 interval cases**
- Clinical-trials: 83 cases of potential VAED/VAERD in AZ-sponsored clinical trials

Potential mechanism: The pathogenesis of VAED in the context of SARS-CoV-2 is unclear, and there are no consistent mechanisms or immune markers of disease enhancement from nonclinical studies (Haynes et al 2020). VAERD refers to the predominantly lower respiratory tract presentation of VAED. The mechanism of the pathogenesis of VAERD may be specific to the lower respiratory tract or may be part of a systemic process.

Risk factors: There are no known risk factors identified for VAED/VAERD.

Missing information

Use of VAXZEVRIA in pregnant and breastfeeding women^{core}/Use during pregnancy and while breastfeeding^{EU}

Data from more than **400 case reports of pregnant women** or women who became pregnant after receiving VAXZEVRIA do not suggest unusual patterns of pregnancy complications or foetal/neonatal outcomes. No increased risk of maternal thrombosis in combination with thrombocytopenia has been observed. Preliminary non-clinical safety studies have not indicated any concern to date, and available non-clinical, clinical and post-marketing data do not suggest a risk to breastfed newborns/infants.

As VAXZEVRIA is intended for use in mass vaccination campaigns in a large proportion of the global population, the collection of pregnancy and infant outcomes data with the aim of further characterising the safety profile in this population, is still considered necessary.

Use of VAXZEVRIA in subjects with severe immunodeficiency^{core}/Use in immunocompromised patients^{EU}

Vaccines may be less effective in severely immunocompromised subjects.

Although there is no evidence that the safety profile of this population receiving VAXZEVRIA will be different to that of the general population, given the paucity of data, the possibility cannot be excluded.

Use of VAXZEVRIA in subjects with severe immunodeficiency will continue to be investigated in the ongoing PASS and additional Pharmacovigilance activity (a post-marketing observational study using existing secondary health data sources and systematic literature review).

Use in patients with autoimmune or inflammatory disorders^{EU}

There is no evidence from VAXZEVRIA clinical studies to date that the safety profile of this population differs from that of the general population. However, given the paucity of data, the possibility cannot be excluded.

Use in patients with autoimmune or inflammatory disorders will be investigated in the ongoing PASS studies.

Safety concerns	Characterisation (DLP 28 June 2023)
Use of VAXZEVRIA in subjects with severe and/or uncontrolled underlying disease^{CORE}/Use in frail patients with co-morbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders)^{EU}	There is no evidence that the safety profile of this population receiving VAXZEVRIA will be different to that of the general population, given the paucity of data, the possibility cannot be excluded. Use of VAXZEVRIA in patients with severe and/or uncontrolled disease will continue to be investigated in the ongoing PASS program (post-marketing observational study using existing secondary health data sources).
Long-term safety^{EU}	There are no known risks with a potentially delayed onset, with the exception of the theoretical concern of VAED/VAERD. There is currently no evidence suggesting an adverse long-term safety concern. At 6-months and 2-year follow-up from Study D8110C00001 the AEs observed were consistent with the safety findings at the primary analysis. In the VAXZEVRIA group, a small proportion of SAEs and AESIs were reported, with no clinically meaningful findings. Overall, VAXZEVRIA remains well-tolerated up to 6 months and 2-years post vaccination. Long-term safety is evaluated through the PASS activity in the VAXZEVRIA clinical development programme.
Interactions with other vaccines^{EU}	There is currently limited information regarding the safety, immunogenicity, and efficacy of AZD1222 when co-administered with other vaccines concurrently seasonal illness vaccines. While there is currently no evidence to suggest the safety profile or efficacy of AZD1222 when co-administered with other vaccines would be impacted, given the paucity of data, the possibility of an interaction causing an altered safety profile or reduced efficacy of either AZD1222, or the co-administered vaccine cannot be excluded. The co-administration of AZD1222 with other vaccines (either together, or 30 days before or after administration) is investigated in the ongoing PASS activity. Vaccines to be evaluated include the influenza and pneumococcal vaccines.

^{CORE} : core-RMP specific safety concern; ^{EU} : EU-RMP specific safety concern

1 : Cumulative data are only available at the DLP of 28.06.2022. However, no new safety issues were raised during the two last reporting periods

Rapporteur assessment comment:

As requested by the PRAC Rapp in the AR of the previous PBRER, the important potential risk 'Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)', and the missing information topics 'Interactions with other vaccines' and 'Long-term safety' have been maintained in the EU-RMP.

'Thrombosis', previously considered as an important potential risk, was reclassified and removed from the list of safety concerns and 'Venous thromboembolism (VTE)' was added as an important identified risk in EU-RMP version 8.0 succession 2.0, which was submitted with variation EMEA/H/C/005675/II/0097 (review ongoing).

3. Benefit evaluation

3.1.1. Newly identified information on efficacy/effectiveness

New information on the efficacy/effectiveness of VAXZEVRIA in the approved indication of prevention of COVID-19 in adults that became available during the reporting period is focused on the Omicron variant.

During the reporting period, data analyses for Oxford studies data was conducted by AstraZeneca to estimate the efficacy of VAXZEVRIA against Omicron variant of concern. As described in detail in section 13 (section 1.3.6 of this AR) there were no new clinical trial efficacy data available during the reporting period.

3.1.2. Vaccine effectiveness against SARS-CoV-2 Omicron variant

Real world studies have demonstrated high vaccine effectiveness (VE) of a 2-dose primary series vaccination with AZD1222 against earlier Omicron variants (up to and including BA4/5) in a variety of settings and populations, particularly with regard to prevention of severe disease. The range of VE in studies focused on severe outcomes in a general adult population (≥ 18 years and/or an older population (≥ 65 years) during a period when Omicron was the dominant variant was presented in the previous PBRER. As of 03 March 2023, the European Centre for Disease Prevention and Control announced there are currently no SARS-CoV-2 variants meeting the Variant of Concern criteria, and Omicron is listed as a Variant of Interest being monitored (ECDC 2023).

Additional studies that have been published during the reported period, whereby vaccine effectiveness of VAXZEVRIA, amongst other vaccines, against the omicron variant are presented below.

The Vaccine Study COvid-19 (VASCO) is a large population- based prospective cohort study with a 5-year FU, conducted in the Netherlands (Huiberts AJ et al 2023). The study was started during the initiation of the COVID-19 vaccination program and between the 03 May 2021 and 15 December 2021, 45,552 community-based adults aged 18 to 85 years participated. In this study participants received primary vaccination series with two doses of VAXZEVRIA or vaccinated with alternative available vaccines such as Comirnaty (BioNTech/Pfizer), Spikevax (Moderna) or Jcovden (Janssen). In addition, they also received one booster vaccinations. The paper provides collective information about vaccine effectiveness and reports that Vaccine Effectiveness in the Omicron era was substantially lower than those in the Delta period and estimated to have been 46% (95%CI 21.7-62.7), decreasing to 25% (25% (95% CI 7.7-39.1) 18-23 weeks after completion of the primary vaccination series. VE increased to 57% (95% CI 51.9-62.3) < 6 weeks after booster vaccination and decreased to 31% (95% CI 16.6-43.5) at 18-23 weeks. For the participants aged ≥ 60 years, the VE against Omicron infection within 6 weeks after the second booster vaccination was 50% (95% CI 34.0-62.1). This paper did not provide effectiveness information against severe infection or hospitalization.

A test-negative case-control study (Sritipsukho et al 2023) was conducted in Thailand to obtain real-life Vaccine Effectiveness data against the Omicron variant between 01 January 2022 to 15 June 2022 when the Omicron variant was the dominant variant (97-100%). Primary series vaccine regimens during the initial period mainly included two-dose CoronaVac (4 weeks apart between the two doses) and two-dose ChAdOx1 nCoV-19 (12 weeks apart between the two doses). The two-dose BNT162b2 (4 weeks apart between the two doses) became available later. The booster doses of the vaccines included one dose of ChAdOx1 nCoV-19 or one to two doses of BNT162b2 given at 3-6 months after the primary series or after the last dose of the previous vaccines. Of the 7971 vaccinated individuals, 3104 (38.9%) were cases and 4867 (61.1%) were controls and none of these individuals had prior COVID-19. For the two dose vaccine regimens received by 2363 individuals, 1209 (51.2%) received ChAdOx1 nCoV-19 vaccine. For the three dose regimens, received by 3100 individuals, 1387(44.7%) received a two dose ChAdOx1 nCoV-19 plus one BNT162b2 booster. The Vaccine Effectiveness of the ChAdOx1 nCoV-19 vaccine was associated with an overall vaccine effectiveness of 38% (95% CI 13-56) though for a period ≤ 90 days since the last dose, vaccine effectiveness was substantially higher at 61% (41-74%). Thereafter, it decreased so that for periods ≥ 90 days to 30% (0-51%). For the three-dose regimen overall vaccine effectiveness was reported to be 39% (95% CI 13-57) increasing to 41% (95% CI 16-58) for the period of ≤ 90 Days since the last dose and decreasing to 26% (95% -12-52) for the period ≥ 90 days since the

last dose. However, when the ChAdOx1 nCoV-19 vaccine was given as part of a 4 dose regimen vaccination (CoronaVac-CoronaVac-ChAdOx1-BNT162b2) overall vaccine effectiveness was substantially augmented to 65%, remaining high at 67% (95%CI 51-78%) for the period ≥ 90 days since the last dose before decreasing to 49% (95% CI 15-70) for the period ≥ 90 days since the last dose. Moreover, vaccine effectiveness for preventing moderate to critical disease was reported as 56% (95% CI 25-75%) for the two dose ChAdOx1 nCoV-19 vaccine, 58% (95% CI 28-75) for the three-dose regimen and 82% (95%CI 59-92) for the 4 dose regimen (CoronaVac-CoronaVac-ChAdOx1-BNT162b2).

In another test-negative study design (Cerqueira-Silva et al 2023) national databases were utilised to estimate the vaccine effectiveness (VE) of a primary series (with ChAdOx1 or BNT162b2) plus an mRNA vaccine booster (with BNT162b2 or mRNA-1273) against symptomatic Syndrome Coronavirus 2 (SARS-CoV-2) infection and severe COVID-19 outcomes (hospitalization or death) during the period of Omicron dominance in Brazil and Scotland compared to unvaccinated individuals. In Brazil, a primary course of ChAdOx1 and a BNT16b2 booster (ChAdOx1-BNT162b2) dose led to an estimated VE against symptomatic infection of 51.6% (95% CI [51.0, 52.2], $p < 0.001$) after 14 to 29 days, waning to 4.2% (95% CI [0.7, 7.6], $p = 0.02$) at ≥ 4 months after the booster dose. In contrast, estimates of VE against severe outcomes of ChAdOx1- BNT162b2 peaked in Brazil at 93.5% (95% CI [93.0, 94.0], $p < 0.001$) at 14 to 29 days and 82.3% (95% CI [79.7, 84.7], $p < 0.001$) after ≥ 4 months. A similar pattern was observed in Scotland ,where after the primary series of ChAdOx1, the VE peak at 98.3% (95% CI [87.3, 99.8], $p < 0.001$) 14 to 29 days past booster dose for ChAdOx1-BNT162b2 and 94.4% (95% CI [87.7, 97.5], $p < 0.001$) for ChAdOx1-mRNA-1273 in the same period, declining to 77.8% (95% CI [51.4, 89.9], $p < 0.001$) and 76.0% (95% CI [59.3, 85.9], $p < 0.001$) at ≥ 4 months, respectively. The authors concluded that although modest short-lived protection against symptomatic infection by the omicron variant were observed, protection against hospitalization or death was substantial for at least 3 months.

A test-negative case-control study in adults from Bogota (Colombia) assessed the comparative vaccine effectiveness (VE) and the duration of protection with homologous primary series and homologous booster immunization using ChAdOx1, CoronaVac, BNT162b2, mRNA-1273, and Ad26.COV2.S vaccines Paternina-Caicedo et al 2023 During the Omicron predominant periods, the VE against symptomatic COVID-19 of primary series vaccination with ChAdOx1 was 36% (95% CI: 24 to 47), while varied between 34% (95% CI: 11 to 51) for Ad26.COV2.S and 65% (95% CI: 54 to 74) for mRNA-1273 during the first month after vaccination. The protection waned quickly and was not observed two months after ChAdOx1 primary series vaccination and lasted up to 3 to 4 months after BNT162b2, mRNA-1273 and Ad26.COV2.S vaccination. The VE of a booster dose of monovalent BNT162b2 against symptomatic COVID-19 was 45% (95% CI: 34 to 54). The booster doses of ChAdOx1, CoronaVac, and Ad26.COV2.S did not show protection against symptomatic COVID-19. The VE of booster vaccination was 69% (95% CI: -14 to 91) for ChAdOx1 and varied between 49% (95% CI: -126 to 88) for BNT162b2 and 68% (95% CI: 48 to 80) for CoronaVac for the prevention of COVID-19 hospitalization caused by Omicron variant.

REFORCO-Brazil test-negative case-control observational study evaluated the relative vaccine effectiveness (rVE) against COVID-19 hospitalization of four monovalent COVID-19 vaccines (AZD1222, Ad26.COV2.S, CoronaVac, and BNT162b2) as second boosters compared with any first boosters received ≥ 4 months previously, and as first boosters compared with primary-series vaccinations completed ≥ 4 months previously (Meeraus et al 2023). The interim analysis results showed that during a 7-month period of Omicron subvariant (BA.1, BA.2, BA.4, and BA.5) predominance, receiving a second booster dose of COVID-19 vaccine increased effectiveness against COVID-19 hospitalization by 24.7 % (95 % CI: 12.6 to 35.1) compared with eligible individuals who had received any first booster dose. The improved protection was similar with second booster doses of AZD1222 (rVE 29.4 %; 95 % CI: 8.6 to 45.5), Ad26.COV2.S (rVE 24.8 %; 95 % CI: 8.1 to 38.4), and BNT162b2 (rVE 25.5 %; 95 % CI: 4.2 to 42.2). The data did not show an improvement in protection against COVID-19 hospitalization with a second

booster dose of CoronaVac relative to any first booster dose. During a 12-month period of Delta and Omicron subvariant predominance, the rVE of first booster doses against COVID-19 hospitalization was 46.8 % (95 % CI: 43.3 to 50.0) among individuals who had completed any primary series. The improvement in protection was similar for first booster doses of AZD1222 (rVE 42.5 %; 95 % CI: 28.0 to 54.0) and BNT162b2 (rVE 50.8 %; 95 % CI: 47.5 to 54.0) but was not seen with Ad26.COV2.S or CoronaVac. In general, rVEs were higher in elderly (≥ 80 years) and immunocompromised/high-risk individuals.

A Brazil-based study (dos Santos et al 2023), linking national registries, estimated the VE of the primary series of vaccinations and the relative effectiveness of the booster against COVID-19-related severe cases and deaths. The VAXZEVRIA primary series provided increased protection against severe COVID-19 to diverse age groups of 20-59 years (VE: 88.3%; 95% CI: 80.2 to 94.3) and 60+ years (VE: 61.7%; 95% CI: 21.6 to 86.2) during the Omicron variant period. The study showed that the VAXZEVRIA 1st boosters were also effective in individuals who received the VAXZEVRIA primary series (VE: 49% in 20-59 years, and 79% in 60+ years). People who received CoronaVac (Sino) primary series plus VAXZEVRIA 1st booster (20-59 years) or BNT162b2 primary series plus VAXZEVRIA 1st booster (60+ years) showed VE of 97% and 93% respectively.

Another TNCC study covering six Latin American countries – Chile, Costa Rica, Ecuador, Guatemala, Paraguay and Uruguay Nogareda et al 2023 estimated the adjusted VE (aVE) of COVID-19 vaccines in preventing COVID-19-related hospitalisation during three different pandemic waves. Overall, during the Omicron variant period, the VAXZEVRIA primary series provided moderate protection against hospitalisation to individuals aged 18-64 years (21%) and ≥ 65 years (39%).

Another test-negative case control study (Kirsebom FMC et al 2022) was conducted to assess the real-world effectiveness of ChAdOx1-S COVID-19 booster vaccination against the Omicron and Delta variants in England. The study reported reassuring real-world evidence (RWE) that booster vaccination with ChAdOx1-S following a primary ChAdOx1-S course provides increased protection against mild and severe diseases with Omicron infection. Protection against the symptomatic disease was similar for both ChAdOx1-S (Spikevax) and BNT162b2 (Pfizer-BioNTech) vaccines among individuals 40–64-year-old but lower with ChAdOx1-S in older adults. Data extracted from NIMS (National Immunisation management System), as of 14 March 2022, on all adults aged 18 and older in England who received a ChAdOx1-S primary course followed by a ChAdOx1-S booster (43,171 individuals) or BNT162b2 booster (13,038,908 individuals) were analysed. The recipients of ChAdOx1-S booster were found to be predominantly female (adjusted odds ratio (OR) 1.67 (1.64–1.71)), from London (adjusted OR 2.84 (2.73–2.95)), health and social care workers (adjusted OR 1.58 (1.54–1.63)), in a clinical risk group (adjusted OR 1.58 (1.54–1.63)), in the clinically extremely vulnerable (CEV) group (adjusted OR 1.84 (1.79–1.89)), severely immunosuppressed (adjusted OR 2.05 (1.96–2.13)). For those aged 40–64 years, VE for symptomatic disease caused by the Omicron variant infection peaked at 61.2% (40.9–74.6%) one week after receiving a ChAdOx1-S booster as compared to 58.2% (57–59.4%) amongst those who received a BNT162b2 booster. However, there was a waning of protection observed after 15 or more weeks post booster vaccination. Similar levels of protection were observed for those aged 65 years and older (66.1% (16.6–86.3%) and 68.5% (65.7–71.2%) for ChAdOx1-S and BNT162b2 booster vaccines, respectively), with waning of protection observed after 5–9 weeks post booster vaccination. The study also showed that the ChAdOx1-S booster provided over 80% protection against hospitalisation following Omicron infection in individuals aged 65 and older, one week after booster vaccination – though lower than that observed following BNT162b2 booster.

In a previously reported retrospective cohort study (Intawong et al 2022) conducted during an omicron predominant period, the duration of enhanced protection against severe Covid-19 with booster doses was investigated by utilizing a Hospital Information System for COVID-19 established in Chiang Mai, Thailand.

Individuals aged 18 years or older, with a laboratory confirmed SARS-CoV-2 infection during 01 February to 31 July 2022 period were recruited into the study. Severe COVID-19 outcome was defined as requiring Invasive Mechanical Ventilation (IMV) during hospital admission or death within 30 days of positive SARS-CoV-2 test. Over half of the subjects with severe outcomes were not fully vaccinated, as compared to just 11% among those without severe outcomes. Subjects without severe outcomes were more likely to have received heterologous primary series with Sinovac/Sinopharm first dose followed by ChAdOx1 nCoV-19 second dose. No significant difference in the type of vaccine used for boosting as third, fourth and fifth dose was seen between the groups.

A couple of studies indirectly elucidated the comparative effectiveness of VAXZEVRIA; a Colombia-based study explored the effectiveness of vaccination schedules on the probability of infection

Marcela Gálvez et al 2023 , and another study (Liu et al 2023) compared rates of Omicron BA.1/2 infection in Australian adults who had received COVID-19 vaccines as either a primary course or a booster dose. Marcela Gálvez et al 2023 found a higher infection rate in participants who received CoronaVac (Odds Ratio (OR) = 1.49, CI 1.06–2.10) and Ad26.COV2.S (OR = 1.63, CI 1.10–2.43) than who received VAXZEVRIA (OR = 1.17, CI 0.79–1.71). On the other hand, Liu et al 2023 showed that compared to recipients of BNT162b2 primary vaccine course, adjusted hazard ratios (aHR) for COVID-19 infection were 1.03 (95% CI 0.82–1.30), 1.19 (0.95–1.49), 1.70 (1.46–1.97) respectively for mRNA-1273 (Moderna), VAXZEVRIA and NVX-CoV2373 (Novavax). Similarly, for booster dose, the respective aHR compared to BNT162b2 were 1.02 (95% CI 1.00–1.04), 1.20 (1.10–1.32), and 1.39 (1.20–1.60).

In summary, despite in vitro evidence of failing neutralising titres against more recent VOC RWE studies in multiple geographical regions continue to support the benefit of vaccination with VAXZEVRIA, suggesting the immune response and protection provided is more complex than humoral responses taken in isolation.

Rapporteur assessment comment:

The benefit-risk balance of Vaxzevria is currently under evaluation within the variation procedure EMEA/H/C/005675/II/0095 (ongoing clock-stop; restart on 26/05/2024). As part of this variation, immune response against omicron variants and real world effectiveness data are discussed. Several of the presented studies on real-world effectiveness during the circulation of Omicron variants are already discussed as part of this variation (Sritipsukho et al. 2023, Cerqueira-Silva et al. 2023, Kirsebom et al. 2023 and Intawong et al. 2023).

In addition, Paternina-Caicedo et al. 2023 reported on the VE in Colombia with homologous primary series and booster immunization. **The authors reported that the booster doses of ChAdOx1, CoronaVac, and Ad26.COV2.S did not show protection for Omicron.** The VE of booster vaccination was 69% (95% CI: –14 to 91) for ChAdOx1 for the prevention of COVID-19 hospitalization caused by Omicron variant.

Meeraus et al. 2023 reported relative vaccine effectiveness (rVE) from Brazil during the Omicron circulation (BA.1, BA.2, BA.4, and BA.5). The overall rVE against COVID-19 hospitalization of second boosters was 24.7 % (95 % CI: 12.6–35.1). **The improved protection was similar with second booster doses of AZD1222 (rVE 29.4 %; 95 % CI: 8.6 to 45.5), Ad26.COV2.S (rVE 24.8 %; 95 % CI: 8.1 to 38.4), and BNT162b2 (rVE 25.5 %; 95 % CI: 4.2 to 42.2).**

Dos Santos et al. 2023 provides estimates of the number of severe cases and deaths due to coronavirus disease (COVID-19) averted during the first year of the mass vaccination campaign in Brazil. The PRAC rapporteur was unable to locate the VE results in the article as they were presented in the PBRER.

Marcela Galvez et al. 2023 reported a higher infection rate following a booster dose in participants who received CoronaVac (Odds Ratio (OR) = 1.49, CI 1.06–2.10) and Ad26.COV2.S (OR = 1.63, CI 1.10–

2.43) than those who received ChAdOx1 (OR = 1.17, CI 0.79–1.71), with mRNA-1273 as comparator.

Data presented by *Liu et al. 2023* (Australia, circulation of BA.1 and BA.2 variants) suggest higher relative effectiveness of mRNA vaccines against SARS-CoV-2 Omicron infection than viral vector and protein subunit vaccines, when all vaccines were based on the ancestral strain.

There are no RWE data on protection conferred by three doses of Vaxzevria on disease caused by variant XBB.1.

4. Benefit-risk balance

See Section 2 Overall conclusions.

5. Rapporteur Request for supplementary information

NA

6. MAH responses to Request for supplementary information

NA

7. Comments from Member States

Member states' comments:

We overall agree with the assessment performed by our BE colleagues. However, we are concerned about the implications of not including information about the potential relationship between ADEM and erythema multiforme and Vaxzevria.

In MS, we have already received several patient claims about ADEM. As you know, the assessment of these cases is complex and if this information is not in the public domain, the evaluation becomes even more complex. We fully understand that it is not possible to update the PI since there is no valid MA currently available. As the recommendation Section for this PSUR is a little bit different from that usually included in the template of the PSURs, we would like to suggest you to include as well your conclusions about ADEM and erythema multiforme. Please, see below in yellow:

3. Recommendations

The marketing authorisation (EU/1/21/1529/002) for Vaxzevria was withdrawn on 7 May 2024 (approved by the European Commission on 27 March 2024).

As a result of the evaluation of this PSUR, PRAC considers that there is sufficient evidence to conclude there is a reasonable possibility that Vaxzevria is causally related to Acute disseminated encephalomyelitis (ADEM) and erythema multiforme. ADEM and erythema multiforme are thus considered as **new ADRs** of Vaxzevria.

Rapporteur assessment comment:

The MS comment is acknowledged and agreed. The recommendation has been updated.

EMA's comments:

[...] The main advice is to further evaluate the precise scope in section 3 but we also added a wording to reference the withdrawal. This advice comes in line with previous discussions at the PRAC for products where a PI update was considered warranted, even though the MA was revoked at the PRAC adoption, [...].

We hope these amendments will increase the transparency of the new ADRs and answers the comments from MS on the potential patients claims on the new information.

We would recommend that this procedure is briefly discussed next week during PRAC plenary. [...]

Rapporteur assessment comment:

The Rapporteur thanks EMA for their advice and support. The recommendation has been updated accordingly.

Medicinal product no longer authorised

Appendix 01: Assessment of the responses to the questions

Responses to Issues to be addressed in the next PSUR

Request 1. Exposure

The MAH is requested to provide estimated exposure data for other countries such as African countries, if available.

AstraZeneca response: Please refer to Section 5.2.1.1 in the PBRER (reporting period 29 December 2022 to 28 December 2023).

Rapporteur assessment comment:

Data were provided as requested (see Section 1.3.3. of the AR).

Issue resolved

Request 2. Thrombosis with Thrombocytopenia Syndrome

The MAH should update the cumulative review on TTS after booster dose and discuss the need to update the SmPC Section 4.4, paragraph on 'Thrombosis with thrombocytopenia syndrome' and paragraph on 'Risk of very rare events after a booster dose'.

AstraZeneca response: Please refer to Section 16.3.2.1 in the PBRER (reporting period 29 December 2022 to 28 December 2023).

Rapporteur assessment comment:

Data were provided and discussed as requested (see Section 2.3.1. of the AR).

Issue resolved

Request 3. Dermatomyositis

The MAH is requested to present new cases of dermatomyositis (DM) and as well as new data from the literature.

AstraZeneca response: Please refer to Section 15.2.2 on Dermatomyositis in the PBRER (reporting period 29 December 2022 to 28 December 2023).

Rapporteur assessment comment:

Data were provided and discussed as requested (see Section 2.3.13. of the AR).

Issue resolved

Request 4. SCARS, in particular Erythema Multiforme

SCAR cases: The MAH is requested to review and discuss all available literature cases (i.e. cases that might have been discussed in the previous PSUR together with any new literature cases)

Erythema multiforme cases: The MAH is requested to present:

- a cumulative review of erythema multiforme (at PT level) based on data from all available sources.

- a causality assessment of the cases (using the WHO-UMC causality assessment) and discuss the cases assessed as WHO Possible, Probable or Certain.
- relevant literature data.
- a discussion on the need for updating product information and/or risk management plan, and submit proposal as required.

AstraZeneca response: Please refer to Section 15.2.3 on SCARs (all literature case reports) specifically Erythema multiforme in the PBRER (reporting period 29 December 2022 to 28 December 2023).

Rapporteur assessment comment:

Data were provided and discussed as requested (see Section 2.3.14. of the AR).

Issue resolved

Request 5. Pemphigus and Pemphigoid

Pemphigus and pemphigoid, closed by EMA in April 2023: the causal relationship with Vaxzevria is uncertain and further discussion is required in next PSURs.

AstraZeneca response: Please refer to Section 15.2.1 on Pemphigus and Pemphigoid in the PBRER (reporting period 29 December 2022 to 28 December 2023).

Rapporteur assessment comment:

Data were provided and discussed as requested (see Section 2.3.12. of the AR).

Issue resolved

Request 6. Menstrual Disorders (Literature Review)

The MAH is requested to provide a more relevant information from the updated review of the literature.

AstraZeneca response: Please refer to Section 15.2.4 on literature reporting menstrual disorders in the PBRER (reporting period 29 December 2022 to 28 December 2023).

Rapporteur assessment comment:

Data were provided and discussed as requested (see Section 2.3.15. of the AR).

Issue resolved

Request 7. Safety Concerns

The MAH is requested to update the safety concerns of the PSUR and RMP as follows:

- To Re-classify the important potential risk of 'Thrombosis' as an important identified risk at the next regulatory opportunity
- To maintain 'Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)' in the important potential risks
- To maintain 'Interactions with other vaccines' and 'Long-term safety' in the missing information.

AstraZeneca response:

The important potential risks 'Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)', and the missing information topics 'Interactions with other vaccines' and 'Long-term safety' have been maintained in the EU RMP. The new information on these topics presented within the PBRER Appendix R3: Section 2 covering the reporting period 29 December 2022 to 28 December 2023.

The following change were included within the EU RMP version 8.0 succession 2.0 which was submitted with variation EMEA/H/C/005675/II/0097 (review ongoing):

- "Thrombosis" is reclassified and removed from the list of safety concerns and "Venous thromboembolism (VTE) without thrombocytopenia" is added as an important identified risk.

Rapporteur assessment comment:

Safety concerns were discussed as requested (see Section 2.4. of the AR).

Issue resolved

Responses following Other requests

Request 1. Myocarditis

On 06 July 2023, as part of the assessment report on the LEG request 115 (EMA/PRAC/283257/2023) on myocarditis the following safety data was requested to be submitted in the next PSUR:

- The MAH is requested to provide a review of the literature for new publications on epidemiologic studies of interest related to myocarditis.
- The MAH is requested to verify the O/E analysis and correct the errors, especially in the analyses by individual regions.
 - in the stratification of UK/Male/20-29 years, the number of expected cases in the RW of 14 days is lower than in the RW of 7 days.
 - in the EEA analysis, the number of expected cases by age group for all cases and BCC level 1-3 cases are not the same.

AstraZeneca response:

Background

As part of the legally binding measure (LEG): Response to Requests from the Pharmacovigilance Risk Assessment Committee dated 14 April 2023, a cumulative review of Myocarditis with Vaxzevria was performed and no changes to product information and risk management plan was proposed Myocarditis being an AESI for VAXZEVRIA and will continue to be kept under close surveillance by AstraZeneca. Upon review of myocarditis data, PRAC (LEG procedure number: EMA/PRAC/283257/2023), PRAC has suggested us to address the following topics in the PBRER.

review of the literature for new publications on epidemiologic studies of interest related to these safety endpoints should be provided.

the MAH is requested to verify the O/E analysis and correct the errors, especially in the analyses by individual regions in the next PBRER.

Literature review

During the reporting interval, a total of 390 articles showing the occurrence of myocarditis in association with VAXZEVRIA and other COVID-19 vaccines were retrieved through 28 December 2023. Three articles with systematic data review/retrospective analysis are presented below. The remaining 387 articles did not have adequate relevant safety information on myocarditis to require further review.

Error! Reference source not found. performed a retrospective analysis of causes related to myocarditis and pericarditis with NVX-CoV2373 vaccination, using reporting odds ratios (RORs) as a measure of disproportionality for reported myopericarditis. As per authors, mRNA vaccines as a positive control for the increased disproportionality since they have been described as casual myopericarditis risk, whereas Vaxzevria and Jcovden have been also associated with the event, a definite association has not been established at the moment. Information provided by the article, do not contribute new safety information regarding causal relationship between Myocarditis and Pericarditis with Vaxzevria.

Error! Reference source not found. analysed several adverse events of interest reported in Korea from 26 February 2021 to 02 June 2022, including Myocarditis. Following the review of medical records to assess diagnostic accuracy, 511 cases were assessed, resulting in 4.1 cases of myocarditis per million COVID-19 vaccine doses. From those, the highest rates were observed after Spikevax (6.2 per million doses) compared to Comirnaty (4.4 per million doses). Authors identified a total of 12 case reports related to Vaxzevria, mostly reported in 60-years-old male vaccinees. The information available in this review is insufficient to suggest a causal association with VAXZEVRIA, considering limited information regarding each individual case report details, such time to onset, medical history, concomitant medication, clinical features, laboratory data, etiology and diagnostic workup.

Error! Reference source not found. through a systematic review aimed to characterize the reported cases of myocarditis after COVID-19 vaccination based on age, gender, and vaccine type from the published literature (until June 30, 2022) and EudraVigilance database (until December 18, 2021). During the assessment of differences in Myocarditis incidence between the vaccines authors do not identify a clear reason, it was reported that the incidence of myocarditis post mRNA COVID-19 vaccines was considerably higher, particularly Spikevax (40 cases per 1 million doses administered) vs Comirnaty (22 cases per 1 million doses administered), and in contrast, systematic literature showed that myocarditis cases were most frequently published after the vaccination with the Comirnaty (n = 710), exceeding the overall incidence rates of myocarditis after non-mRNA vaccines. Information provided by the article, do not contribute new safety information regarding causal relationship between Myocarditis and Pericarditis with Vaxzevria.

Based on the available information, there is insufficient evidence to confirm a causal association between VAXZEVRIA and myocarditis.

Observed-to-Expected Analysis

Observed-to-expected analyses (O/E) was performed using multiple risk windows (7, 14, 21, 28 and 42 days), based on the request received from the PRAC. The case reports included both diagnostically confirmed cases of myocarditis based on BCC Levels 1 to 3 and unconfirmed cases BCC Levels 4-5. As per the comment received from PRAC (EMA/PRAC/283257/2023), the expected numbers captured for regions UK and EEA were cross checked.

For the UK data stratified by age group and gender, the expected case count with the risk window of 14 days was updated to reflect the correct numbers. Details are included in Appendix A.

With respect to EEA data, the O/E ratio and conclusion remains correct. However, the observed vs expected case counts were incorrect within the Table: Observed Versus Expected Analysis of Myocarditis Cases from EEA by Age Group. The numbers are now updated, and details are included in Appendix B.

Conclusion

Based on currently available data, it is AstraZeneca's opinion that there is insufficient evidence to suggest a causal association between myocarditis and VAXZEVRIA. This review did not find evidence of a new or emerging signal for myocarditis to suggest a need to update the VAXZEVRIA product information or risk management plan. Myocarditis is an AESI for AXZEVRIA and will continue to be kept under close surveillance by AstraZeneca.

Rapporteur assessment comment:

Data were provided and discussed as requested (see Section 2.3.17. of the AR).

Issue resolved

Periodic Safety Update Report

Medicinal Product COVID-19 Vaccine (ChAdOx1-S
[recombinant])

Date 23 February 2024

Periodic Safety Update Report

for

VAXZEVRIA™ (AZD1222)

ATC Code(s): J07BX03

Note: The format and content of the PSUR are based on those for the Periodic Benefit-Risk Evaluation Report (PBRER) as described in the ICH E2C(R2) guideline – the term PBRER is used within the report itself.

VAXZEVRIA™ is a trade mark of the AstraZeneca group of companies.

Medicinal Products Covered:

Invented name of the medicinal product(s)	Marketing authorisation number(s)	Date(s) of authorisation ^a	Marketing authorisation holder
VAXZEVRIA	EU/1/21/1529/002	29 January 2021	AstraZeneca AB

^a International Birth Date is underlined. This footnote is particularly applicable if there are numerous authorisation dates; if the list of authorisations is presented separately this footnote may be deleted

Authorisation procedure in the European Union (EU): Centralised

International Birth Date (IBD): 29 December 2020

EU Reference Date (EURD): 29 December 2020

Period covered: 29 December 2022 to 28 December 2023

Date of report: 23 February 2024

Marketing authorisation holder's name and address: AstraZeneca AB
151 85 Södertälje

Sweden

E-mail address: [REDACTED]

Name and contact details of QPPV:

Magnus Ysander
Pepparedsleden 1, 431 83 Mölndal,
Sweden

Telephone number: [REDACTED]

E-mail address: [REDACTED]

The content of this Periodic Safety Update Report has been reviewed and endorsed by:

Magnus Ysander
Qualified Person for
Pharmacovigilance in the EU

Electronic signature is available at the end of the document

This PSUR is submitted according to the guidance:

User Guidance for Marketing Authorisation Holders (MAHs) for PSUR Repository

Periodic Benefit-Risk Evaluation Report

Medicinal Product	VAXZEVRIA (ChAdOx1-S [recombinant])
Date	23 February 2024

VAXZEVRIA™ (AZD1222)
Periodic Benefit -Risk Evaluation Report

Period covered: 29 December 2022 to 28 December 2023

International birth date: 29 December 2020 (United Kingdom)

Note: This report contains unblinded clinical trial adverse event data.

VAXZEVRIA™ is a trade mark of the AstraZeneca group of companies.

This document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

VAXZEVRIA™ (AZD1222)

Periodic Benefit-Risk Evaluation Report

Period covered: 29 December 2022 to 28 December 2023

International birth date: 29 December 2020 (United Kingdom)

The content of this Periodic Benefit-Risk Evaluation Report has been reviewed and endorsed by: Magnus Ysander
Qualified Person for Pharmacovigilance in the EU

Electronic signature is available at the end of the document

EXECUTIVE SUMMARY

- **Introduction:** This Periodic Benefit-Risk Evaluation Report (PBRER) for VAXZEVRIA™ (AZD1222) summarises safety and efficacy/effectiveness data received and evaluated by AstraZeneca from 29 December 2022 to 28 December 2023, and places it in the context of the cumulative data and the overall benefit-risk profile.
- **Medicinal product:** VAXZEVRIA is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of the Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2). Following administration, the S glycoprotein of SARS-CoV-2 is expressed locally stimulating neutralizing antibody and cellular immune responses. VAXZEVRIA is indicated for active immunization of individuals ≥ 18 years old for the prevention of coronavirus disease 2019 (COVID-19). VAXZEVRIA is supplied as a vial containing either 8 doses or 10 doses per vial, 0.5 mL per dose for intramuscular (IM) injection. The VAXZEVRIA primary vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 4 and 12 weeks after the first dose. It is recommended that individuals who receive a first dose of VAXZEVRIA complete the vaccination course with VAXZEVRIA. A booster dose (third dose) of 0.5 ml may be given to individuals who completed the primary vaccination course with VAXZEVRIA or another authorised COVID-19 vaccine at least 3 months after completing the primary vaccination course. The approval and dosing interval of booster dose for VAXZEVRIA may vary according to the countries of authorisation.
- **Marketing approval:** VAXZEVRIA is either approved as Marketing Authorisation (MA), Conditional Marketing Authorisation (CMA) or Emergency Use Authorisation (EUA) in multiple countries worldwide and managed by AstraZeneca and its partners – Serum Institute of India (SII), R-Pharm and Fiocruz. VAXZEVRIA was first approved for active immunisation in individuals 18 years of age and older for the prevention of COVID-19 in United Kingdom (UK) on 29 December 2020. It received CMA in the EU on 29 January 2021.
- **Actions taken or proposed for safety reasons:** No significant actions related to safety were taken or proposed during the reporting period.
- **Safety changes to Reference Safety Information:** During this reporting period, there were 3 updates to the VAXZEVRIA Core Data Sheet (CDS) to include the following safety-related changes:
 - Section 4.8 was updated to include Decreased appetite (frequency: uncommon).
 - Section 4.4 of the CDS was updated to include information about circulating variants at the time VAXZEVRIA was developed and clinical efficacy studies were conducted and to make health care professionals aware to consider the characteristics of the circulating variants including regional or geographical differences for the use of VAXZEVRIA.
 - Frequencies of adverse drug reactions (ADRs) and percentage numbers were revised in Section 4.8 of the CDS based on the final study data from the pooled University of Oxford sponsored studies COV001, COV002, COV003 and COV005, US study D8110C00001 and the Booster Study D7220C00001.

- **Estimated cumulative exposure of clinical trial subjects:**

Approximately 60597 patients and/or healthy volunteers have been enrolled into the clinical development programme, of which approximately 35942 have received VAXZEVRIA and the studies are completed.

- **Estimated cumulative and reporting period patient exposure from post-approval (marketing) experience:** AstraZeneca is working directly with health departments in individual countries to determine the number of doses administered. Presently, administration data is available from the European Union, United Kingdom, Afghanistan, Argentina, Australia, Bangladesh, Brazil, Canada, Chile, Colombia, Ecuador, Guatemala, India, Iran, Iraq, Japan, Lebanon, Malaysia, Mexico, Nepal, New Zealand, Peru, Philippines, Saint Lucia, South Korea, Taiwan, Thailand, and Uruguay. The cumulative worldwide post-approval patient exposure (by doses distributed) since launch is estimated to be over 2.99 billion (in previous PBRER it was incorrectly captured as 3.02 billion when the actual distributed doses was 2.99 billion). The patient exposure (by doses distributed) during the reporting period is estimated to be over 5.9 million doses.

- **Late-breaking information:** No new safety concerns identified post data lock point (DLP) during the late breaking period.

- **Summary of overall benefit-risk evaluation:** The data received during this reporting period, combined with analyses of the cumulative efficacy, effectiveness and safety data available, AstraZeneca acknowledges that the level of humoral immunity and cell-mediated immunity (CMI) induced protection reduces as new variants emerge and evolve from the ancestral SARS-CoV-2 strain.

It is AstraZeneca's opinion that the benefits of VAXZEVRIA continues to outweigh the risks and that the CDS accurately reflect the known benefit-risk profile.

TABLE OF CONTENTS

TITLE PAGE.....	1
SIGNATURE PAGE.....	2
EXECUTIVE SUMMARY	3
TABLE OF CONTENTS	5
LIST OF ABBREVIATIONS.....	16
1 INTRODUCTION	24
2 WORLDWIDE MARKETING APPROVAL STATUS	25
3 ACTIONS TAKEN IN THE REPORTING PERIOD FOR SAFETY REASONS	25
4 CHANGES TO REFERENCE SAFETY INFORMATION.....	25
5 ESTIMATED EXPOSURE AND USE PATTERNS.....	26
5.1 Cumulative subject exposure in clinical trials	26
5.2 Cumulative and interval patient exposure from marketing experience	28
5.2.1 Post-approval (non-clinical trials) exposure.....	28
5.2.1.1 Patient Exposure – Dose distributed.....	29
5.2.1.2 Post-marketing patient exposure data for reporting period and cumulatively	30
5.2.2 Post-approval use in special populations	34
5.2.3 Other post-approval use	34
6 DATA IN SUMMARY TABULATIONS.....	34
6.1 Reference information.....	34
6.2 Cumulative summary tabulations of serious adverse events from clinical trials	34
6.3 Cumulative and interval summary tabulations from post--marketing data sources	35
6.3.1 Lack of efficacy from Post-Marketing.....	37
6.3.2 Fatal events, including case reports involving Preferred Term of Sudden Death	39
6.3.2.1 Fatal Events	39
6.3.2.2 Case reports involving PT of Sudden Death	45
7 SUMMARIES OF SIGNIFICANT FINDINGS FROM CLINICAL TRIALS DURING THE REPORTING PERIOD.....	48
7.1 Completed clinical trials.....	48
7.2 Ongoing clinical trials.....	58
7.3 Long-term follow-up.....	58
7.4 Other therapeutic use of medicinal product	58
7.5 New safety data related to fixed-combination therapies.....	58
8 FINDINGS FROM NON-INTERVENTIONAL STUDIES.....	58
9 INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES.....	59

9.1	Other clinical trials.....	59
9.2	Vaccination errors.....	59
9.2.1	Fatal Cases Associated with Vaccination errors.....	75
10	NON-CLINICAL DATA	76
11	LITERATURE.....	76
12	OTHER PERIODIC REPORTS	82
13	LACK OF EFFICACY IN CONTROLLED CLINICAL TRIALS.....	82
14	LATE-BREAKING INFORMATION	84
15	OVERVIEW OF SIGNALS (NEW, ONGOING OR CLOSED)	85
15.1	Overview of Validated Signals (New, Ongoing or Closed).....	85
15.2	Health Authority requests.....	86
15.2.1	Pemphigus and Pemphigoid	87
15.2.2	Myositis-specifically Dermatomyositis	108
15.2.3	SCARs in particularly erythema multiforme.....	113
15.2.3.1	SCARs (Literature case reports).....	113
15.2.3.2	Erythema Multiforme (EM)	130
15.2.4	Menstrual disorder (literature review)	140
15.2.5	Hearing loss	143
15.2.6	Guillain Barre syndrome (GBS) including cases of Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	149
16	SIGNAL AND RISK EVALUATION.....	170
16.1	Summary of safety concerns	170
16.2	Signal evaluation.....	171
16.2.1	Closed and rejected/refuted signals	171
16.2.2	Closed signals categorised as important potential risks.....	171
16.2.3	Closed signals categorised as important identified risks.....	171
16.2.4	Closed signals that are potential risks not categorised as important.....	171
16.2.5	Closed signals that are identified risks not categorised as important.	171
16.2.5.1	Decreased appetite	171
16.2.5.2	Potential Vaccination Failure/Lack of Efficacy against Emerging Variants (including Omicron XBB).....	172
16.3	Evaluation of risks and new information	173
16.3.1	New information on important potential risks.....	173
16.3.1.1	Cerebrovascular venous and sinus thrombosis without thrombocytopenia	173
16.3.1.2	Immune-mediated neurological conditions.....	207
16.3.2	New information on important identified risks	268
16.3.2.1	Thrombosis in combination with thrombocytopenia / Thrombosis with thrombocytopenia syndrome	268
16.3.3	New information on other potential risks not categorised as important	324
16.3.4	New information on other identified risks not categorised as important.....	324
16.3.5	Update on missing information	324
16.3.5.1	Use of VAXZEVRIA in pregnant and breastfeeding women.....	324

16.3.5.2	Use of VAXZEVRIA in subjects with severe immunodeficiency	336
16.3.5.3	Use of AZD1222 in subjects with severe and/or uncontrolled underlying disease /Use in frail patients with co-morbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorder)	356
16.4	Characterisation of risks.....	373
16.4.1	Important identified risks	373
16.4.1.1	Thrombosis in combination with thrombocytopenia	373
16.4.2	Important potential risks	374
16.4.2.1	Immune-mediated neurological conditions.....	375
16.4.2.2	Cerebrovascular venous sinus thrombosis (CVST) without thrombocytopenia	376
16.4.3	Missing information.....	377
16.4.3.1	Use of VAXZEVRIA in pregnant and breastfeeding women	377
16.4.3.2	Use of VAXZEVRIA in subjects with severe immunodeficiency	377
16.4.3.3	Use of VAXZEVRIA in subjects with severe and/or uncontrolled underlying disease	378
16.5	Effectiveness of risk minimisation	378
17	BENEFIT EVALUATION.....	378
17.1	Important baseline efficacy/effectiveness information.....	378
17.2	Newly identified information on efficacy/effectiveness.....	379
17.3	Vaccine effectiveness against SARS-CoV-2 Omicron variant	379
17.4	Characterisation of benefits.....	384
18	INTEGRATED BENEFIT-RISK ANALYSIS FOR APPROVED INDICATIONS.....	385
18.1	Benefit-risk context - medical need and important alternatives	386
18.1.1	Medical need for the product.....	386
18.1.2	Important alternatives available.....	387
18.2	Benefit-risk analysis evaluation.....	387
18.2.1	Active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older	388
18.2.1.1	Context of use of the medicinal product	388
18.2.1.2	Considerations relating to key benefit(s)	388
18.2.1.3	Considerations relating to risk.....	389
18.2.1.4	Strengths, weaknesses, and uncertainties of the evidence	390
18.2.1.5	Methodology and reasoning used to develop the benefit-risk evaluation.....	390
19	CONCLUSIONS AND ACTIONS	391
20	APPENDICES TO THE PBRER	391
21	REFERENCES	392

LIST OF TABLES

Table 1	Summary of safety-related changes to the VAXZEVRIA CDS during the reporting period.	25
Table 2	Cumulative subject exposure from clinical trials	26
Table 3	Cumulative subject exposure to AZD1222 and AZD2816 from completed clinical trials by age and sex.....	27
Table 4	Cumulative subject exposure to AZD1222 and AZD2816 from completed clinical trials by racial group	27
Table 5	VAXZEVRIA exposure, based on doses distributed, by Region.....	29
Table 6	VAXZEVRIA interval and cumulative exposure based on doses administered, by Region/Country	30
Table 7	Vaccine Doses Administered by Age Group (EEA and UK)	33
Table 8	Vaccine Doses Administered by Gender Group.....	33
Table 9	Summary tabulation of SAE case reports received from VAXZEVRIA (AZD1222) and AZD2816 clinical trials ^a	34
Table 10	Summary tabulation of VAXZEVRIA case reports and adverse events received from spontaneous sources ^a	36
Table 11	Fatal cases per age group (in years).....	40
Table 12	Reported cause of death in Fatal Cases with VAXZEVRIA (n = 386) during the Interval period: 29 December 2022 – 28 December 2023	41
Table 13	Observed versus expected analyses for Fatal cases overall	43
Table 14	Observed versus expected analyses for Fatal cases by age group from EU+UK+Brazil+Australia region.....	43
Table 15	Observed versus expected analyses for Fatal cases by age group in UK ...	44
Table 16	Observed versus expected analyses for Sudden death.....	47
Table 17	Distribution of Serious Adverse Events Associated with Vaccination Errors with VAXZEVRIA by MedDRA SOC from 29 December 2022 to 28 December 2023	60
Table 18	Distribution of Serious Adverse Events Associated with Vaccination Errors with COVID-19 VACCINE ASTRAZENECA by MedDRA SOC through 28 December 2023	62
Table 19	Summary tabulation of Vaccination Error Adverse Events (interval and cumulative).....	65
Table 20	List of Health Authority requests	86
Table 21	Pemphigus cases with histopathological findings and WHO-UMC.....	89
Table 22	Pemphigoid cases with histopathological findings and WHO-UMC	97

Table 23	Summary of Dermatomyositis cases received during the PBRER period	110
Table 24	Distribution of SCARs events by MedDRA PTs with VAXZEVRIA during the reporting interval.....	114
Table 25	Summary of all literature case reports on SCARs with VAXZEVRIA....	116
Table 26	Overview of Events/Cases (Cumulatively)	131
Table 27	Distribution of most frequently co-reported events (≥ 5) in case reports for Erythema multiforme, cumulatively	132
Table 28	Overview of WHO-UMC Causality Assessments for Erythema Multiforme Case Reports with VAXZEVRIA reported Cumulatively through 28 December 2023	133
Table 29	Summary of recurrence Erythema multiforme Case Reports as per WHO-UMC causality criteria Cumulatively through 28 December 2023	134
Table 30	Relevant Risk factors/Confounders identified for Erythema Multiforme Case Reports Cumulatively through 28 December 2023	135
Table 31	Erythema multiforme cases from literature articles.....	137
Table 32	Hearing loss case reports received with VAXZEVRIA cumulatively through DLP 28 December 2023 by reporting source and seriousness	144
Table 33	Hearing Loss Cases with Age Grouping.....	144
Table 34	Hearing Loss Cases – Age group with Time to Onset.....	145
Table 35	O/E analysis of global reports of hearing loss.....	145
Table 36	O/E analysis of hearing loss cases reports from EU, UK, AU and BZ.....	146
Table 37	O/E analysis of hearing loss cases reports from UK	147
Table 38	Overview of WHO-UMC Causality Assessment for case reports of GBS with VAXZEVRIA reported during the reporting period (29 December 2022 – 28 December 2023) for cases of diagnostic certainty (BCC levels 1, 2, and 3).....	150
Table 39	Summary of GBS cases with fatal outcome with VAXZEVRIA reported during the reporting period [29 December 2022 – 28 December 2023]...	154
Table 40	Observed Versus Expected Analysis for Global GBS cases.....	164
Table 41	Observed Versus Expected Analysis for cases meeting the Brighton Criteria Level 1, 2 or 3 (Global reports) within three risk windows	164
Table 42	Observed Versus Expected Analysis for cases meeting the Brighton Criteria Level 1, 2 or 3 and stratified by age for EEA/UK/Brazil/ Australia regions	165
Table 43	Observed Versus Expected analysis for GBS cases meeting the Brighton Criteria (BC) Level 1, 2 or 3 and stratified by age and gender for UK only	166

Table 44	Summary of safety concerns – AstraZeneca Core Risk Management Plan for VAXZEVRIA (Version no.08.0, dated 05 October 2022)	170
Table 45	Decreased appetite	172
Table 46	Potential Vaccination Failure/Lack of Efficacy against Emerging Variants (including Omicron XBB).....	172
Table 47	Distribution of MedDRA PTs (n = 43) pertaining to CVST without co-reported Thrombocytopenia with VAXZEVRIA received during the reporting period	174
Table 48	Overview of CVST without co-reported thrombocytopenia Cases (n=32) during the reporting period.....	174
Table 49	Overview of WHO-UMC Causality Assessments for case reports of CVST without Thrombocytopenia with VAXZEVRIA reported during the reporting period	177
Table 50	Observed versus expected analysis for CVST without thrombocytopenia (using SIDIAP PC HOSP incident rate)	179
Table 51	Observed versus expected analysis for CVST without thrombocytopenia (using Truven 14 incident rates).....	183
Table 52	Observed versus expected analysis for CVST without thrombocytopenia (with known normal platelet count) (using SIDIAP_PC HOSP incident rate)	190
Table 53	Observed versus expected analysis for CVST without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates)	198
Table 54	Overview of Encephalitis events/cases for the interval period of PBRER214	
Table 55	Distribution of MedDRA PTs (n =13) pertaining to Encephalitis with VAXZEVRIA Cumulatively through 28 December 2023.....	216
Table 56	Overview of BCC and WHO-UMC Causality Assessments / for case reports of (Encephalitis) with VAXZEVRIA reported during the reporting period of PBRER	218
Table 57	Observed Versus Expected Analysis for all cases reporting encephalitis (Global reports) reported cumulatively till DLP 28 December 2023	220
Table 58	Observed Versus Expected Analysis for encephalitis cases stratified by age for EEA/UK, Brazil & Australia reported cumulatively till DLP 28 December 2023	221
Table 59	Observed Versus Expected Analysis for encephalitis cases meeting the Brighton Criteria Level 1, 2 or 3 and stratified by age for EEA/UK Brazil & Australia regions reported cumulatively till DLP 28 December 2023.	223

Table 60	Overview of BCC and WHO-UMC Causality Assessments / for case reports of Transverse myelitis with VAXZEVRIA reported during the reporting period	230
Table 61	Observed versus Expected Analysis for Transverse Myelitis Overall and for Brighton Collaboration cases	233
Table 62	Observed versus expected analysis, stratified by age, BCC and with and without cases with an unknown TTO in the UK	234
Table 63	Observed versus expected analysis, stratified by age and gender in the UK in the context of the UK THIN BG rates	236
Table 64	Observed versus expected analysis, stratified by age and gender, BCC levels 1-3 in the UK in the context of the UK THIN BG rates	239
Table 65	Observed versus expected analyses stratified by Dose number, age and gender, BCC in UK.....	242
Table 66	Observed versus expected analysis, stratified by Dose, age, BCC in the UK	246
Table 67	Overview of BCC and WHO-UMC Causality Assessments / for case reports of ADEM with VAXZEVRIA in the reporting interval.....	255
Table 68	Observed Versus Expected Analysis for all Reports of ADEM (Global Reports).....	258
Table 69	Observed Versus Expected Analysis for Cases for ADEM Meeting BCC Level 1, 2 or 3 (Global Reports).....	258
Table 70	Observed Versus Expected Analysis for ADEM Cases Stratified by Age for EU, UK, Brazil, and Australia Regions	260
Table 71	Observed Versus Expected Analysis for ADEM Cases Meeting BCC Level 1, 2 or 3 and Stratified by Age for EU, UK, Brazil, and Australia Regions	261
Table 72	An O/E analysis of cases meeting case definition according to BCC Level 1, 2 or 3 stratified by age and gender for UK is presented.....	262
Table 73	Time to onset for thrombosis in combination with thrombocytopenia cases	269
Table 74	Observed Versus Expected analysis for Thrombosis with thrombocytopenia (Overall)	271
Table 75	Observed Versus Expected analysis for Thrombosis with thrombocytopenia by age group (EU+UK+Brazil+Australia).....	274
Table 76	Observed Versus Expected analysis for Thrombosis with thrombocytopenia by age group/sex (UK).....	277

Table 77	Clinical characteristics of thrombosis in combination with thrombocytopenia case reports	286
Table 78	Comparison of platelet levels, thrombosis event, PF-4 antibodies and D-dimer levels in Thrombosis in combination with thrombocytopenia case reports (N=2811)	296
Table 79	Thrombosis with Thrombocytopenia Syndrome Case Reports by age/gender, Dose, MHRA Case Classification and fatality (N).....	298
Table 80	Thrombosis with Thrombocytopenia Syndrome Case Reports by age/gender and fatality	301
Table 81	TTS fatality/survival rate over time.....	302
Table 82	Post-Marketing Cases of Thrombosis with Thrombocytopenia Syndrome Related to VAXZEVRIA COVID-19 Vaccine Booster	308
Table 83	Cerebral venous sinus thrombosis with Thrombocytopenia Case Reports by age/gender	315
Table 84	Reporting rate for CVST and thrombocytopenia (UK and EEA data) by risk window of 21 days.....	317
Table 85	Observed versus Expected Analysis for CVST+TCP.....	320
Table 86	Spontaneous Abortion Observed Versus Expected Analysis (UK cases only).....	328
Table 87	Adverse Maternal Outcomes – Interval and Cumulative Period.....	329
Table 88	Adverse Events in Maternal Vaccinees (with a Frequency of ≥ 3)	335
Table 89	Age group and Sex in Immunocompromised groups	337
Table 90	Most frequently reported events (>100) in the IC group.....	337
Table 91	Adverse Events Reported by Authors of Included Studies by SOC And In Relation to the Number of Doses of VAXZEVRIA in Immunocompromised Individuals	347
Table 92	Description of Immunocompromised Groups.....	349
Table 93	AEs Reported by Authors of Included Studies Grouped by System Organ Class and Immunocompromised Groups	353
Table 94	Indicators of Frailty	357
Table 95	Summary of safety concerns – AstraZeneca Core Risk Management Plan for VAXZEVRIA (Version no. 9.0, dated 03 March 2023)	373
Table 96	<i>Important identified risk - Thrombosis in combination with thrombocytopenia</i>	<i>373</i>
Table 97	<i>Important potential risk - Immune mediated neurological conditions</i>	<i>375</i>

Table 98	<i>Important potential risk - Cerebrovascular venous sinus thrombosis (CVST) without thrombocytopenia</i>	376
----------	---	-----

LIST OF FIGURES

Figure 1	Medicines and Healthcare products Regulatory Agency case definition for thrombosis in combination with thrombocytopenia	285
Figure 2	TTS fatality/survival rate over time.....	303

LIST OF APPENDICES

Appendix 1	Reference Information (AstraZeneca Core Data Sheet)
Appendix 2	Cumulative Summary Tabulation of Serious Adverse Events from Clinical Trials + Interval/Cumulative Summary Tabulations of Serious and Non -Serious Adverse Reactions from Marketed Experience
Appendix 3	Tabular Summary of Validated Safety Signals
Appendix 4	Listings of All Post-Authorisation Safety Studies
Appendix 5	List of the Sources of Information Used to Prepare the PBRER (Not produced as not considered necessary for this report)
Appendix 6	Exposure Data
Appendix 7	Standardised MedDRA Queries (SMQ) and MedDRA search term (MST) lists used for Adverse Events of Special Interest (AESIs) and Safety Concerns in the VAXZEVRIA Risk Management Plan (RMP)
Appendix 8	Observed versus Expected Analyses
Appendix 9	Observed versus Expected Analyses Supporting Information
Appendix 10	Lot Analysis (Not produced as not applicable/Not produced as no information to report)
Additional Appendix 11	Search criteria for immunocompromised persons
Additional Appendix 12	Review of Myositis with VAXZEVRIA
Additional Appendix 13	CDS Vs listedness terms captured in database for automated expedition of case reports

Regional Appendices are relevant for submission as follows

European Union (EU) and United Kingdom (UK)

EU and UK Appendix R1	Proposed Product Information
EU and UK Appendix R2	Proposed Additional Pharmacovigilance and Risk Minimisation Activities (Not produced as no proposals to report)
EU and UK Appendix R3	Summary of Ongoing Safety Concerns in the European Union
EU and UK Appendix R4	Reporting of Results from Post-Authorisation Safety Studies (Not produced as no information to report)

EU and UK Appendix R5

Effectiveness of Risk Minimisation (Not produced as
not applicable)

Medicinal product no longer authorised

LIST OF ABBREVIATIONS

The following abbreviations are used in this Periodic Benefit-Risk Evaluation Report.

Abbreviation or special term	Explanation
ABSIS	Autoimmune Bullous Skin Disorder Intensity Score
ACE	Angiotensin-Converting Enzyme
ACTH	Adrenocorticotrophic Hormone
ADEM	Acute Disseminated Encephalomyelitis
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
AGEP	Acute Generalized Exanthematous Pustulosis
AHA	Acquired Hemophilia
AHEM	Acute Haemorrhagic Encephalomyelitis
AIBD	Autoimmune Skin Blistering Diseases
ALEP	Acute Localized Exanthematous Pustulosis
ALT	Alanine Aminotransferase
AMN	Acute Macular Neuroretinopathy
ANA	Antinuclear Antibodies
ANCA	Antineutrophil Cytoplasmic Antibodies
aPTT	Activated Partial Thromboplastin Time
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate Aminotransferase
AU	Australia
AV	Atrioventricular
AZ	AstraZeneca
BAER	Brainstem Auditory Evoked Response
BCC	Brighton Collaboration Classification
BG	Background
BMI	Body Mass Index
BPDAI	Bullous Pemphigoid Disease Area Index
BSA	Body Surface Area
BZ	Brazil
CDS	Core Data Sheet
CEM	Cohort Event Monitoring
ChAdOx1	Chimpanzee Adenovirus

Abbreviation or special term	Explanation
CI	Confidence Interval
CIDP	Chronic Inflammatory Demyelinating Polyradiculoneuropathy
CMA	Conditional Marketing Authorisation
CMAP	Compound Muscle Action Potential
CMI	Cell-Mediated Immunity
CMV	Cytomegalovirus
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease Of 2019
CPK	Creatinine Phosphokinase
CPRD	Clinical Practice Research Database
CRP	C-Reactive Protein
CSF	Cerebrospinal Fluid
CSR	Clinical Study Reports
CT	Clinical Trial
CVD	Cardiovascular Disease
CVST	Cerebrovascular Venous and Sinus Thrombosis
CVT	Cerebral Venous Thrombosis
DCO	Data Cut Off
DEJ	Dermal-Epidermal Junction
DH	Dermatitis Herpetiformis
DIBD	Development International Birth Date
DIF	Direct Immunofluorescence
DIM	Digitales Impfquotenmonitoring
DLP	Data Lock Point
DMARD	Disease Modifying Antirheumatic Drug
DNA	Deoxyribonucleic Acid
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
DSRU	Drug Safety Research Unit
DSUR	Development Safety Update Report
DVT	Deep Vein Thrombosis
EC	Excess of Cases
EEA	European Economic Area
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency

Abbreviation or special term	Explanation
EMEA	Europe, Middle East, and Africa
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
F	Female
FBC	Full Blood Count
FDP	Facial Diplegia with Paraesthesia
FLAIR	Fluid-Attenuated Inversion Recovery
FSI	First Subject In
FU	Follow-Up
FVC	Forced Vital Capacity
GABA	Gamma-aminobutyric acid
GBS	Guillain-Barré Syndrome
GCS	Glasgow Coma Scale
GMT	Geometric Mean Titre
HBV	Hepatitis B Virus
HCP	Healthcare Professional
HDL	High-Density Lipoprotein
HIT	Heparin-Induced Thrombocytopenia
HIV	Human Immunodeficiency Virus
HLT	High Level Term
HSV	Herpes Simplex Virus
HTLV	Human T-cell Leukaemia Virus
IBD	International Birth Date
IC	Intracardiac
IC	Immunocompromised
ICD	International Classification of Diseases
ICMR	Indian Council of Medical Research
ICMRA	International Coalition of Medicines Regulatory Authorities
ICS	Intracavernous
ICSR	Individual Case Safety Reports
ICU	Intensive Care Unit
ID	Identifier
ID	Intradermal
IFN	Interferon
IgG	Immunoglobulin

Abbreviation or special term	Explanation
IIF	Indirect immunofluorescence
IIM	Idiopathic Inflammatory Myopathies
IL	Interleukin
IM	Intramuscular
IR	Incidence Rate
IRR	Incidence Rate Ratio
ISTH	The International Society on Thrombosis and Haemostasis
ITP	Immune Thrombocytopenia
IV	Intravenous
JAK 2	Janus kinase 2
LD	Low Dose
LDH	Lactate Dehydrogenase
LDL	Low-Density Lipoprotein
LETM	Longitudinal Extensive Transverse Myelitis
LFT	Liver Function Test
LSO	Last Subject Out
LLT	Lowest Level Terms
LMP	Last Menstrual Period
LP	Lumbar Puncture
M	Male
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MB	Myocardial Band
MC	Medically Confirmed
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
ME	Myalgic Encephalomyelitis
MELAS	Mitochondrial Encephalopathy Lactic Acidosis and Stroke-like episodes
MGUS	Monoclonal Gammopathy of Undetermined Significance
MH	Medical History
MHRA	Medicines And Healthcare Products Regulatory Agency
MIS-C/A	Multisystem inflammatory syndrome in children/adults
MMII	Multimodal Image Integration
MOG	Myelin Oligodendrocyte glycoprotein
MOGAD	Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease

Abbreviation or special term	Explanation
MRI	Magnetic Resonance Imaging
MRV	Magnetic Resonance Venography
MS	Multiple Sclerosis
mSSR	Monthly Safety Summary Report
MST	MedDRA Search Term
NA	Not Applicable
NCS	Nerve Conduction Study
NEJM	New England Journal of Medicine
NHS	National Health Service
NIMS	National Immunisation Management System
NK	Natural Killer
NMDA	N-methyl-D-Aspartate
NMO	Neuromyelitis Optica
NMOSD	Neuromyelitis Optica Spectrum Disorder
NS	Non-Serious
OCB	Oligoclonal Bands
OE	Observed-To-Expected
OHDSI	Observational Health Data Science and Informatics
ONS	Office for National Statistics
OS	Other System
PAMM	Paracentral Acute Middle Maculopathy
PASS	Post-Authorisation Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PCNA	Proliferating Cell Nuclear Antigen
PCR	Polymerase Chain Reaction
PDAI	Pemphigoid Disease Area Index
PF	Pemphigus Foliaceus
PF 4	Platelet Factor 4
PI	Prescribing Information
PN	Pemphigoid nodularis
POTS	Postural Orthostatic Tachycardia Syndrome
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PSV	Pyostomatitis Vegetans
PT	Preferred Term

Abbreviation or special term	Explanation
PV	Pemphigus Vulgaris
PVFS	Post Viral Fatigue Syndrome
PY	Patient Years
RBC	Red Blood Cell
RBD	Receptor-binding domain
RD	Rheumatic Diseases
RMP	Risk Management Plan
RNA	Ribonucleic Acid
RNP	Antinuclear Ribonucleoprotein
ROW	Rest of the world
RR	Relative Risk
RS	Respiratory system
RT	Reverse Transcriptase
RW	Risk Window
RWE	Real-world evidence
SA	South Africa
SAB	Spontaneous Abortion
SAE	Serious Adverse Event
SARS	Severe acute respiratory syndrome
SARSCoV-2	Severe Acute Respiratory Coronavirus 2
SCARS	Severe Cutaneous Adverse Reactions
SCCS	Self-Controlled Case Series
SCORTEN	SCORE of Toxic Epidermal Necrosis
SD	Subdermal
SD	Standard Dose
SDSD	2 Standard Doses
SFDA	The Saudi Food and Drug Authority
SIDIAP	Information System for Research in Primary Care
SII	Serum Institute of India
SJS	Stevens-Johnson syndrome
SLE	Systemic Lupus Erythematosus
SLR	Systematic Literature Review
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SNAP	Sensory Never Action Potential

Abbreviation or special term	Explanation
SSaMT	Safety Strategy and Management Team
SOC	System Organ Class
SP	Spontaneous
SS	Sweet Syndrome
SSEP	Somatosensory Evoked Potential
SSR	Safety Summary Report
SSS	Salt-Split skin
STAT	Signal Transducer and Activator of Transcription
TCP	Thrombocytopenia
TE	Thromboembolism
TEN	Toxic epidermal necrolysis
TGA	Therapeutic Goods Administration
TM	Transverse Myelitis
TMA	Thrombotic Microangiopathy
TNCC	Test-Negative Case-Control Design
TNF	Tumour Necrosis Factor
TPL	Transplacental
TPO	Thrombopoietin Receptor
TRE	Trusted Research Environment
TTO	Time to Onset
TTP	Thrombotic Thrombocytopenic Purpura
TTS	Thrombosis with Thrombocytopenia Syndrome
UC	Ulcerative Colitis
UK	United Kingdom
UKTHIN	United Kingdom the Health Improvement Network
UL	Upper Limbs
UMC	Uppsala Monitoring Centre
UNK	Unknown
US	United States
VAED	Vaccine Associated Enhanced Disease
VAERD	Vaccine-Associated Enhanced Respiratory Disease
VAERS	Vaccine Adverse Event Reporting System
VAN	Vaccine Associated Neurological Disorders
VASCO	Vaccine Study COvid-19
VE	Vaccine Efficacy

Abbreviation or special term	Explanation
VEP	Visual Evoked Potentials
VGKC	Voltage-Gated Potassium Channel
VIPER	Vaccines International Pregnancy Exposure Registry
VIPIT	Vaccine-Induced Prothrombotic Immune Thrombocytopenia
VITT	Vaccine-Induced Immune Thrombotic Thrombocytopenia
VOC	Variants of Concern
WBC	White Blood Cells
WHO	World Health Organization

1 INTRODUCTION

This Periodic Benefit-Risk Evaluation Report (PBRER) prepared by AstraZeneca for VAXZEVRIA™ (AZD1222) summarises the safety and efficacy/effectiveness information received and evaluated by AstraZeneca from worldwide sources between 29 December 2022 and 28 December 2023. It is compiled in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E2C(R2) PBRER guideline and EU Good Pharmacovigilance Practices Module VII (Revision 1); the terms/terminology used in this report are consistent with this guidance, and applicable international regulatory requirements.

The VAXZEVRIA International Birth Date (IBD) is 29 December 2020.

VAXZEVRIA is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of the Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2). Following administration, the S glycoprotein of SARS-CoV-2 is expressed locally stimulating neutralizing antibody and cellular immune responses.

VAXZEVRIA is indicated for active immunisation of individuals ≥ 18 years for the prevention of Coronavirus Disease 2019 (COVID-19). The use of VAXZEVRIA should take into account the available efficacy, effectiveness and immunogenicity data.

VAXZEVRIA is supplied as a vial containing either 8 doses or 10 doses per vial, 0.5 mL per dose for intramuscular (IM) injection. VAXZEVRIA primary vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 4 and 12 weeks after the first dose. It is recommended that individuals who receive a first dose of VAXZEVRIA complete the primary vaccination course with VAXZEVRIA. The core data sheet (CDS) indicates that a booster dose (third dose) of 0.5 ml may be given to individuals who completed the primary vaccination course with VAXZEVRIA or another authorised COVID-19 vaccine. The third dose should be administered at least 3 months after completing the primary vaccination course. The status of approval and the recommendation in national prescribing information (PI) documents relating to the booster dose vary.

The inclusion of any information relating to a validated signal, important potential risk, or missing information within this PBRER should not be taken to imply that a causal association with the use of VAXZEVRIA has been established.

2 WORLDWIDE MARKETING APPROVAL STATUS

VAXZEVRIA is either approved as Marketing Authorisation (MA), Conditional Marketing Authorisation (CMA) or Emergency Use Authorisation (EUA) in multiple countries worldwide and managed by AstraZeneca and its partners – Serum Institute of India (SII), R-Pharm and Fiocruz. VAXZEVRIA was first approved for active immunisation in individuals 18 years of age and older for the prevention of COVID-19 in United Kingdom (UK) on 29 December 2020. It received CMA in the EU on 29 January 2021.

3 ACTIONS TAKEN IN THE REPORTING PERIOD FOR SAFETY REASONS

No significant actions related to safety were taken or proposed during the reporting period.

4 CHANGES TO REFERENCE SAFETY INFORMATION

AstraZeneca's reference safety information is the CDS. The CDS covers material relating to safety, indications, dosing, pharmacology, and other information concerning the medicinal product (providing the medical and scientific information AstraZeneca believes is necessary for the safe and effective use of a product); it serves as the master document for regular implementation of material changes in national or local authorised product information.

The VAXZEVRIA CDS in effect at the beginning of the reporting period was dated 08 November 2022 (version 21.0).

During this reporting period, the VAXZEVRIA CDS was updated three times to include the safety-related changes summarised in Table 1.

Table 1 Summary of safety-related changes to the VAXZEVRIA CDS during the reporting period.

CDS version date	CDS Section Number – CDS Section Title Detail of the safety-related change	PBRER Section cross-reference, where applicable
Version 22.0 21 February 2023	CDS Section 4.8 Undesirable Effects - Addition of Decrease appetite as an adverse drug reaction with frequency uncommon. - Revision of numbers and frequencies in Table 1 adverse drug reactions. - Information in Overall summary of the safety profile updated to reflect data from the final pooled analysis DC03.	Decreased appetite: Section 16.2.5.1

Table 1 **Summary of safety-related changes to the VAXZEVRIA CDS during the reporting period.**

CDS version date	CDS Section Number – CDS Section Title Detail of the safety-related change	PBRER Section cross-reference, where applicable
Version 23.0 30 August 2023	CDS Section 4.4 Special Warnings and Special Precautions for Use - to include information about circulating variants at the time Vaxzevria was developed and clinical efficacy studies were conducted. - and to consider the characteristics of the circulating variants including regional or geographical differences for the use of Vaxzevria.	Section 16.2.5.2
Version 24.0 01 November 2023	CDS Section 4.8 Undesirable Effects Booster dose (third dose) - Revision to the number of participants who had previously received a 2-dose primary vaccination course with Vaxzevria. Summary of the safety data from D8110C00001 - To the number of participants aged ≥ 18 years who received at least one dose and - To the number of participants in the placebo group.	Not applicable

CDS Core Data Sheet; PBRER Periodic Benefit Risk Evaluation

A copy of the VAXZEVRIA CDS in effect at the end of the reporting period is presented in Appendix 1. For the purpose of this PBRER, this CDS Version 24.0, dated 01 November 2023 is the reference for both the benefit and risk sections.

5 ESTIMATED EXPOSURE AND USE PATTERNS

5.1 Cumulative subject exposure in clinical trials

Overall cumulative subject exposure is provided in Table 2, based on actual exposure data from completed clinical trials. There are no ongoing clinical trials enrolling participants and no further clinical development is planned for VAXZEVRIA.

Table 2 **Cumulative subject exposure from clinical trials**

Treatment	Number of subjects
AZD1222	35942
AZD2816 ^a	1523

Table 2 Cumulative subject exposure from clinical trials

Treatment	Number of subjects
MenACWY	10960
Rabies	200
Placebo	11972

Cumulative numbers from initiation of the first clinical trials up to 28 December 2023.

All dosed subjects are included. All studies are reported using actual arm. Participants rolled over from COV001 and COV002 into COV009, no additional dosing in COV009. COV009 excluded to avoid double-reporting.

216 participants received the fourth dose of AZD1222 in the 4th dose sub-study of COV003. These participants are not counted separately to avoid double-reporting.

^a AZD2816 is a discontinued vaccine developed from AZD1222 targeting Beta variant of SARS-CoV-2. AZD2816 is used in Study D7220C00001 which is further described in Section 7.1

Cumulative summary tabulations of exposure by age/sex and by racial group are presented in Table 3 and Table 4 respectively.

Table 3 Cumulative subject exposure to AZD1222 and AZD2816 from completed clinical trials by age and sex

Age range (years)	Number of subjects (VAXZEVRIA)			Number of subjects (AZD2816)		
	Male	Female	Total	Male	Female	Total
1-11	56	55	111	0	0	0
12-17	76	74	150	0	0	0
18-64	23720	24026	47746	1186	1065	2251
>=65	5538	4119	9657	330	253	583
Missing	70	29	99	0	0	0
Total	29460	28303	57763	1516	1318	2834

Data from completed clinical trials as of 28 December 2023. All dosed subjects are included. Gender is based on biological sex at birth in COV008 study. 216 participants received the fourth dose of AZD1222 in the 4th dose sub-study of COV003. These participants are not counted separately to avoid double-reporting. This summary table contains the participants in the following studies: COV001, COV002, COV003, COV004, COV005, COV006, COV008, D7220C00001, D8111C00002, D8110C00001, D8110C00010.

Table 4 Cumulative subject exposure to AZD1222 and AZD2816 from completed clinical trials by racial group

Racial group	Number of subjects (VAXZEVRIA)	Number of subjects (AZD2816)
American Indian or Alaska Native	1281	8
Asian	2569	57

Table 4 Cumulative subject exposure to AZD1222 and AZD2816 from completed clinical trials by racial group

Racial group	Number of subjects (VAXZEVRIA)	Number of subjects (AZD2816)
Black or African American	5194	714
Native Hawaiian or Other Pacific Islander	81	0
White	44227	1795
Other	1569	0
Multiple Categories Checked	1854	53
Missing	588	207
Total	57363 ^a	2834

Data from completed clinical trials as of 28 December 2023. Other race category includes multiple race categories. This summary table contains the participants in the following studies: COV001, COV002, COV003, COV004, COV005, COV006, COV008, D7220C00001, D8111C00002, D8110C00001, D8111C00010.

400 subjects from study COV004 were excluded as race was not collected in this study. 216 participants received the fourth dose of AZD1222 in the 4th dose sub-study of COV003. These participants are not counted separately to avoid double-reporting.

5.2 Cumulative and interval patient exposure from marketing experience

5.2.1 Post-approval (non-clinical trials) exposure

The post-marketing patient exposure data in this report is presented by number of doses distributed and doses administered. All exposure is intended for the same indication and route of administration.

For doses distributed, this information has been provided below in section 5.2.1.1 and it includes dose distribution information across all markets, those where AstraZeneca is the Marketing Authorisation Holder (MAH) and those supported by the licence partners (SII, R Pharm, and Fiocruz).

For doses administered to vaccinees, this is a more accurate measure of vaccinee exposure and provides more detailed vaccinee-level data (eg, gender and age category). Therefore, AstraZeneca has been collecting data from respective health databases where VAXZEVRIA is administered.

Exposure data based on doses administered to vaccinees in specific countries/regions are provided in Section 5.2.1.2 below.

5.2.1.1 Patient Exposure – Dose distributed

During this reporting period, the global post-marketing patient exposure (by doses distributed) to VAXZEVRIA was estimated to be over 5.9 million doses (0.20% of cumulative).

The cumulative global post-marketing patient exposure (by doses distributed) to VAXZEVRIA, since launch to 30 December 2023, have been estimated to be over 2.99 billion doses.

The regional dose distribution data is presented in Table 5.

Table 5 VAXZEVRIA exposure, based on doses distributed, by Region

Region ^b	Exposure by doses distributed			Percentage (%)	
	Cumulative (Up to previous DLP 28 December 2022)	Interval (01 January 2023 to 30 December 2023)	Cumulative (Up to 30 December 2023)	Interval	Cumulative
Europe	24,81,97,720	0	24,81,97,720	0	8.28
International	68,03,70,580 65,03,70,580 ^c	0	65,03,70,580	0	21.70
North America	3,32,67,900	0	3,32,67,900	0	1.11
Japan	6,27,20,740	0	6,27,20,740	0	2.09
Serum Institute of India ^a	1,74,57,73,940	59,39,380	1,75,17,13,320	0	58.46
Fiocruz ^a	20,99,57,440	0	20,99,57,440	0	7.01
R-Pharm ^a	1,03,58,700	0	1,03,58,700	0	0.35
BKT ^a	3,00,00,000	0	3,00,00,000	0	1.00
Total	3,02,06,47,020 2,99,06,47,020	59,39,380	2,99,65,86,400	0	100

^a Serum Institute of India data is as of March 2023, Fiocruz data is as of October 2022, R-Pharma data is as of November 2022, BKTa data is as of November 2022.

^b Where AstraZeneca (AZ) is the Marketing Authorisation Holder, dose volumes cited represent doses dispatched from AZ manufacturing sites and contracted manufacturing sites. The destinations noted 'Region' represent what is known at the time of dispatch. Country to country donations may or may not be reflected dependent on the timing and type of donation.

^c Note: In the previous PBRER with DLP 28 December 2022, the overall cumulative exposure numbers represented under "International" was incorrect (680370580 changed to 650370580) and hence, the cumulative numbers (until previous DLP) were recalculated to reflect the correct exposure (3020647020 changed to 2990647020).

The dose distributed of reporting interval is derived by subtracting the previous report's cumulative from current cumulative values (Current Cumulative - Previous Cumulative = Current Interval) across all the Regions.

BKT Biokangtai; DLP Data Lock Point.

A more detailed breakdown of doses distributed across the countries within the EU can be found in Appendix 6.

5.2.1.2 Post-marketing patient exposure data for reporting period and cumulatively

AstraZeneca has obtained exposure data based on doses administered to vaccinees in EU, Afghanistan, Argentina, Australia, Bangladesh, Brazil, Canada, Chile, Colombia, Ecuador, Ghana, Guatemala, India, Iran, Iraq, Japan, Lebanon, Malaysia, Mexico, Nepal, New Zealand, Peru, Philippines, Saint Lucia, South Korea, Taiwan, Thailand, UK and Uruguay. This information is summarised in Table 6 below and it represents the interval and cumulative exposure (by doses administered). This data has either been provided to AstraZeneca directly from Government bodies or has been sourced from country specific websites.

Administration data from the licence partners (SII, Fiocruz and R-Pharm) have not been provided to AstraZeneca directly.

Please note that administration in other markets where VAXZEVRIA is authorised has not yet been made available to AstraZeneca. As such, the doses administered presented in this report is less than the doses distributed. The cumulative global post-marketing patient exposure (by doses administered) to VAXZEVRIA, since launch to 30 December 2023, have been estimated to be over 2.36 billion doses.

Negative values under the reporting interval indicate dose corrections or alignment of the missing data by certain countries (within a region (eg, EU)). This is due to the fact that administered data for specific time period, age group and dose was not published by many health authorities. Therefore, administered data for the PBRER reporting interval is derived by subtracting the current cumulative data with the previous report's cumulative values (Current Cumulative - Previous Cumulative = Current Interval) across all the Countries.

Most of the countries stopped publishing the exposure numbers and in many countries the product was not dispatched or administered since August 2022. However, exposure numbers reflecting under reporting interval are based on data published in health authority database. Thus, the derived interval exposure calculated, may not be a true reflection of the doses administered during the reporting interval.

Table 6 VAXZEVRIA interval and cumulative exposure based on doses administered, by Region/Country

Region	Interval			Cumulative			Percentage (%)	
	Dose 1	Dose 2	Dose3/ Dose 4/ Booster	Dose 1	Dose 2	Dose3/ Dose 4/ Booster	Interv al	Cumul ative
European Union*	-14816	-14795	21999	38921043	29815982	53950	-0.083	2.910

Table 6 VAXZEVRIA interval and cumulative exposure based on doses administered, by Region/Country

Region	Interval			Cumulative			Percentage (%)	
	Dose 1	Dose 2	Dose3/ Dose 4/ Booster	Dose 1	Dose 2	Dose3/ Dose 4/ Booster	Interval	Cumulative
United Kingdom	0	0	0	24725401	24141350	59155	0	2.070
Afghanistan		0			975338		0.000	0.041
Australia	0	0	0	6710682	6644072	479167	0	0.585
Philippines		1796112			23931246		20.531	1.012
India		4206681			1749417978		48.086	74.009
Canada	-2684	-968	41	2233943	576120	1829	-0.039	0.119
Argentina	2442	3454	6872	10184070	9947533	6650638	0.138	1.133
Bangladesh	76	2058	36891	20769467	19505767	16005534	0.423	2.381
Colombia	269035	375720	415620	6030298	4261806	2455414	11.500	0.539
Ecuador	17	12	174	1764566	1470117	5039182	0.002	0.350
Iran	0	0	0	5601073	5045996	3779468	0	0.610
Japan	11	43	0	58700	59203	0	0.001	0.005
Brazil	76768	164566	1764497	62346597	56605568	34627963	21.754	6.497
Chile	-16	-6	-76	410029	139637	2656524	-0.001	0.136
Guatemala	640	836	719	2038728	1613090	838201	0.024	0.190
Ghana		0			10545038		0.234	0.446
Lebanon		7328			730198		0.001	0.031
Iraq		0			717233		0.000	0.030
Mexico		0			49783383		0.000	2.106
Malaysia	-56	65	188	2047926	2027769	1631991	0.002	0.241
Nepal	0	0	0	5506364	4789110	4703764	0.000	0.635
Peru	2666	3253	79730	2247245	2113704	3827508	0.929	0.346
Saint Lucia	0	0	0	37850	34810	0	0.000	0.003
Taiwan		368			15298079		0.004	0.647
Thailand	2112	2011	10024	14100757	28684215	5933269	0.153	2.061
New Zealand	4	2	7	3321	3648	2083	0.000	0.000
South Korea		-3			20348870		0.000	0.861
Uruguay	463	425	180	47150	44879	359	0.012	0.004
Grand Total		9220690			2363802948		100	100

The data cut off for Iraq is 29 August 2021

The data cut off for Afghanistan is 30 April 2022

The data cut off for United Kingdom is 12 September 2022

The data cut off for Nepal is 25 September 2022

The data cut off for Saint Lucia is 18 October 2022

The data cut off for Mexico is 30 December 2022

The data cut off for Thailand is 10 March 2023

The data cut off for Philippines is 30 September 2023

The data cut off for Peru is 31 August 2023

The data cut off for Ecuador is 16 March 2023

The data cut off for Canada is 03 December 2023

The data cut off for New Zealand is 02 May 2023

The data cut off for Ghana is 30 November 2023

The data cut off for EU is 01 October 2023. *EU - AZ vaccine administration data for Germany is not available

The data cut off for Iran 20 August 2023

The data cut off for South Korea is 23 December 2023

The data cut off for Australia is 21 December 2022

The data cut off for Taiwan is 17 September 2023

The data cut off for Japan is 24 December 2023

The data cut off for Chile is 10 August 2023

The data cut off for Guatemala is 24 December 2023

The data cut off for Brazil is 29 December 2023

The data cut off for Argentina, Colombia, Malaysia, Bangladesh, India, Lebanon and Uruguay is 28 December 2023

A more detailed presentation of doses administered by country/states as well as vaccine administration by dose number, age and/or gender were provided for specified countries can be found in Appendix 6. However, a summary of the post-marketing patient exposure by age and gender (as currently available) is presented in Table 7 and Table 8, respectively.

A request has been received from Pharmacovigilance Risk Assessment Committee (PRAC) (Procedure number: EMEA/H/C/PSUSA/00010912/202212) as part of the review of the previous PBRER data lock point (DLP) 28 December 2022 where, the MAH is requested to provide estimated exposure data for other countries such as African countries, if available. The exposure data is available for Ghana until 30 November 2023 and is included within Table 6. For the rest of the African countries, data is unavailable.

Table 7 presents the vaccine doses administered by Age Group for the following specific countries:

Australia, Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and UK.

Table 7 Vaccine Doses Administered by Age Group (EEA and UK)

Age Group	Interval				Cumulative			
	Dose 1	Dose 2	Total	Percentage (%)	Dose 1	Dose 2	Total	Percentage (%)
18-24	-18931	-15994	-34925	120.005	1032510	881248	1913758	1.735
25-49	-27749	-25402	-53151	182.631	13705733	12558664	26264397	23.808
50-59	-13690	-12977	-26667	91.62972889	10767860	10107292	20875152	18.923
60-69	-18004	-22785	-40789	140.153936	17344813	16684714	34029527	30.847
70-79	54174	52886	107060	-367.86585	10155275	9951905	20107180	18.227
≥80	9087	9208	18295	-62.863	1934900	1892782	3827682	3.470
Unknown	538	536	1074	-3.690	1728250	1570905	3299155	2.991
Total	-14575	-14528	-29103	100	56669341	53647510	110316851	100

The total doses administered by Age group do not reflect the total doses administered that appear in Table 6. This is due to the fact that doses administered by Age group are not available for all countries that have provided vaccine administration information.

EEA European Economic Area; UK United Kingdom

Table 8 present the vaccine doses administered by Gender Group for the following specific countries:

- United Kingdom**

Table 8 Vaccine Doses Administered by Gender Group

Gender group	Total doses administered		Percentage (%)
	Interval	Cumulative	Cumulative
Male	0	22377923	45.74
Female	0	23252503	47.53
Unspecified	0	3295480	6.74
Total	0	48925906	100

The total doses administered by Gender group does not reflect the total doses administered that appears in Table 6. This is due to the fact that doses administered by Gender group is not available for all countries that have provided vaccine administration information.

For current reporting period UK data was available and Australia data was not available as per gender group

Exposure by doses administered is used as part of Observed versus Expected (O/E) Analyses, refer to Appendix 8 for further details. Based on the trend analysis performed most of the cases are reported until December 2022 and the exposure numbers are also mostly available until December 2022 in most of the countries, we have used observed case count and exposure numbers until December 2022 for O/E analysis.

5.2.2 Post-approval use in special populations

It is not possible to provide an estimate of patient numbers exposed from post-approval use in special populations.

5.2.3 Other post-approval use

AstraZeneca is not aware of any patterns of use (for example overdose, drug abuse, misuse or off-label use) of VAXZEVRIA considered to be relevant for the interpretation of safety data.

6 DATA IN SUMMARY TABULATIONS

6.1 Reference information

The Medical Dictionary for Regulatory Activities (MedDRA), version 26.1 has been used for coding adverse events (AEs). The summary tabulations are arranged in the internationally agreed order by primary MedDRA System Organ Class (SOC) and refer to the Preferred Term (PT) level.

6.2 Cumulative summary tabulations of serious adverse events from clinical trials

A cumulative summary tabulation of serious adverse events (SAEs) from AstraZeneca-sponsored interventional clinical trials that have been reported during the VAXZEVRIA clinical development programme, from the Development International Birth Date (DIBD) to the DLP (28 December 2023), organised by SOC, is presented in Appendix 2.

A summary of the total number of case reports with SAEs from VAXZEVRIA clinical trials along with the total number of SAEs for each treatment is provided in Table 9. Compared to the previous interval, there is a decrease in the case and event counts for the current reporting interval. This is due to decreased vaccine uptake in many regions, compared to the previous intervals and most of the reports received during the current reporting interval were also related to vaccinations in the earlier reporting interval.

Table 9 Summary tabulation of SAE case reports received from VAXZEVRIA (AZD1222) and AZD2816 clinical trials^a

Treatment	Previous PBRER Interval (29 December 2022 – 28 December 2022)		Current PBRER reporting interval (29 December 2022 – 28 December 2023)		Cumulative (Through 28 December 2023)	
	Number of Cases	Number of Serious Adverse Events	Number of Cases	Number of Serious Adverse Events	Number of Cases	Number of Serious Adverse Events
AZD1222	1011	1130	1221	1435	2198	2523

Table 9 Summary tabulation of SAE case reports received from VAXZEVRIA (AZD1222) and AZD2816 clinical trials^a

Treatment	Previous PBRER Interval (29 December 2022 – 28 December 2022)		Current PBRER reporting interval (29 December 2022 – 28 December 2023)		Cumulative (Through 28 December 2023)	
	Number of Cases	Number of Serious Adverse Events	Number of Cases	Number of Serious Adverse Events	Number of Cases	Number of Serious Adverse Events
AZD2816 ^c	5	5	25	27	40	42
MENACWY	84	92	43	46	140	151
Meningococcal Group B Vaccine	1	1	-	-	5	6
Placebo	531	599	519	597	1614	1876
Study procedure	4	4	3	3	13	16
Total^b	1636	1831	1786	2081	2216	4614

^a Numbers presented in this table will not match those presented in Appendix 2, Table 1 due to differences in the date that the table and appendices were generated from the AstraZeneca Global Safety database.

^b AZD2816 is a vaccine developed from AZD1222 targeting variants of SARS-CoV-2. AZD2816 is used in Study D7220C00001 which is further described in Section 7.1

^c Cases may have more than one treatment listed. Therefore, the sum of cases and SAEs will exceed the total. There is an increase in the CT cases, this is because the D8111C00010 was unblinded and the cases were edited to add the treatment allocation. This is the reason for spike in the cases.

A review of Table 1 of Appendix 2 has been completed for the PBRER period from 29 December 2022 to 28 December 2023 and there are no noteworthy changes in the absolute frequency numbers from the previous PBRERs.

6.3 Cumulative and interval summary tabulations from post--marketing data sources

Cumulative and interval summary tabulations of adverse reactions (ie, AEs considered as “a reasonable possibility of a causal relationship between the medicinal product and the event” for Table 2 Appendix 2) that have been reported from marketed experience with VAXZEVRIA, from the IBD to the DLP, organised by SOC, are presented in Appendix 2, Table 2.

A summary of the total number of VAXZEVRIA case reports and corresponding AEs/SAEs received from Spontaneous sources for both the interval and cumulative periods is provided in Table 10. Compared to the previous interval, there is a decrease in the case and event counts for the current reporting interval. This is due to decreased vaccine uptake in many regions, compared

to the previous intervals and most of the reports received during the current reporting interval were also related to vaccinations in the earlier reporting interval.

Table 10 Summary tabulation of VAXZEVRIA case reports and adverse events received from spontaneous sources^a

Case/Event Seriousness	Previous PBRER Interval (29 June 2022 to 28 December 2022)		Current PBRER Interval (29 December 2022 to 28 December 2023)		Cumulative to 28 December 2023	
	Number of Cases	Number of Adverse Events	Number of Cases	Number of Adverse Events	Number of Cases	Number of Adverse Events
Serious	10689	34706	5827	28003	269863	1000099
Non-Serious	49237	210221	16172	73447	560153	2151280
Not available/ Not entered	0	0	0	0	2	0
Total	59926	244927	21999	101450	830018	3151379

^a Numbers presented in this table will not match those presented in Appendix 2 due to differences in the date that the table and appendices were generated from the AstraZeneca Global Safety database.

In the post-marketing experience, there are fewer cases compared to last reporting interval. This is due to the decreased uptake of VAXZEVRIA in many regions.

A review of Table 2 Appendix 2 has been completed for the PBRER period from 29 December 2022 to 28 December 2023 and there are no noteworthy changes in the absolute frequency numbers from the previous PBRERs.

AstraZeneca has conducted a review of core listedness for VAXZEVRIA. The CDS has been compared with the listed PTs in AstraZeneca's global safety database, where these terms control the automatic expedited submission of reports including unexpected adverse events to Health Authorities globally.

The review identified some discrepancies between the CDS and the listed terms in the database. This divergence has been remedied by the removal of 43 PTs previously considered listed from the metadata specification in the AstraZeneca global safety database. In the majority, these PTs have been reported in cases originating from Health Authorities.

A review of the impacted cases was conducted by the AstraZeneca surveillance team and no new signal or safety concern has been identified.

Please see Appendix 13 for the list of PTs..

6.3.1 Lack of efficacy from Post-Marketing

Interval Period (29 December 2022 – 28 December 2023)

A search of the AstraZeneca Global Safety database for the reporting interval using the Lack of Efficacy standardised MedDRA query (SMQ), retrieved 342 reports with the following 350 AEs (PTs): Drug ineffective (271), Vaccination failure (49), Therapeutic product effect decreased (10), Therapeutic product effect incomplete (7), Disease progression (6), Therapeutic response shortened (2) and Therapy non-responder, Treatment failure, Device defective, Therapeutic response decreased and therapeutic product ineffective (1, each).

Of the 342 reports, 137 (40.0%) were medically confirmed (MC) and the remaining 205 (60.0%) were consumer reports. 296 of the 342 reports were initial and 46 were follow-ups (FU). A total of 233 (68.1%) reports were considered serious due to the AE being considered medically important (184), required hospitalization (36), was life threatening (LT) (3), resulted in disability (4), and/or resulted in death (6). Cases may have met more than one seriousness criteria. The remaining 109 (31.9%) reports were non-serious (NS). Of the 342 reports, 111 (32.5%) were reported from Canada followed by Germany (17%, n=58), Australia (14%, n=48), UK (10.5%, n=36), Portugal (4.4%, n=15), France (3.2%, n=11) and Spain and Austria (2.6%, n=9). No trend in reporting pattern was observed from these countries.

There were 10 fatal cases in the reporting interval. Age of the vaccinees were reported in 8 cases (4 female and 4 male) with a median age of 64 years (44 to 87 years). In 7 cases, events were reported only after 6 months of vaccination. Of the remaining three cases, in one case lack of effect lead to hospitalization with breakthrough COVID-19 infection and other two cases drug ineffective is reported with no details on events or information on COVID-19 infection. Cause of death PTs (≥ 2) included: COVID-19 pneumonia (5), Vaccination failure (5), COVID-19 (3), Thrombocytopenia (TCP) (2), Respiratory failure (2) and Antibody-dependent enhancement (2).

Of the 332 non-fatal cases, the outcomes were as follows: Not recovered (48), Recovered (44), Recovering with Sequelae (2), Recovering (16), and Unknown (222). The information of the lot/batch number was not available in 224 cases (65.5%) and no specific trend or pattern was observed upon review of cases with lot/batch numbers.

Information on COVID-19 testing was available in 113 reports; of these 105 (92.9%) were reported as COVID-19 test positive, 2 (1.8%) were reported as COVID-19 test negative and 6 (5.3%) were reported as unknown. Of the 105 cases reporting COVID-19 positive, 17 cases had a history of COVID-19 infection before vaccination and details on remaining 88 cases reports (including 44 with first dose, 36 with second dose, 1 with booster dose, and 7 with unknown dose) with a positive COVID-19 test are presented below. Most of them tested positive (60%) during the period of June 2021 to December 2022 (most of the cases reported COVID-19

infection approximately 6 months after vaccination). Information on virus genotype sequencing was available in only one case.

- In 44 (50%) of the 88 reports, COVID-19 test was positive after the receipt of the first dose of the vaccine; time to positive COVID-19 test was available for 32 (72.7%) cases and ranged from 132 to 780 Days with a median of 313 Days. In one case where vaccinee tested positive for COVID-19 after 290 Days of vaccination, genotyping assay was performed and confirmed omicron variant with the presence of the 417N mutation (absence of 484K and 452R mutations). In 11 (25%) reports, time to positive Covid-19 test after first dose of vaccine was unknown.
- In 36 (5.8%) reports, COVID-19 test was positive after the receipt of the second dose of the vaccine; time to positive COVID-19 test was available for 34 (94.4%) cases and the vaccinees tested positive between 23 to 913 Days of vaccination (with a median of 212 Days). In 2 (5.6%) reports, time to positive COVID-19 test after second dose of vaccine was unknown.
- In 1 (1.4%) report, COVID-19 test was positive after the receipt of the booster dose (different from the primary series) with an unknown time to positive COVID-19 test.
- In 7 (6.9%) reports, COVID-19 test was positive after the receipt of unknown dose of the vaccine.

Upon review of these cases, in most of the cases, the concern on vaccine efficacy (VE) was reported mostly after 6 months of vaccination and hence, no trend was observed with specific batch or lot.

Cumulative Review (29 December 2020 – 28 December 2023)

A cumulative search of the Global Safety database using the Lack of Efficacy SMQ, retrieved 25594 reports with the following 25627 PTs: Vaccination failure (23838), Drug ineffective (1515), Therapy partial responder (70), Therapeutic product effect decreased (44), Therapeutic product ineffective (31), Therapeutic product effect incomplete (24), Treatment failure (22), Disease progression (19), Therapeutic response shortened (13), Therapy non-responder (10), Therapeutic response decreased (10), Drug effect less than expected (5), Drug tolerance (4), Drug level decreased (3), Therapeutic product effect delayed (3), Drug resistance (2), Paradoxical drug reaction (2), Therapeutic reaction time decreased (2), Device defective (2), Therapeutic reaction time decreased (2), Drug resistance (2), Paradoxical drug reaction (2), Diet failure (1), Absence of immediate treatment response (1), Drug ineffective for unapproved indication (1), Therapeutic response changed (1), Remission not achieved (1), Drug level abnormal (1) and Therapeutic response delayed (1).

Of the 25594 reports, 24223 (94.6%) were MC and the remaining 1371 (5.4%) were consumer reports. A total of 23925(93.5%) reports were considered serious due to the AE being considered medically important (23131), the AE was reported to have resulted in disability (24), required hospitalization (531), was life threatening (76), and/or resulted in death (153). Cases may have

met more than one criterion for seriousness. The remaining 1543 (6%) reports were non-serious. Of the 25594 reports, 86.4% (22107) were reported from Austria. Cumulatively, there have been 169 fatal cases (note in few cases, the cause of death may not be related to lack of efficacy).

Of the 25425 non-fatal cases, the outcomes were as follows:

Not recovered (659), Recovered (872), Recovered with sequelae (11), Recovering (520), and Unknown (23263).

Conclusion

Review of all the lack of efficacy reports did not demonstrate any specific trend or safety information associated with use of VAXZEVRIA. There was a decrease in the number of case reports for lack of efficacy during this interval (342) compared to the previous PBRER (2716) covering the period 29 June 2022 to 28 December 2022.

Cumulatively, of the 25594 lack of efficacy reports, there have been 169 fatal cases. Of the 25594 reports, 86.4% (22107) were reported from Austria. This is due to a local reporting system where cases from the epidemiological reporting system for COVID-19 are linked with the vaccination passport and submitted to EudraVigilance/AstraZeneca in bulk.

6.3.2 Fatal events, including case reports involving Preferred Term of Sudden Death

6.3.2.1 Fatal Events

Interval Review (29 December 2022 to 28 December 2023)

A total of 461 fatal cases were retrieved during the reporting period (29 December 2022 to 28 December 2023) which includes 146 (32%) of initial case reports and 315 (68.3%) FU reports. Two cases were excluded from analysis as they were considered as potentially duplicated. In 31.8% of initial cases, reportedly the exposure to vaccine occurred in the previous reporting intervals and as these cases were reported to AstraZeneca during the current reporting interval, considered under interval data analysis. Most of fatal cases were received from UK (n=121, 26.4%), Brazil (n=76, 16.6%), United states (n=60, 13.1%), Germany (n=36, 7.8), Philippines and Canada (n=22, 4.8%, each). Around 53 (88.3%) cases from United States (US) were from a single completed Study ID: D8110C00001 and the new information received during the reporting interval was the unblinding information.

Of these 459 fatal cases, in 353 (77%) cases, the vaccinees' age was reported and in 106 (23%) cases, age was unknown (See Table 11). In 147 (32%) of 459 cases, the vaccinees were aged 65 years and above. The median age was 62 years. The gender was reported in 427 (93%) vaccinees; 249 (58.3%) were male and 178 (41.7%) were female. Of the 459 case reports 274 (59.6%) were MC and 185 (40.4%) were consumer reports.

During the reporting period, in 18 cases, events with fatal outcome were reported after booster doses [Dose 3 (n=16) and Dose 4 (n=2)]. The cases were reported from UK (n=8), Philippines (n=5), Brazil and Greece (n=2, each) and Canada (n=1). In one case, the patient received Ribonucleic Acid (mRNA) vaccine as booster (different booster vaccine from the primary vaccine or primary vaccination series) and in 16 cases the patient received unknown booster dose. Of the 459 cases, 5 (1.1%) were reported with sudden Death. Case reports of Sudden Death are included in the overall number of cases with fatal outcome and are discussed in Section 6.3.2.2.

Distribution of fatal cases per age group during the reporting interval is presented in Table 11.

Table 11 Fatal cases per age group (in years)

Age group	Number of cases (%)
18-29	15 (3.3)
30-39	32 (7)
40-49	44 (9.6)
50-59	58 (12.6)
60-69	95 (20.7)
70-79	69 (15)
≥80	40 (8.7)
Unknown	106 (23.1)
Grand total	459

Percentage is calculated based on the known values.

Information regarding comorbid conditions was available in 205 (44.7%) out of 459 cases. Important comorbid conditions included hypertension (n=56), Obesity (n=31), diabetes mellitus (n=26), myocardial ischemia (n=17), Atrial fibrillation and Osteoarthritis (n=10, each), COVID-19 and asthma (n=9, each), coronary artery disease, Hyperlipidaemia, Chronic Obstructive Pulmonary Disease (COPD) (n=8, each), and chronic kidney disease and cerebrovascular accident (CVA) (n=7, each).

Most of the cases are reported in vaccinees over 60 years of age group and around 44.4% were elderly age group. The time of vaccination and onset of event with fatal outcome, was available in 326 cases (71%) and in 49% of the cases event with fatal outcome was reported beyond the risk window (RW) of 42 Days. Of the remaining 51% cases, most of the cases were confounded by underlying medical condition or concomitant therapy or COVID-19 infection. The median TTO of event to fatal outcome is 12 Days (range: 0-859 Days).

Out of 459 cases, the cause of death was not reported in 51 (17%) case reports. The reported cause of death in remaining 386 fatal case reports are presented in Table 12 (Note: In some

cases, a single most relevant cause of death could not be determined due to insufficient information. Also, one case might have multiple causes of death).

Table 12 **Reported cause of death in Fatal Cases with VAXZEVRIA (n = 386) during the Interval period: 29 December 2022 – 28 December 2023**

Cause of Death	Fatal cases ^a
Cardiorespiratory causes (includes Sudden cardiac death, Pulmonary embolism, Myocardial Infarction, Dyspnoea, Acute respiratory failure, Acute myocardial infarction, Cardiac arrest, Cardio-respiratory arrest, Acute coronary syndrome, Respiratory failure, Coronary artery disease, Severe acute respiratory syndrome, Acute respiratory distress syndrom etc)	166
Thrombosis with Thrombocytopenic syndrome ^b	51
(Including haemorrhage)	30
(Including cerebral venous thrombosis (CVST))	29
(Including Ischaemic stroke)	4
(Including Cerebral venous thrombosis (CVT))	1
(Including intraabdominal thrombosis)	4
(Including pulmonary embolism)	9
Infection	46
Gastrointestinal causes	13
Malignancy	24
Thrombocytopenia	24
Multiple organ failure	10
Seizure	10
Thrombocytopenia with haemorrhage	9
Thrombosis (without thrombocytopenia)	9
Cerebrovascular accident without reported thrombocytopenia	9
Cerebral haemorrhage	5
Guillain Barre Syndrome	5
Renal dysfunction	4
Hepatic failure	1
Aneurysm	1
Anaphylaxis/ Hypersensitivity	1
Pancreatitis	1
Others	52

^a The cause of death is either grouped by event and their symptoms or related diseases. In some cases, single most relevant cause of death could not be determined due to insufficient information. Note: 53 cases were from a single Study: D8110C00001 and unblinding information was the only new information received during the reporting interval.

^b The 6 subsets of Thrombosis with Thrombocytopenic syndrome (TTS) were placed in the brackets.

CVST Cerebral venous sinus thrombosis, CVT Cerebral venous thrombosis

Of the 166 cases reports with cardiorespiratory causes, 90 (54.2%) cases were confounded by advanced age and underlying medical condition. The most frequent cause of death included Hypertension (n=23), Myocardial infarction (n=17), Diabetes mellitus (n=14), COPD and Coronary artery disease (n=6) and Dyspnoea (n=4). Of the 46 case reports where infections were reported as the cause of death, 78.2% reported Sepsis, COVID-19 infection and COVID-19 Pneumonia as the cause of death.

Additionally, a literature article by Nafilyan et al 2023 assessing the risk of cardiac and all-cause mortality in young people is summarized in Section 11.

Among the cases reporting fatal outcome during the reporting interval and the literature review, no specific pattern regarding underlying conditions or cause of death could be identified. In the cases reporting fatal outcome post booster dose, there was insufficient information on dates of vaccination, medical history, and cause of death in many reports.

Cumulative Review (29 December 2020 – 28 December 2023)

Cumulatively from 29 December 2020 to 28 December 2023, there have been 7180 fatal cases. Out of 7180 cases, age of vaccinees was reported in 5912 cases (82.3%) and was unknown in 1268 cases (17.7%). In 3021 (51%) of the 5912 case reports, the vaccinees were aged 65 years and above. The median age of the fatal cases was 63.5 years. Out of 7180 cases, gender was reported in 6769 cases (94.3%). There were 3048 females (45%) and 3721 males (55%).

Cumulatively, of the 7180 case reports with fatal outcome, 4397 (61.2%) were MC and 2783 (38.8%) were consumer reports. Cumulatively, 64 fatal cases were reported with booster dose, and 18 cases are already discussed under reporting period analysis. The remaining cases had insufficient information on relevant medical history and cause of death. Of the 7180 cases, 403 (5.6%) were reported as sudden Death. Case reports of sudden Death, see Section 6.3.2.2, are included in the overall number of cases with fatal outcome.

Cumulative O/E analyses were conducted for fatal cases and were stratified by age group and gender where administration data was available. Reference for background (BG) estimates obtained from the literature are provided in Appendix 9. The O/E analysis of fatal reports showed that observed cases occurred significantly less frequently than the expected for all the ages and by different age stratifications from European Economic Area (EEA) + UK + Brazil + and Australia. Results of the O/E analyses are presented in Table 13, Table 14 and Table 15. Conservatively, the exposure for global reports until December 2022 (466115644) is based on doses administered in 13 regions/markets as explained in Appendix 8. Exposure was considered until December 2022 as exposure to vaccinee reduced during the reporting period.

Table 13 Observed versus expected analyses for Fatal cases overall

Medical Concept	Observed cases	Expected cases	Risk Window	BG rate/100,000 person years	Rate ratio (CI 95%)	Conclusion
Fatal Reports RW 42 ^a	3914	196040.6	42	365.75	0.02 (0.02 - 0.02)	Observed significantly < expected
Fatal Reports RW42 + Unk TTO	6259	196040.6	42	365.75	0.03 (0.03 - 0.03)	Observed significantly < expected

^a Includes global reports irrespective of age and gender.

Global exposure was 466115644 (until 28 December 2022).

BG Background; CI Confidence Interval, RW Risk Window, TTO Time to onset, Unk Unknown.

Table 14 Observed versus expected analyses for Fatal cases by age group from EU+UK+Brazil+Australia region

Medical Concept	Age Group	Risk Window	BG rates	Exposure	Observed cases ^b	Expected cases	Rate ratio (CI 95%)	Conclusion
Fatal Reports ^a (from EU+UK +Brazil+ Australia)	18 – 49 RW 42	42	65.86	110094983	453	8337.9	0.05 (0.05 - 0.06)	Observed significantly < expected
	50 – 59 RW42	42	193.2	58336094	428	12960.2	0.03 (0.03 - 0.04)	Observed significantly < expected
	60 – 69 RW42	42	314.82	57960860	806	20982.9	0.04 (0.04 - 0.04)	Observed significantly < expected
	70+ RW 42	42	1010.74	32376365	1256	37630.1	0.03 (0.03 - 0.04)	Observed significantly < expected
	18 – 49 RW 42 + Unk TTO	42	65.86	110094983	673	8337.9	0.08 (0.07 - 0.09)	Observed significantly < expected
	50 – 59 RW42 + Unk TTO	42	193.2	58336094	533	12960.2	0.04 (0.04 - 0.04)	Observed significantly < expected

Table 14 Observed versus expected analyses for Fatal cases by age group from EU+UK+Brazil+Australia region

Medical Concept	Age Group	Risk Window	BG rates	Exposure	Observed cases ^b	Expected cases	Rate ratio (CI 95%)	Conclusion
	60 – 69							
	RW42 + Unk TTO	42	314.82	57960860	973	20982.9	0.04 (0.04 - 0.05)	Observed significantly < expected
	70+							
	RW 42 + Unk TTO	42	1010.74	32376365	1586	37630.1	0.04 (0.04 - 0.04)	Observed significantly < expected

^a Fatal report O/E by age group is based on cases reported from EU+UK+Brazil+Australia, as corresponding exposure was only available from this region.

^b Includes cases reported within risk window of 42 Days.

BG background; CI Confidence Interval; EU European Union, RW Risk window; TTO Time To Onset, UK United Kingdom.

Table 15 Observed versus expected analyses for Fatal cases by age group in UK

Medical Concept	Age Group	Risk window in Days	BG rates	Exposure	Observed cases ^b	Expected cases	Rate ratio (CI 95%)	Conclusion
	18-29 (RW 42) UK	42	28.22	1918869	25	62.3	0.4 (0.26 - 0.59)	Observed significantly < expected
	30-39 (RW 42) UK	42	48.8	3308256	33	185.7	0.18 (0.12 - 0.25)	Observed significantly < expected
	40-49 (RW 42) UK	42	100.86	8954709	74	1038.6	0.07 (0.06 - 0.09)	Observed significantly < expected
Fatal Reports ^a (from UK)	50-59 (RW 42) UK	42	193.2	12455887	134	2767.3	0.05 (0.04 - 0.06)	Observed significantly < expected
	60-69 (RW 42) UK	42	314.82	9718273	155	3518.2	0.04 (0.04 - 0.05)	Observed significantly < expected
	70-79 (RW 42) UK	42	553.23	5580432	204	4207.2	0.05 (0.04 - 0.06)	Observed significantly < expected

Table 15 Observed versus expected analyses for Fatal cases by age group in UK

Medical Concept	Age Group	Risk window in Days	BG rates	Exposure	Observed cases ^b	Expected cases	Rate ratio (CI 95%)	Conclusion
	80+ (RW 42) UK	42	1638.26	2655389	282	5002.4	0.06 (0.05 - 0.06)	Observed significantly < expected
	18-29 (RW 42+Unk) UK	42	28.22	1918869	37	62.3	0.59 (0.42 - 0.82)	Observed significantly < expected
	30-39 (RW 42+Unk) UK	42	48.8	3308256	57	185.7	0.31 (0.23 - 0.4)	Observed significantly < expected
	40-49 (RW 42+Unk) UK	42	100.86	8954709	105	1038.6	0.1 (0.08 - 0.12)	Observed significantly < expected
	50-59 (RW 42+Unk) UK	42	193.2	12455887	175	2767.3	0.06 (0.05 - 0.07)	Observed significantly < expected
	60-69 (RW 42+Unk) UK	42	314.82	9718273	202	3518.2	0.06 (0.05 - 0.07)	Observed significantly < expected
	70-79 (RW 42+Unk) UK	42	553.23	5580432	247	4207.2	0.06 (0.05 - 0.07)	Observed significantly < expected
	80+ (RW 42+Unk) UK	42	1638.26	2655389	326	5002.4	0.07 (0.06 - 0.07)	Observed significantly < expected

^a Fatal report O/E by age group is based on cases reported from UK, as corresponding exposure was only available from this region.

^b Includes cases reported within risk window of 42 Days.

BG background rate CI Confidence Interval; UK United Kingdom, Unk Unknown.

6.3.2.2 Case reports involving PT of Sudden Death

Interval Review (29 December 2022 to 28 December 2023)

During the reporting period, 5 cases (4 Male and 1 Female) of sudden death/sudden cardiac death were reported. Age was reported in three cases (2 male: 66 years; 60 years and 1 female: 96 years).

- First case (Clinical trial, MC) refers to a female patient (96 years) with a medical history of atrial fibrillation received VAXZEVRIA (Dose 1) and after 112 Days patient died of sudden cardiac death. The event was considered as not related to study medication.
- Second case (Spontaneous, consumer report) refers to a male patient (age unknown) with a medical history of thrombocytosis received two doses of VAXZEVRIA and received Dose 3 with m-RNA COVID-19 vaccine after 6 months. On an unknown date after Dose 3, patient experienced sudden death. The event was considered as not related to VAXZEVRIA.
- Third case (Regulatory, consumer report) refers to a 66 year-male patient with a medical history of arteriosclerosis, hypertension, angina pectoris and stent placement died after 3 Days of Dose 1 of VAXZEVRIA. It was unknown if autopsy was performed, and the case is confounded by underlying condition.
- Fourth case (Regulatory, consumer report) refers to a 60 year-male patient who is a chain smoker, received two doses of VAXZEVRIA and booster dose with mRNA (different from primary series). Patient experienced sudden death after 612 Days. It was unknown if autopsy was performed.
- Fifth case (Regulatory, consumer report) refers to a male patient with unknown medical history received VAXZEVRIA had reported sudden death after 15 Days of vaccination. It was unknown if autopsy was performed.

In three cases, the cause of death was not related to VAXZEVRIA and in two cases information on clinical course of the event leading to death were not provided. No new safety information was identified based on these 5 new cases.

Cumulative Review (29 December 2020 – 28 December 2023)

Cumulatively between 29 December 2020 to 28 December 2023, out of 403 cases, 22 (55.1%) cases containing the PT of sudden death (one case with AEs sudden death and sudden cardiac death), 180 (44.6%) case containing the PT of sudden cardiac death and 1 (0.3%) case reported with sudden unexplained death in epilepsy.

Of the 403 case reports with sudden death, 337 (83.6%) were MC and 66 (16.4%) were consumer reports. Gender of the vaccinees was reported in 399 cases. Around 152 (38.1%) vaccinees were female and 247 (61.9%) were male. Age of vaccinees ranged from 20 to 97 years with a median age of 65.4 years.

Of the 403 cases, TTO was available in 192 (47.6%) cases. Out of 192 cases, 59 cases (30.7%) had time to death ranged from 0 to 263 Days after receiving the first dose of the vaccine and 20 cases (10.4%) where time to death ranged from 0 to 612 Days after receiving the second dose.

Of the 403 cases of sudden death, the causes of death were identified in 255 cases (63.3%) and included the PTs of sudden cardiac death; dyspnoea; pulmonary embolism (PE); pyrexia; cardiac arrest; myocardial infarction; fatigue; acute myocardial infarction; cardio-respiratory arrest; hypertension; arteriosclerosis; myocardial ischaemia; malaise; arteriosclerosis coronary artery; headache; cardiac failure; loss of consciousness; coronary artery disease; COPD; pneumonia; circulatory collapse; coronary artery occlusion; respiratory failure; cardiac death; thrombosis; emphysema; pulmonary oedema; cardiovascular disorder; pain in extremity; chest pain; acute pulmonary oedema; aneurysm ruptured; syncope; deep vein thrombosis (DVT); arthralgia, aortic dissection, subarachnoid haemorrhage, aneurysm ruptured, contusion, cardiomegaly, multiple organ dysfunction syndrome, acute coronary syndrome, cardiovascular disorder, visceral venous thrombosis, cor pulmonale acute, respiratory arrest, hypertension, haemorrhage intracranial, dyspnoea, cardiac fibrillation, cerebral infarction, gastrointestinal (GI) haemorrhage, cerebrovascular accident, cardiac failure chronic, petechiae, coronary artery occlusion, coronary artery disease, sudden unexplained death in epilepsy, and circulatory collapse.

The medical history was reported in 270 cases (67%) (vaccinees may have had >1 comorbidity) and it includes hypertension, diabetes mellitus, coronary artery disease, COPD, tobacco user, type 2 diabetes mellitus, myocardial ischaemia, obesity, cerebrovascular accident, asthma, cardiac failure, myocardial infarction, atrial fibrillation, osteoarthritis, alcoholic, hypothyroidism, dyslipidaemia, essential hypertension, epilepsy, drug hypersensitivity and chronic kidney disease. The medical history was not reported in 133 (33%) cases.

In 67% of the cases, the cause of the deaths was due to pre-existing medical condition or risk factors. Upon review of the cases cumulatively, no new trend or pattern was observed in the cases reported with sudden death.

Table 16 Observed versus expected analyses for Sudden death

Medical Concept	Observed cases	Expected cases	Risk Window	BG rate/100,000 person years	Exposure	Rate ratio (CI 95%)	
Sudden death (RW7)	106	5251	7	58.78	466115644	0.02 (0.02 – 0.02)	Observed significantly < expected
Sudden death (RW7 + Unk TTO)	317	5251	7	58.78	466115644	0.06 (0.05 – 0.07)	Observed significantly < expected

Reference for sudden death IR is ACCESS Rates. Willame et al 2021 (A) (Meta-analysis IR from 2010-2013 – 2017-2019 – Sudden Death (Narrow))

BG Background; CI Confidence Interval; RW Risk Window; Unk Unknown; TTO Time to Onset

Conclusion

From the review of data available during the reporting period for all fatal case reports (including sudden death) and also taking into account the cumulative experience along with the O/E analysis of fatal cases, there is no new safety information identified on this topic in association with VAXZEVRIA.

7 SUMMARIES OF SIGNIFICANT FINDINGS FROM CLINICAL TRIALS DURING THE REPORTING PERIOD

7.1 Completed clinical trials

There were 10 (D7220C00001, COV001, COV002, COV003 including booster sub-study, COV004, COV005, COV006, COV008, D8110C00001, and D8110C00010) completed clinical trials during the reporting period. There were no additional clinically important emerging efficacy or safety findings obtained from the clinical trials completed during the reporting period.

D7220C00001 (A Phase II/III Partially Double-Blinded, Randomised, Multinational, Active-Controlled Study in Both Previously Vaccinated and Unvaccinated Adults to Determine the Safety and Immunogenicity of AZD2816, a Vaccine for the Prevention of COVID-19 Caused by Variant Strains of SARS-CoV-2): Phase II/III

This was an AstraZeneca-sponsored, multi-country Phase II/III study to evaluate the safety and immunogenicity of AZD2816, an AstraZeneca's candidate ChAdOx1 vector vaccine against SARS-CoV-2 variant strain B.1.351, as single-dose vaccination in previously vaccinated adult participants (AZD1222 or an mRNA COVID-19 vaccine) and as a 2-dose primary vaccination in previously unvaccinated adult participants (homologous AZD2816 vaccination and heterologous vaccination with AZD1222 as first dose). The participant population included adults ≥ 18 years of age. In both the single-dose booster treatment regimen and the 2-dose primary vaccination treatment regimen, participants received study intervention consisting of IM administration of either AZD1222 (5×10^{10} vp) or AZD2816 (5×10^{10} vp). Participants receiving a 2-dose primary vaccination were dosed at intervals of 4 weeks (for AZD1222 and AZD2816) or 12 weeks (AZD2816 only). All study participants were followed up for 180 Days after the administration of their last vaccination dose to collect safety related information.

A total of 1394 participants were randomised in the single-dose booster arms in previously vaccinated treatment regimen. Non-inferiority of booster doses of AZD1222 and AZD2816 was demonstrated for the primary and all key secondary endpoints. The humoral immune response to a booster dose of AZD1222 was non-inferior to the response elicited by primary vaccination with AZD1222 (AZD1222 cohort Geometric Mean Titer [GMT] ratio: 1.02 [95% CI 0.90, 1.14]; mRNA cohort GMT ratio: 3.47 [95% CI 3.09, 3.89]). Strong humoral responses to SARS-CoV-2 were observed by 28 Days after booster doses of either AZD1222 or AZD2816 in seronegative

participants previously vaccinated with AZD1222 or an mRNA vaccine. The safety (through Day 29), extended safety (through 6 months), and reactogenicity (through Day 8) of booster doses of AZD1222 or AZD2816 in participants previously vaccinated with either AZD1222 or an mRNA vaccine was consistent with the known safety profile of AZD1222 administered as a 2-dose primary series. No emergent safety issues were identified. There were no clinically meaningful differences between the safety profiles of booster doses of AZD1222 and AZD2816.

A total of 1449 previously unvaccinated participants were randomised and 1441 received at least one dose of AZD2816 or AZD1222 as primary series vaccination. The non-inferiority of AZD2816 was demonstrated for the co-primary and first key secondary endpoints. The GMT ratio for the comparison of the AZD2816 treatment group (4-week interval) against the Beta variant versus the AZD1222 treatment group against the Wuhan-Hu-1 strain was 1.19 (95% CI 1.08, 1.32) and the seroresponse difference was 1.7 (95% CI -3.1, 6.5). The GMT ratio for the comparison of the AZD2816 treatment group (4 week interval) against the Beta variant versus the AZD1222 treatment group against the Beta variant was 3.21 (95% CI 3.06, 3.36). The safety (through 29 Days post-dose), extended safety (through 6 months), and reactogenicity (through Day 8 post-dose) of AZD1222 and/or AZD2816 in previously unvaccinated participants was consistent with the known safety profile of AZD1222 administered as a 2-dose primary series. No emergent safety issues were identified. There were no clinically meaningful differences between the safety profiles across the treatment groups.

COV001 (A phase I/II study to determine efficacy, safety and immunogenicity of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19 in UK healthy adult volunteers): Phase I/II

COV001 was an Oxford-sponsored, single-blinded, multi-centre randomised, controlled Phase I/II trial assessing the safety, efficacy, and immunogenicity of ChAdOx1 nCoV-19 (VAXZEVRIA) in 1067 healthy adults 18 to 55 years of age in the UK. Trial participants were healthy and at increased risk for being exposed to the SARS-CoV-2 virus. Participants received either a single IM dose or a 2-dose IM regimen of the low dose (LD) ($\sim 2.5 \times 10^{10}$ vp) and/or the standard dose (SD) ($\sim 5 \times 10^{10}$ vp) of AZD1222 or the comparator, meningococcal vaccine (MenACWY). The participants were followed for 12 months from the last vaccination.

AZD1222, when administered as a 2- dose SD regimen, had a VE estimate of 77.68% and a lower bound of the 95% CI of 22.29%. These results should be interpreted cautiously due to the small population size and few COVID-19 cases. AZD1222 generated a strong humoral response.

Analyses of solicited AEs post-vaccine administration showed that AZD1222 was reactogenic and that reactogenicity reduced after the second dose compared with the first dose. Most AEs were mild or moderate, and no clinically meaningful imbalances between AZD1222 and control in SAEs were observed. Most of the events considered as related to AZD1222 by the investigator

were AEs that commonly observed following vaccine administration. Overall, AZD1222 had an acceptable safety profile.

COV002 (A phase II/III study to determine the efficacy, safety and immunogenicity of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19): Phase II/III

COV002 was an Oxford-sponsored, single-blinded, multi-centre, randomised, controlled Phase II/III trial assessing the safety, efficacy and immunogenicity of ChAdOx1 nCoV-19 (VAXZEVRIA) in 10,717 participants in the UK. Trial participants were ≥ 18 years of age. Participants were enrolled by age groups of 18 to 55 years, 56 to 69 years, and ≥ 70 years. Recruitment for this study focused on health care professionals and other adults with high potential for exposure to COVID-19. Participants received a single IM dose or a 2-dose IM regimen of the LD ($\sim 2.5 \times 10^{10}$ vp) and/or the SD ($\sim 5 \times 10^{10}$ vp) of VAXZEVRIA or the comparator, quadrivalent capsular group A, C, W, and Y meningococcal protein-polysaccharide conjugate vaccine (MenACWY), depending on the study group. The participants were followed for 12 months from the last vaccination.

The primary efficacy analysis resulted in a VE estimate of 74.34%, with a lower bound of the 95% CI of 62.39%. AZD1222 provided complete protection against COVID-19 hospital admission, severe disease, and death during the blinded period, with no cases observed. Overall, AZD1222 generated a strong humoral immune response.

Solicited local and systemic AEs were reported by 81.6% and 79.8% of evaluated participants, respectively, in the AZD1222 group and 63.2% and 71.3% of evaluated participants, respectively, in the control group. Most solicited local and systemic AEs and unsolicited AEs following any dose of AZD1222 were mild or moderate in severity, and most related AEs were mild or moderate in severity. Reactogenicity was reduced after the second dose compared with the first dose across all solicited AEs in the AZD1222 group. Most of the commonly reported unsolicited AEs were consistent with solicited AEs commonly observed following vaccination (eg, headache, fatigue, pyrexia) and were reported at a higher frequency in the AZD1222 group compared with the control group. No clinically meaningful imbalances in the incidence of SAEs were noted. Overall, VAXZEVRIA had an acceptable safety profile.

COV003 (A Randomised, Controlled, Phase III Study to Determine the Safety, Efficacy, and Immunogenicity of the Non-Replicating ChAdOx1 nCoV-19 Vaccine): Phase III

COV003 was an Oxford-sponsored, single-blinded, multi-centre, randomised, controlled Phase III trial assessing the safety, efficacy, and immunogenicity of ChAdOx1 nCoV-19 Vaccine (VAXZEVRIA) in 10,416 participants in Brazil. Trial participants were ≥ 18 years of age, who were healthy or have medically stable chronic diseases and were at increased risk for being exposed to the SARS COV- 2 virus. Participants were randomised to receive either a 2-dose

regimen of the SD ($\sim 5 \times 10^{10}$ vp) of VAXZEVRIA or MenACWY as the first dose and saline placebo as the second dose by means of an IM injection. In the main study, the participants were followed up for 12 months from the last vaccination. Approximately 7% of participants in the main safety analysis set were aged ≥ 65 years, which is relatively similar to the proportion of the overall Brazilian population aged ≥ 65 years (9.6% in 2020 World Bank 2022).

A subsequent optional booster third and fourth dose of ChAdOx1 nCov-19 vaccine was offered to a subgroup of participants who previously received ChAdOx1 nCov-19 within the trial. Participants in this booster sub-study were followed for 6 months from the booster vaccination. In the safety analysis population, the median age prior to dose 4 of AZD1222 was 36.8 years (range: 20.5–78.3), 94.8% were aged 18–64 years, 55.8% were male, 64.0% were White, mean BMI was 26.6 kg/m² (SD: 3.95), 29.1% had at least one protocol-defined comorbid condition, and 32.6% were seropositive prior to dose 4.

A total of 10,416 participants were randomised and received at least one dose of study intervention. The primary efficacy analysis resulted in a VE estimate of 57.61%, with a lower bound of the 95% CI of 40.73%. Overall, AZD1222 generated a strong humoral immune response in this study.

Solicited local and systemic AEs were reported by 81.7% and 69.0% of evaluated participants, respectively, in the AZD1222 group and 59.2% and 65.0% of evaluated participants, respectively, in the control group. Most solicited local and systemic AEs and unsolicited AEs following any dose of AZD1222 were mild or moderate in severity, and most related AEs were mild or moderate in severity. Most of the common unsolicited AEs were AEs commonly observed following vaccine administration. Reactogenicity was reduced after the second dose compared with the first dose in the AZD1222 group. No clinically meaningful imbalances in the incidence of SAEs were noted. Overall, VAXZEVRIA had an acceptable safety profile.

In the subsequent booster sub-study, a total of 172 participants were enrolled and 58 had solicited AEs collected. The humoral immune response elicited by Dose 3 of AZD1222 was noninferior to that after Dose 2 (ie, after a primary series of AZD1222) for all assays used (including anti-Spike antibodies and nAbs) and for all SARS-CoV-2 strains tested (including the Wuhan, Alpha, Beta, Gamma, Delta, and Omicron BA.1 [anti-Spike assay]/BA.5 [nAb assay] strains). The humoral immune response elicited by Dose 4 was noninferior to that after Dose 3 for all assays used and for all SARS-CoV-2 strains tested, although the magnitude of the response elicited by Dose 4 was smaller than that elicited by Dose 3 due to high pre-Dose 4 titres. Finally, the humoral immune response elicited by Dose 4 also noninferior to that after Dose 2 for all assays used and for all SARS-CoV-2 strains tested.

Of the 58 participants who had received 4 doses of AZD1222 and who were evaluated for solicited AEs within 7 Days after Dose 4, solicited local and systemic AEs were reported by 60.3% and 43.1% of evaluated participants, respectively. Most solicited local and systemic AEs

following any dose of AZD1222 were mild or moderate in severity. Of the 172 participants who received 4 doses of AZD1222, most of the unsolicited AEs related to study intervention were AEs commonly observed following vaccine administration, all were mild or moderate in severity, and none occurred in more than one participant. No SAEs were reported, and no participants had fatal AEs. Overall, the safety data after Dose 3 and Dose 4 of AZD1222 in adult participants did not raise any new safety concerns and the safety profile remained consistent with that observed after 2 doses (ie, primary series) of AZD1222.

COV004 (A phase Ib/II single-blinded, randomised, controlled study to determine safety, immunogenicity and efficacy of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19 in adults in Kenya): Phase Ib/II

Results from the COV004 were reported in a manuscript and summarized below, as no Clinical Study Report was produced for this clinical trial. COV004 was an Oxford-sponsored, phase Ib/II trial single-blinded, randomised, controlled study of the SD ($\sim 5 \times 10^{10}$ virus particles (vp) of ChAdOx1 nCoV-19 (VAXZEVRIA) in comparison to the rabies control vaccine in Kenya. The primary endpoints of the trial were vaccine safety and immunogenicity of VAXZEVRIA vaccine as compared to the rabies control vaccine, with VE against COVID-19 evaluated as a secondary endpoint. A total of 400 healthy adults ≥ 18 years of age with ChAdOx1 nCoV-19 (n=200) or rabies vaccine (n=200) were randomized and received at least one vaccination. Baseline participant characteristics were similar across vaccine groups, although males comprised 81% (n=325) of the study participants. The most commonly reported local AEs were tenderness (98 in ChAdOx1 nCoV-19 and 36 in rabies; relative risk [RR] 2.72, 95% CI 1.84 to 4.11), pain at injection site (74 in ChAdOx1 nCoV-19 and 32 in rabies; RR 2.31, 95% CI 1.51 to 3.62), and induration (5 in ChAdOx1 nCoV-19 and 1 in rabies group; RR 5.0, 95% CI 0.56 to 236.49). Headache was the most common systemic reaction with both vaccines occurring in 52 (26%) of 200 participants in ChAdOx1 nCoV-19 group and 25 (13%) of 200 participants in rabies group (RR 2.10, 95% CI 1.21). Myalgia was the second most common AE occurred in 35 (18%) of 200 participants in the ChAdOx1 nCoV-19 group and 10 (5%) of 200 participants in the rabies vaccine group (RR 1.47, 95% CI 0.73 to 3.04). The least common systemic adverse reaction was fever which occurred in one participant in each vaccine group. No participant reported a severity grade of 3 or 4 for all solicited local and systemic adverse reactions, except for one participant in the ChAdOx1 nCoV-19 group who had a grade 4 fever. In total, 79 unique unsolicited adverse reactions (60 in ChAdOx1 nCoV-19 and 53 in rabies vaccine groups) were reported throughout the study. Three serious adverse events, of which one resulted in death, were reported throughout the trial, all considered unrelated to study vaccination. The geometric mean anti-spike IgG titres 28 Days after second dose vaccination were higher in the ChAdOx1 group (2773 Enzyme-Linked Immunosorbent Assay [ELISA] units [EU], 95% CI 2447, 3142) than in the rabies vaccine group (61 EU, 95% CI 45, 81) and persisted over the 12 months FU. Vaccine efficacy against clinically apparent infection could not be determined given the lack of symptomatic infections. Vaccine efficacy against asymptomatic SARS-CoV-2 infection was 38.4% (95% CI -

26.8% to 70.1%; $p=0.188$). In conclusion, the safety and immunogenicity of ChAdOx1 nCoV-19 was consistent with the known profile of the vaccine (Hamaluba M et al 2023)

COV005 (An adaptive phase I/II randomised placebo-controlled trial to determine safety, immunogenicity and efficacy of non-replicating ChAdOx1 SARSCoV-2 vaccine in South African (SA) adults living without HIV; and safety and immunogenicity in adults living with HIV): Phase I/II

COV005 was a double-blind, multi-centre, randomised, placebo-controlled Phase I/II trial in adults living with and without HIV in SA to assess the safety, efficacy, and immunogenicity of ChAdOx1 SARSCoV-2 vaccine (VAXZEVRIA). 2021 HIV-uninfected trial participants aged 18-65 years received a 2-dose IM regimen of the SD ($5-7.5 \times 10^{10}$ vp) of VAXZEVRIA or saline placebo. The total duration of the study was 12 months from the day of enrolment for all participants.

The primary efficacy analysis resulted in a VE estimate of 37.04% (95% CI -277.20 to 89.49; $p=0.612$). The low efficacy against symptomatic COVID-19 observed in the study was due to the B.1.351 variant emerged in SA. AZD1222 generated a strong humoral response to SARS-CoV-2 ancestral strain.

Solicited local and systemic AEs were reported by 52.6% and 56.9% of participants, respectively, in the AZD1222 group and 22.8% and 44.3% of participants, respectively, in the control group. Most solicited local and systemic AEs and unsolicited AEs following any dose of AZD1222 were mild or moderate in severity, and most AEs considered related to study treatment were mild or moderate in severity. Most of the commonly reported unsolicited AEs were consistent with solicited AEs commonly observed following vaccination (eg, headache, influenza-like illness, vaccination-site erythema). Reactogenicity was reduced after the second dose compared with the first dose across all solicited AEs in the AZD1222 group. There were no clinically meaningful imbalances in the incidence of SAEs between the AZD1222 and control groups. Overall, VAXZEVRIA had an acceptable safety profile and was well tolerated in healthy adult participants.

Efficacy, safety, and immunogenicity results from pooled analyses including data from COV001, COV002, COV003 and COV005 studies:

The evaluation of the efficacy, immunogenicity and safety of VAXZEVRIA for prevention of COVID-19 was based on the pooled data from 4 clinical studies COV001 (UK), COV002 (UK), COV003 (Brazil), and COV005 (SA).

The primary efficacy analysis demonstrated effective protection against COVID-19 with a VE of 66.73% (95% CI 57.41 to 74.01; $p<0.001$) from 15 Days after the second dose in seronegative participants receiving two standard doses (SDSD) or 1 LD and 1 standard dose (LDSD) of

VAXZEVRIA. The pooled analyses demonstrated that VAXZEVRIA provided complete protection against COVID-19 hospital admission ≥ 22 Days after the first SD dose in the seronegative analysis set. For the SDSD regimen, it was demonstrated that vaccine protection begins from 22 Days after the first dose and extends at least until 12 weeks, allowing the second dose to be given in a flexible window between 4 to 12 weeks. VAXZEVRIA elicited a strong humoral immune response, as measured by different serological assays following the first dose and the second dose of VAXZEVRIA regardless the presence of co-morbid conditions at baseline, country, and age. The vaccine was well tolerated in pooled safety analyses. The incidence of SAEs in both the AZD1222 and control groups was low, with no difference in either frequency or type between the treatment groups. There was not a significant change in the safety profile during the reporting period.

The safety profile of AZD1222 was generally similar in participants 18 to 64 and ≥ 65 years of age, although older adults reported fewer solicited AEs of grade 3 severity compared with younger adults.

AstraZeneca has modified the list of Adverse Drug Reactions (ADRs) in the CDS based on the final pooled analysis results. See Section 4 and 16.2.5.1 for more information.

COV006 (A single-blind, randomised, phase II study to determine safety and immunogenicity of the Coronavirus Disease (COVID-19) vaccine ChAdOx1 in UK healthy children and adolescents [aged 6-17]): Phase II

COV006 was an Oxford-sponsored, Phase II, single-blinded, active-controlled, randomized study in healthy children and adolescents aged 6-17 years in the UK of 2 doses 4 or 12 weeks apart of ChAdOx1 nCoV-19 (VAXZEVRIA) or active control (licensed Meningococcal Group B vaccine - MenB) administered IM (Li et al 2022). The study assessed the safety, tolerability and immunogenicity of a SD dose ($\sim 5 \times 10^{10}$ vp) of ChAdOx1 nCoV-19. The total duration of the study was 12 months from the day of enrolment for all participants.

Overall, 262 participants were randomised and 261 participants received study intervention. The disposition of participants was generally balanced across all study arms, with the majority of participants receiving both doses of study intervention (250 [95.4%] participants).

Across all AZD1222 study arms, neutralizing antibodies and Spike protein (S)- and receptor-binding domain (RBD)-binding antibodies increased after the first dose, increasing further after the second dose. Antibody levels peaked at 28 Days post second dose in all study arms, with higher antibody levels observed in the D112/12-17 years study arm than in the D28/12-17 years study arm, and the highest antibody levels observed in the D112/6-11 years study arm. At 28 Days post second dose, in the D28/12-17 years, D112/12-17 years, and D112/6-11 years AZD1222 study arms, seroresponse was recorded in 86.0%, 92.1%, and 100% of participants, respectively, for neutralizing, and in 100% of participants for S-binding and RBD-binding

antibodies. At this time point, across AZD1222 study arms, antibody levels were comparable with or numerically greater than the levels for adults post second dose from pooled AZD1222 studies. Across all AZD1222 study arms, interferon (IFN)- γ ELISpot responses to SARS-CoV-2 Spike protein increased post first dose; responses did not increase further post second dose.

Overall, 100% of participants experienced solicited AEs after any dose of study intervention. The incidence of solicited AEs was similar across all study arms. Local and systemic solicited AEs were reported in fewer participants after the second dose of study intervention than after the first dose. Across all study arms, the majority of participants had mild (Grade 1) or moderate (Grade 2) local or systemic solicited AEs, with pain and tenderness being the most common local solicited AEs and fatigue and headache being the most common systemic solicited AEs. Unsolicited AEs after any dose of study intervention were reported in a similar proportion of participants in the D28/12-17 years and D112/12-17 years AZD1222 study arms (25/58 [43.1%] and 20/62 [32.3%] participants, respectively) and corresponding MenB study arms (5/16 [31.3%] and 5/14 [35.7%] participants, respectively), and in a numerically higher proportion of participants in the AZD1222/D112/6-11 years study arm than in the corresponding MenB study arm (49/90 [54.4%] and 6/21 [28.6%] participants, respectively). The majority of unsolicited AEs in any study arm were mild (Grade 1) or moderate (Grade 2) in severity. No participant died during the study. Five participants in the AZD1222 study arms had SAEs, none of which were considered related to study intervention by the Investigator. In summary, AZD1222 administered in 2 intramuscular injections was well-tolerated in children and adolescents 6-17 years of age, at dosing intervals of 28 Days or 112 Days. No safety concerns were raised in this study.

COV008 (A Phase I study to determine safety, tolerability and immunogenicity of intranasal administration of the COVID vaccine ChAdOx1 nCoV-19 in healthy UK adults): Phase I

COV008 was a Phase I open-label study investigating intranasal (IN) administration of ChAdOx1 nCoV-19, sponsored by the University of Oxford, has completed and a manuscript published. The aim of the study was to evaluate the safety and immunogenicity of intranasally-administered ChAdOx1 nCoV-19 both in vaccine-naïve participants and in participants who had previously received intramuscularly administered SARS-CoV-2 vaccines. A total of 42 healthy volunteers under the age of 55 years participated in this study. Solicited local and systemic reactions in all groups were predominantly mild (grade 1), following both first and second IN vaccinations. The most frequent solicited adverse reactions were sore throat (52%), nasal discharge (45%), headache (48%) and fatigue (48%). There was no obvious relationship between the frequency or severity of solicited AEs and dose level, first versus second IN vaccination, or previous receipt of IM COVID-19 vaccines. Occasional moderate (grade 2) reactions were reported. No SAEs were reported during the study. Three (3) non-serious AEs of note were reported: grade 3 (severe) chest pain without identified cause; grade 3 diplopia due to decompensation of a pre-existing esodeviation (an adverse event of special interest (AESI) but

assessed as unlikely to be related to IN vaccination); and grade 1 (mild) transient anosmia 10 Days after vaccination, for which the investigators' assessment was that the most likely cause was intercurrent upper respiratory tract infection, although relatedness to IN vaccination could not be excluded. Antigen-specific mucosal antibody responses to IN vaccination were detectable in a minority of participants, rarely exceeding levels seen after SARS-CoV-2 infection. Systemic responses to IN vaccination were typically weaker than after intramuscular vaccination with ChAdOx1 nCoV-19 (Madhavan M et al 2022).

D8110C00001 (A Phase III Randomised, Double-blind, Placebo-controlled Multicentre Study in Adults to Determine the Safety, Efficacy, and Immunogenicity of VAXZEVRIA, a Non-replicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19): Phase III

D8110C00001 was an AstraZeneca-sponsored, Phase III randomised, double-blind, placebo controlled, multi-centre study assessing the safety, efficacy, and immunogenicity of VAXZEVRIA compared to saline placebo for the prevention of COVID-19. Participants were adults ≥ 18 years of age who were healthy or have medically stable chronic diseases and were at increased risk for SARS-CoV-2 acquisition and COVID-19. All participants were planned remain on study for 2 years following administration of first dose of study intervention (Day 730).

A total of 32379 participants were randomised and received at least one dose of study intervention (21583 in the AZD1222 group; 10796 in the placebo group). A total of 30720 participants (94.7%) had received 2 doses of study intervention, with 20769 participants receiving AZD1222. Most participants in both treatment groups (16099 participants [74.4%] AZD1222; 7213 participants [66.7%] placebo) completed the study through 2 years. By the end of the study, most participants in both treatment groups had received a non-study COVID-19 booster vaccination (14665 participants [67.8%] AZD1222; 6109 participants [56.5%] placebo).

In the primary efficacy analysis using 203 adjudicated cases, AZD1222 showed a VE estimate of 74.0% against SARS-CoV-2 Reverse Transcriptase (RT)-PCR-positive symptomatic illness, with a lower bound of the 95.0% CI of 65.34%. The VE estimate of 100.0% (95% CI 71.62 to NE) was observed for prevention of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness (due to no cases in the AZD1222 group). Efficacy assessment following first dose demonstrated a VE estimate of 54.5% (95% CI 46.48 to 61.26) against symptomatic illness and a VE estimate of 85.0% (95% CI 58.97 to 94.50) against severe or critical illness.

Overall, AZD1222 generated a strong humoral response, including when stratified by age, race, and ethnicity. Spike (S)-binding and receptor binding domain (RBD)-binding antibodies peaked at 14 Days post-second dose of AZD1222 and were maintained above the levels achieved by the first dose through at least Day 90. Neutralizing antibody responses were elevated above baseline at 14 Days post-first dose of AZD1222 with responses peaking at 28 Days post-second dose.

Overall, vaccination with AZD1222 had an acceptable safety profile up to 2 years post-dose and was well tolerated in healthy adult participants, as well as in high-risk adult populations of older adults and adults with comorbidities, who have an increased risk of death and severe disease associated with COVID-19. Unsolicited AEs were consistent with AEs commonly observed following vaccination. The majority of solicited (local and systemic) AEs and unsolicited AEs following vaccination with AZD1222 were mild or moderate in severity and completely resolved within 2 to 3 Days. Reactogenicity, as evaluated by the incidence of solicited AEs for 7 Days after each dose, was lower following the second dose. The incidences of SAEs were low, and there were no clinically meaningful imbalances between the AZD1222 and placebo groups. None of the fatal events in either treatment group were considered related to study intervention by the investigator. A review of the pregnancy cases did not raise any safety concerns.

D8111C00010 (A Phase IV Open-Label, Non-Randomized, Multi-Cohort, Multi-centre Study in Previously Unvaccinated Immunocompromised Adults to Determine the Immunogenicity and Safety of AZD1222 Vaccine for the Prevention of COVID-19): Phase IV

This was an AstraZeneca-sponsored, Phase IV open-label, non-randomized, multi-cohort, multicentre study to evaluate the immunogenicity and safety of AZD1222 for the prevention of COVID-19 in previously unvaccinated immunocompromised adults ≥ 18 years. Due to recruitment challenges from increasing COVID-19 vaccination rates globally, particularly in the immunocompromised population, the study could not recruit the required 360 unvaccinated/naïve participants and was terminated prematurely.

A total of 34 participants were enrolled, of these 23 were immunocompetent and 11 were immunocompromised. The two cohorts were not balanced in terms of age and gender.

The results showed that immunological responses to vaccination were lower in the immunocompromised cohort than in the immunocompetent cohort after each vaccination dose. However, in both cohorts, dose titers were increased after each vaccination compared to the previously measured titers showing the intended effect of the vaccination.

Solicited local and systemic AEs were slightly more frequent in the immunocompetent cohort compared to the immunocompromised cohort. The frequency of local and systemic AEs was higher after Dose 1 compared to after Dose 2 in both cohorts, even though the decrease was more pronounced in the immunocompetent cohort than in the immunocompromised cohort. Unsolicited AEs were more frequently reported in the immunocompromised cohort than in the immunocompetent cohort. No SAEs or AEs leading to discontinuation of vaccination were considered related to AZD1222 by the Investigator. Overall, the safety profile of AZD1222 was acceptable in both cohorts.

7.2 Ongoing clinical trials

There was one ongoing clinical trial sponsored by University of Oxford during the reporting period (COV009). There was no clinically important information that arose from ongoing clinical trials during the reporting period. The clinical trial described below has completed subjects' recruitment and follow-up, but neither a final Clinical Study Reports (CSRs) nor a manuscript presenting the study results had yet been published by the end of the reporting period and therefore the study is not considered as completed.

COV009 (Post-approval follow-up for the COV001 and 002 trials, to determine the long-term safety and character of immunological response to the ChAdOx1 nCoV-19 coronavirus vaccine): Long-term follow-up

COV009 was an Oxford-sponsored, FU study of participants previously enrolled on the phase I/II (COV001) and phase II/III (COV002) trials to determine the long-term safety and character of immunological responses to the ChAdOx1 nCoV-19 vaccine. Up to 1,077 participants were eligible for enrolment for the COV001 cohort and up to 10,812 participants for the COV002 cohort. No treatment will be given during this Study. Study duration is 12 months.

7.3 Long-term follow-up

Patients who have completed VAXZEVRIA clinical trials are not subject to long-term FU beyond the 12-24 months as mentioned in the study protocols.

7.4 Other therapeutic use of medicinal product

There were no other AstraZeneca programmes that follow a specific protocol with solicited reporting for VAXZEVRIA.

7.5 New safety data related to fixed-combination therapies

This section is not applicable as VAXZEVRIA is not approved or under development as part of a fixed-combination product or a multi-drug regimen.

8 FINDINGS FROM NON-INTERVENTIONAL STUDIES

No relevant safety information or information with potential impact on the benefit or risk evaluations arose from AstraZeneca sponsored non-interventional studies of VAXZEVRIA during the reporting period.

A listing of AstraZeneca sponsored non-interventional Post-Authorisation Safety Studies (PASS) completed or ongoing during the reporting period is provided in Appendix 4.

9 INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES

9.1 Other clinical trials

R-Pharm is the sponsor of three studies investigating the safety and immunogenicity of a heterologous prime-boost immunization with AZD1222 and another adenoviral vector, the recombinant rAd26 (CV03872097, formerly known as D8111C00003, CV03872091 and CV03872092), which were ongoing during the reporting period.

No information relevant to the benefit-risk assessment of AZD1222 or AZD2816 have been identified from studies known to be performed by other sponsors (Fiocruz, R-Pharm and SII) during the reporting period.

9.2 Vaccination errors

Case reports of medication errors where no other AEs have been reported do not fulfil the criteria for inclusion in the tabulation in Appendix 2 but are included in the searches below.

The search strategy for vaccination errors includes following PTs:

- *PTs in the SMQ Medication errors and*
- *PT's: Device failure , Device deployment issue , Prescription drug used without a prescription , Device delivery system issue , Product advertising issue , Counterfeit product administered , Device mechanical issue , Device safety feature issue , Device environmental compatibility issue , Device data issue , Device temperature issue , Device user interface issue , Device signal transmission issue , Device wireless communication issue , Unevaluable device issue , Prosthetic cardiac valve malfunction , Device calibration failure , Product sterility issue.*

Interval Period (29 December 2022 – 28 December 2023)

A total of 1645 case reports (1231 initial and 414 follow-up), including 1748 vaccination error AEs, have been identified during the reporting period, which represents 07.45% cases of the cumulative (22075 case reports). Of those 1645 case reports, 352 were reported as serious (134 case reports were MC and 218 were consumer reports). In 1117 (67.90%) of the 1645 cases reports no other AEs were reported in connection with the vaccination error. AEs were reported in the remaining 528 (32.10 %) case reports.

The frequently reported (>50) vaccination errors were Expired product administered (508), Interchange of vaccine products (491), Off label use (155), Wrong product administered (144), Product administered to patient of inappropriate age (141), Inappropriate schedule of product administration (108), Medication error (91), and Incorrect dose administered (56). Out of the 528 cases with other AEs, 344 (65.15 %) cases were serious and 184 (34.85 %) were non-serious. Of

the 528 cases, 182 (34.47%) were MC and 346 (65.53%) were non-medically confirmed. Out of 344 serious cases, the reported seriousness criteria were fatal/death in 10 case reports, life threatening in 34 case reports, hospitalisations in 126 cases and the remaining were medically important.

A review of all the cases with seriousness fatal/death received during the reporting period suggested fatal outcome in 13 cases (10 cases with AE and 3 cases without AE) in association with vaccination error.

Out of 528 case reports there were 3029 events (1764 serious and 1267 non-serious). Most of the AE's were reported from the SOC of General disorders and administration site conditions Table 17.

Table 17 Distribution of Serious Adverse Events Associated with Vaccination Errors with VAXZEVRIA by MedDRA SOC from 29 December 2022 to 28 December 2023

MedDRA (SOC)	Events Count	Serious	Non-Serious	Percentage
General disorders and administration site conditions	716	390	327	16.47
Injury, poisoning and procedural complications	557	279	279	12.81
Nervous system disorders	506	317	190	11.64
Surgical and medical procedures	354	99	255	8.14
Infections and infestations	326	194	132	7.50
Musculoskeletal and connective tissue disorders	312	141	173	7.18
Gastrointestinal disorders	274	190	84	6.30
Respiratory, thoracic and mediastinal disorders	230	175	55	5.29
Psychiatric disorders	166	100	66	3.82
Investigations	151	116	35	3.47
Skin and subcutaneous tissue disorders	147	85	62	3.38
Cardiac disorders	103	79	24	2.37
Vascular disorders	95	74	21	2.19
Ear and labyrinth disorders	71	46	25	1.63
Social circumstances	71	59	12	1.63
Eye disorders	58	30	28	1.33
Renal and urinary disorders	40	37	3	0.92
Immune system disorders	32	20	12	0.74
Blood and lymphatic system disorders	26	16	10	0.60
Pregnancy, puerperium and perinatal conditions	24	10	14	0.55
Metabolism and nutrition disorders	20	10	10	0.46

Table 17 Distribution of Serious Adverse Events Associated with Vaccination Errors with VAXZEVRIA by MedDRA SOC from 29 December 2022 to 28 December 2023

MedDRA (SOC)	Events Count	Serious	Non-Serious	Percentage
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	20	19	1	0.46
Reproductive system and breast disorders	15	8	7	0.35
Hepatobiliary disorders	13	8	5	0.30
Product issues	10	6	4	0.23
Endocrine disorders	8	6	2	0.18
Congenital, familial and genetic disorders	2	2	0	0.05
Total	4347	2516	1836	100

MedDRA Medical Dictionary for Regulatory Activities, SOC System Organ Class

The reported vaccination error AEs are presented in Table 17. The reported vaccination error AEs have been grouped according to specific vaccination error groups suggested in the literature (Hibbs et al 2015), see Table 19.

Most reported AEs (≥ 50) in the 538 vaccination error cases were COVID-19 (152), Drug ineffective (107), Pyrexia (83), Headache (81), Fatigue (80), Pain in extremity (80) and Pain (67).

During the reporting period there was one case each reported with Intravenous (not otherwise specified), Other (with AE) and Unknown routes of administration that was not associated with AE. Two cases were reported with Intracavernous route that were associated with AE. Four cases were reported with Subcutaneous route that were associated with AE. Twelve cases were reported with Transplacental (TPL) route that were associated with AE. 1601 cases were reported with intramuscular (487 with AE and 1114 without AE). Additionally, there were 23 cases where the route of administration was unspecified of these 02 were without AE and 21 were associated with AE.

Review of events associated with these inappropriate route of administration events did not identify any safety issues. These cases do not indicate any trends of systemic substantial errors or a need for additional risk mitigation activity.

Cumulative Review (29 December 2020 – 28 December 2023)

A total of 22075 case reports, including 23654 vaccination error AEs, have been identified during the cumulative period. Of those 22075 case reports, 2244 were considered serious (707 case reports were MC and 1537 were consumer reports). In 15855 (71.82 %) of the 22075 cases

reports no other AEs were reported in connection with the vaccination error. Adverse events were reported in the remaining 6220 (28.18 %) case reports.

The frequently reported (>50) vaccination errors were Interchange of vaccine products (3859), Wrong product administered (3456), Expired product administered (3042), Inappropriate schedule of product administration (2231), Product administered to patient of inappropriate age (1867), Medication error (1460), Incorrect dose administered (1457), Incorrect route of product administration (745), Product dose omission issue (558), Incomplete course of vaccination (482), Product storage error (471), Product temperature excursion issue (391), Product administration error (357); Vaccination error (327), Intercepted medication error (307), Accidental exposure to product (301); Contraindication to vaccination (265), Underdose (253), Circumstance or information capable of leading to medication error (229), Intercepted product storage error (211), Product administered at inappropriate site (175), Overdose (169), Incorrect product formulation administered (115), Poor quality product administered (106); Product use issue (86); Extra dose administered (67); Wrong technique in product usage process (65) and Accidental overdose (54).

Out of the 6220 cases with AEs, 2112 (33.95%) cases were serious and 4108 (66.05%) were non-serious. Of the 6220 cases, 1958 (31.48 %) were MC and 4262 (68.52%) were non- MC. Out of 2112 cases, the seriousness criteria were fatal/death in 79 case reports, life threatening 249, hospitalisations in 679, cases and the remaining were medically important.

Out of 5953 case reports there were 33423 events (9017 serious and 24466 non-serious). Most of the AE's were reported from the SOC of General disorders and administration site conditions (Table 18).

Table 18 Distribution of Serious Adverse Events Associated with Vaccination Errors with COVID-19 VACCINE ASTRAZENECA by MedDRA SOC through 28 December 2023

MedDRA (SOC)	Events Count	Serious	Non-Serious	Percentage
General disorders and administration site conditions	7898	1679	6237	22.77
Injury, poisoning and procedural complications	6657	1051	5611	19.19
Nervous system disorders	4283	1614	2683	12.35
Musculoskeletal and connective tissue disorders	2857	737	2131	8.24
Surgical and medical procedures	2275	263	2012	6.56
Gastrointestinal disorders	1595	541	1056	4.60
Investigations	1482	347	1136	4.27

Table 18 **Distribution of Serious Adverse Events Associated with Vaccination Errors with COVID-19 VACCINE ASTRAZENECA by MedDRA SOC through 28 December 2023**

MedDRA (SOC)	Events Count	Serious	Non-Serious	Percentage
Respiratory, thoracic and mediastinal disorders	1183	526	658	3.41
Infections and infestations	1156	500	657	3.33
Skin and subcutaneous tissue disorders	1044	333	715	3.01
Psychiatric disorders	829	258	572	2.39
Vascular disorders	602	352	251	1.74
Cardiac disorders	474	285	189	1.37
Eye disorders	444	178	266	1.28
Ear and labyrinth disorders	311	131	181	0.90
Reproductive system and breast disorders	257	98	160	0.74
Blood and lymphatic system disorders	237	144	95	0.68
Immune system disorders	224	100	124	0.65
Metabolism and nutrition disorders	203	72	131	0.59
Social circumstances	190	104	86	0.55
Renal and urinary disorders	159	105	54	0.46
Pregnancy, puerperium and perinatal conditions	105	79	26	0.30
Product issues	62	12	50	0.18
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	62	52	10	0.18
Hepatobiliary disorders	55	36	19	0.16
Endocrine disorders	28	20	8	0.08
Congenital, familial and genetic disorders	11	11	0	0.03
Total	34683	9628	25118	100

MedDRA Medical Dictionary for Regulatory Activities, SOC System Organ Class

The reported vaccination error AEs are presented in Table 18. The reported vaccination error AEs have been grouped according to specific vaccination error groups suggested in the literature (Hibbs et al 2015), see Table 19.

Most frequently reported AEs ≥ 50 within the 6220 case reports of vaccination error were Headache (1472), Pyrexia (1466), Fatigue (880), Pain (786), Chills (731), Pain in extremity (714), Myalgia (557), Arthralgia (462), COVID-19 (459), Malaise (457), Asthenia (418), Dizziness (401), Nausea (374), Injection site pain (287), Dyspnoea (250), Paraesthesia (227), Diarrhoea (218), Vomiting (212), Hypoaesthesia (188), Feeling abnormal (167), Rash (148), Cough (144), Chest pain (141), Back pain (134), Tremor (131), Application site pain (129), Vaccination site pain (129), Pruritus (128), Somnolence (118), Tinnitus (115), Hyperhidrosis (113), Insomnia (111), Abdominal pain (110), Influenza like illness (108), Thrombosis (108), Peripheral swelling (105), Limb discomfort (105), Decreased appetite (102), Hypersensitivity (100), Illness (100), Palpitations (96), Migraine (96), Muscular weakness (93), Feeling cold (90), Nasopharyngitis (90), Erythema (90), Gait disturbance (86), Oropharyngeal pain (86), Contusion (85), Heart rate increased (84), Syncope (79), Muscle spasms (78), Vertigo (77), Condition aggravated (77), Cerebrovascular accident (77), Anxiety (77), Vision blurred (75), Pulmonary embolism (75), Tachycardia (74), Depression (73), Hypertension (72), Urticaria (71), Abdominal pain upper (70), Body temperature increased (70), SARS-CoV-2 test negative (70), Weight decreased (70), Neck pain (70), Eye pain (69), Blood pressure increased (67), Chest discomfort (66), Fall (65), Discomfort (64), Influenza (64), Rhinorrhoea (63), Injection site erythema (62), Feeling hot (60), Confusional state (58), Lymphadenopathy (58), Stress (57), SARS-CoV-2 test positive (56), Seizure (56), Therapy partial responder (56), Burning sensation (55), Abdominal discomfort (55), Inflammation (54), DVT (54), Musculoskeletal stiffness (53), Disturbance in attention (53) and Bone pain (50).

During the cumulative period, there was one reported with Intraperitoneal reported without AE. There was one case each reported with Intracardiac (IC), Intradiscal (intraspinous), Intrasynovial, Gastroenteral, Subconjunctival, Intravesical, Infiltration and Respiratory (inhalation) was reported with AE. 2 cases each were reported with Nasal (with AE); Auricular (otic) (with AE); Intravenous bolus (with AE) and Intra-articular (with AE); Other (with AE). There were 3 cases reported Intrameningeal (IMEN) (1 with AE and 2 without AE). 4 cases with Subdermal (SD) which were associated with AE. 5 cases were reported with Transmammary (TM) route (without AE) and Intraocular (IOC) route (1 with AE and 4 without AE). 7 cases were reported with Parenteral (PAR) route which were associated with AE. 11 cases were reported with Oral (PO) route which were associated with AE. 13 cases were reported with Cutaneous (CU) route which were associated AE and 14 cases were reported with Intracavernous (ICS) route which were associated AE. 20 cases with Intradermal (ID) route of administration that were associated with AE. 26 cases with TPL route of administration that were associated with AE. 132 cases with Intravenous (not otherwise specified) (IV) route (130 with AE and 2 without AE) and 233 cases with subcutaneous route (226 with AE and 7 without AE). There were 21500 cases reported with intramuscular route of administration (5703 with AE and 15797 without AE). Additionally, there were 82 cases where the route of administration was unspecified of these, 40 were associated with AE and 42 without AE.

Table 19 Summary tabulation of Vaccination Error Adverse Events (interval and cumulative)

Vaccination error group	Adverse Event (MedDRA PT)	With AE				Without AE				Total Cumulative
		Interval		Cumulative		Interval		Cumulative		
		Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	
Accidental	Accidental exposure to product	0	1	22	22	0	30	7	250	301
	Accidental exposure to product packaging	0	0	0	1	0	0	3	0	1
	Accidental underdose	0	0	1	3	0	0	1	15	19
	Exposure to contaminated device	0	0	1	0	0	0	6	0	1
	Intercepted accidental exposure to product by child	0	0	0	0	0	0	1	1	1
Administration errors	Counterfeit product administered	0	0	0	0	0	0	9	1	1
	Drug administered in wrong device	0	0	0	0	0	0	3	1	2
	Drug monitoring procedure not performed	0	0	0	1	0	0	2	0	1
	Drug titration error	2	2	4	1	0	0	46	0	5
	Duplicate therapy error	0	0	0	0	0	0	6	2	2

Vaccination error group	Adverse Event (MedDRA PT)	With AE		Cumulative		Without AE		Cumulative		Total Cumulative
		Interval		Serious	Non-Serious	Interval		Serious	Non-Serious	
	Inadequate aseptic technique in use of product	0	0	1	1	0	0	7	0	2
	Incorrect product administration duration	1	1	3	3	0	0	2	11	17
	Incorrect product formulation administered	0	0	0	1	0	4	1	108	115
	Incorrect route of product administration	4	6	271	404	0	0	5	70	745
	Lack of vaccination site rotation	0	0	1	0	0	0	3	0	1
	Product administered at inappropriate site	4	8	60	63	0	4	8	49	175
	Product administered to patient of inappropriate age	0	2	24	130	1	138	1	1705	1867
	Product administration error	4	9	36	196	0	0	1	124	357
	Product administration interrupted	0	0	0	1	0	0	3	1	2

Vaccination error group	Adverse Event (MedDRA PT)	With AE		Cumulative		Without AE		Cumulative		Total Cumulative
		Interval				Interval				
		Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	
Contraindication	Product monitoring error	0	0	2	2	0	0	19	2	6
	Wrong route	0	0	1	1	0	0	1	0	2
	Wrong technique in device usage process	0	0	0	1	0	0	7	0	1
	Wrong technique in product usage process	5	5	19	20	0	1	3	25	65
	Contraindicated product administered	0	0	3	4	0	0	1	1	8
	Contraindicated product prescribed	0	0	8	2	0	0	6	0	10
	Contraindication to medical treatment	0	0	0	1	0	0	1	0	1
	Contraindication to vaccination	0	0	7	11	0	6	9	241	265
	Documented hypersensitivity to administered product	0	0	0	1	0	0	3	0	1
	Labelled drug-drug interaction issue	0	0	1	1	0	0	2	0	2

Vaccination error group	Adverse Event (MedDRA PT)	With AE		Cumulative		Without AE		Cumulative		Total Cumulative
		Interval		Interval		Interval		Interval		
		Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	
Equipment	Labelled drug-drug interaction medication error	0	0	2	0	0	0	46	0	2
	Device connection issue	0	0	0	0	0	0	6	3	3
	Device delivery system issue	0	0	0	1	0	0	7	0	1
	Device maintenance issue	0	0	0	0	0	0	2	1	1
	Device use confusion	0	0	1	0	0	0	1	0	1
	Device use error	0	0	0	1	0	0	5	1	2
	Device use issue	0	0	1	0	0	0	3	0	1
	Injury associated with device	0	0	9	9	0	0	8	0	18
	Medical device monitoring error	0	0	0	0	0	0	1	1	1
	Needle issue	2	4	4	9	0	0	1	8	22
General error	Syringe issue	0	0	0	3	0	0	3	10	13
	Wrong device used	0	0	0	1	0	0	19	0	1
	Medication error	77	80	275	381	0	11	1	802	1460
	Occupational exposure to product	0	0	3	4	0	0	7	8	15
	Product use issue	5	6	29	42	0	0	3	15	86

Vaccination error group	Adverse Event (MedDRA PT)	With AE		Without AE		Without AE		Without AE		Total Cumulative
		Interval	Cumulative	Interval	Cumulative	Interval	Cumulative			
		Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	
Inappropriate schedule	Vaccination error	0	0	15	71	0	2	1	241	327
	Inappropriate schedule of product administration	54	66	293	574	0	42	6	1361	2231
Incorrect dose	Wrong schedule	0	0	0	6	0	0	1	17	23
	Accidental overdose	21	21	24	12	1	0	9	15	54
	Booster dose missed	0	0	2	6	0	0	3	17	25
	Dose calculation error	0	0	2	6	0	0	2	1	9
	Extra dose administered	2	3	7	17	0	1	46	43	67
	Incomplete course of vaccination	3	4	111	123	0	2	6	246	482
	Incorrect dosage administered	0	0	2	9	0	0	7	25	36
	Incorrect dose administered	0	5	91	120	1	50	2	1200	1457
	Incorrect dose administered by device	0	0	0	1	0	0	1	1	2
	Incorrect dose administered by product	0	0	1	0	0	0	5	1	2
	Incorrect product dosage form administered	0	0	2	0	0	0	3	0	2

Vaccination error group	Adverse Event (MedDRA PT)	With AE		Without AE		Without AE		Total Cumulative		
		Interval	Cumulative	Interval	Cumulative					
		Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious			
Off-Label	Overdose	1	5	74	63	5	1	8	27	169
	Prescribed overdose	0	0	0	1	0	0	1	0	1
	Prescribed underdose	0	0	3	4	0	0	1	0	7
	Product dose omission in error	0	0	0	17	0	0	3	11	28
	Product dose omission issue	22	27	117	203	0	14	19	238	558
	Underdose	1	1	9	18	0	1	1	223	253
	Product use in unapproved indication	22	22	24	3	0	0	7	0	27
Potential errors	Drug ineffective for unapproved indication	0	0	1	0	0	0	3	0	1
	Circumstance or information capable of leading to device use error	0	0	0	0	0	0	1	2	2
	Circumstance or information capable of leading to medication error	0	0	26	61	0	0	6	141	229
	Intercepted medication error	0	0	3	7	0	0	1	297	307

Vaccination error group	Adverse Event (MedDRA PT)	With AE		Cumulative		Without AE		Cumulative		Total Cumulative
		Interval		Serious	Non-Serious	Interval		Serious	Non-Serious	
	Intercepted product administration error	0	0	1	3	0	0	9	9	13
	Intercepted product dispensing error	0	0	0	0	0	0	3	1	1
	Intercepted product preparation error	0	0	0	0	0	0	2	5	5
	Intercepted product storage error	0	0	0	1	0	0	46	210	211
Preparation error	Prescription drug used without a prescription	0	0	2	0	0	0	6	0	2
	Product preparation error	0	0	0	3	0	0	7	23	26
	Product preparation issue	0	0	2	7	0	0	2	12	21
	Product reconstitution quality issue	0	0	0	2	0	0	1	2	4
Prescribing error	Transcription medication error	0	0	1	1	0	0	5	1	3
Product labelling/packaging	Product barcode issue	0	0	1	0	0	0	3	0	1
	Product confusion	0	0	0	1	0	0	8	1	2
	Product identification number issue	0	0	0	0	0	0	1	1	1

Vaccination error group	Adverse Event (MedDRA PT)	With AE				Without AE				Total Cumulative
		Interval		Cumulative		Interval		Cumulative		
		Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	
Product quality	Product label confusion	0	0	0	1	0	0	1	2	3
	Product label issue	0	0	0	2	0	0	3	6	8
	Product lot number issue	0	0	0	0	0	0	19	9	9
	Product name confusion	0	0	1	1	0	0	1	1	3
	Product packaging confusion	0	0	0	2	0	0	7	0	2
	Product packaging issue	2	2	2	0	0	0	3	1	3
	Poor quality product administered	1	1	5	1	0	1	1	100	106
	Product use complaint	0	0	1	0	0	0	6	1	2
Storage/dispensing	Device dispensing error	0	0	0	1	0	0	1	2	3
	Expired product administered	0	2	30	137	0	506	9	2866	3042
	Product communication issue	0	0	0	3	0	0	3	7	10
	Product dispensing error	0	0	12	6	0	3	2	28	46
	Product dispensing issue	0	0	0	0	0	0	46	1	1

Vaccination error group	Adverse Event (MedDRA PT)	With AE		Cumulative		Without AE		Cumulative		Total Cumulative
		Interval		Interval		Interval		Interval		
		Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	
	Product prescribing error	1	1	4	5	0	0	6	14	23
	Product prescribing issue	0	0	1	0	0	0	7	2	3
	Product selection error	0	0	0	0	0	0	2	2	3
	Product storage error	0	1	4	39	0	0	1	428	471
	Product substitution error	0	0	0	0	0	0	5	1	1
	Product temperature excursion issue	0	0	1	5	0	1	3	385	391
Wrong vaccine	Interchange of vaccine products	198	330	687	1464	0	161	8	1701	3859
	Unintentional use for unapproved indication	0	0	0	0	0	0	1	1	1
	Wrong dosage form	0	0	0	1	0	0	1	0	1
	Wrong dose	0	0	0	2	0	0	3	1	3
	Wrong drug	0	0	0	0	0	0	19	5	5
	Wrong patient received product	0	0	0	1	0	0	1	0	1
	Wrong product administered	2	6	14	124	0	137	7	3299	3456

Vaccination error group	Adverse Event (MedDRA PT)	With AE		Cumulative		Without AE		Cumulative		Total Cumulative
		Interval		Serious	Non-Serious	Interval		Serious	Non-Serious	
Other	Exposure via direct contact	0	0	0	1	0	0	3	0	1
	Exposure via partner	0	0	1	0	0	0	1	0	1
	Exposure via unknown route	0	0	0	1	0	0	6	0	1
Grand Total		434	621	2366	4459	08	1116	135	16691	23651

Seriousness was evaluated at the event level, which may differ from the seriousness assigned to the report level.

Cases with no reported AEs are also included.

Case reports may include more than one vaccination error AE.

AE Adverse Event, MedDRA Medical Dictionary for Regulatory Activities; PT Preferred Term

Most frequently (>1000) reported vaccination error PTs were Interchange of vaccine products, Wrong product administered, Expired product administered, Inappropriate schedule of product administration, Product administered to patient of inappropriate age, Incorrect dose administered and Medication error, most of the reports (72%) were not associated with other AEs apart from these medication errors. The above medication errors related to interchange, wrong product administered is related to interchange of vaccine (heterologous administration) for Dose 1, Dose 2 and Dose 3 in many countries, and inappropriate schedule may be related to vaccine doses given at spacing intervals not aligned with the product information. Most of the reports were received from Brazil (56.2%), UK (9.7%), France (4.8%), A review of the PT Interchange of vaccine products found that these medications errors were received mainly from following countries Brazil (39.62%), France (14.95%), Germany (11.12%) and UK (7.33%).

The vaccines most often interchanged with VAXZEVRIA included mRNA-PFIZER, CoronaVac, mRNA-Moderna, Janssen, mRNA-unspecified, Sputnik and Covaxin Vaccine.

CoronaVac, mRNA PFIZER, Janssen, and mRNA Moderna. vaccines were most often used in reports of the PT Wrong product administered. However, there was limited information available in narrative to interpret whether the vaccinees received wrong product/vaccine voluntarily or by mistake.

9.2.1 Fatal Cases Associated with Vaccination errors

A review of interval vaccination error case reports with case level outcome of death/fatal had 06 cases. Overdose (n=3), Inappropriate schedule of product administration (n=2) and Interchange of vaccine products (n=1) were most frequently reported vaccination error events in these reports.

The reported AEs in these case reports were: Overdose (3), Heart rate increased (2), Oxygen saturation decreased (2), Chest pain (2), Oropharyngeal pain (2), Diarrhoea (2), Pneumonia (2), Dyspnoea exertional (2), Wound (2), Eye irritation (1), Thermal burns of eye (1), Partial seizures (1), Vaccination site pain (1), Death (2), Blood pressure increased (1), General physical health deterioration (1), Injection site pain (1), Body temperature increased (1), Interchange of vaccine products (1), Hospitalisation (1), Off label use (1), Inappropriate schedule of product administration (1), Inappropriate schedule of product administration (1) and Blood pressure increased (1).

Reported causes of death in these case reports were Overdose (3), General physical health deterioration (2), Inappropriate schedule of product administration (2), Blood pressure increased (2), Pneumonia (2), Chest pain (2), Wound (2), Death (2), Oropharyngeal pain (2), Diarrhoea (2), Oxygen saturation decreased (2), Dyspnoea exertional (2), Eye irritation (2), Heart rate increased (2), Injection site pain (1), Vaccination site pain (1), Interchange of vaccine products (1), Acute kidney injury (1), Off label use (1), Body temperature increased (1) and Hospitalization (1).

Review of these fatal cases did not identify safety issues in relation to type of vaccination errors.

Summary and Conclusion

Most frequently reported vaccination errors along with other AEs included Inappropriate schedule of product administration, Incorrect route of product administration, Product administered to patient of inappropriate age, Wrong product administered, Interchange of vaccine products, Medication error, Product dose omission issue, Incorrect dose administered, Incomplete course of vaccination, and Expired product administered. Most of the AEs reported for these vaccination errors were related to the reactogenicity events such as Pyrexia, Headache, Chills, Fatigue, Pain, Pain in extremity, Myalgia, Arthralgia, and Malaise. There was no clustering of AEs or AESI's with any of the vaccination error types.

Review of these fatal cases did not identify safety issues in relation to type of vaccination errors.

A review of all the vaccination error AE reports received during this interval and cumulative period did not demonstrate any medication error-emergent safety pattern associated with VAXZEVRIA. No new relevant patterns of vaccination errors or new safety concerns were identified during the reporting period.

Reports related to VAXZEVRIA vaccination errors will continue to be monitored by AstraZeneca through standard surveillance activities.

10 NON-CLINICAL DATA

No AstraZeneca-sponsored nonclinical in vivo and in vitro studies of AZD1222 were ongoing or completed during the reporting period.

11 LITERATURE

AstraZeneca has reviewed the published non-clinical scientific literature relevant to AZD1222. No publications were identified that included any relevant new safety information or information with potential impact on the benefit or risk evaluations during the reporting period.

AstraZeneca conducts comprehensive reviews of peer-reviewed published scientific literature and unpublished manuscripts routinely on an ongoing basis. The search strategy includes VAXZEVRIA and other COVID-19 vaccines in order to identify potential class related findings.

Relevant literature articles containing new and significant safety findings relevant to VAXZEVRIA published during the review period were retrieved. Important identified and Potential risks or Missing information have been included in section. Articles containing new and significant safety findings are summarized below.

Jia et al 2023 examines reported instances of Sweet syndrome (SS) emergence subsequent to COVID-19 vaccines such as VAXZEVRIA, Jcovden, BNT162b2, Spikevax and BBIBP-CorV. A total of 16 patients (8 females, 7 males, 1 unknown) with a median age set as 60, reveals a varied spectrum of onset intervals for SS post-vaccination, reported after 8 hours to 1 month. From the 16 vaccinee, 5 received VAXZEVRIA. Most of the events were related to Dose 1 of vaccination. The most common clinical manifestations were mentioned as, skin reactions like red plaques, papules, edema, and pustules. Neurological symptoms, such as myoclonus and tendon hyperreflexia, were observed in one patient. As reported by the authors, majority of the patient reported elevated neutrophil levels, elevated C-reactive protein (CRP), and elevated erythrocyte sedimentation rate (ESR), and during the assessment of skin biopsy, the main manifestation reported was dermal neutrophilic infiltration, papillary edema, and vascular neutrophilic infiltration, however one patient reported myelodysplastic syndrome (MDS) during bone marrow biopsy. Authors agreed upon the pathophysiological mechanism of vaccine-induced SS is not cleared, however, a potential mechanism as hypersensitivity phenomenon, which was supported by frequent occurrence after infection and less involvement of the remaining organs in response to glucocorticoid therapy, however other theory mentioned in the article, suggested the characteristics of fever and increased ESR from the perspective of cytokine involvement. The authors concluded that SS, despite reported as a very rare AE caused by vaccine, needs to be distinguished from other AEs, since it is generally associated with haematological malignancies.

AstraZeneca comment

During the study, authors came across with few numbers of cases related to SS, mostly related to BNT162b2 (6 reports out of 16), following by VAXZEVRIA (5 reports). However, as known, the low incidence of SS, moreover the even reduced incidence of vaccine-induced SS requires a higher number of patients to provide a reliable data, considering the exclusion of several reports due to limited information provided by the time of the research. Still, during the inclusion criteria and discussion, a complete upper respiratory infections analysis was not incorporate to consider other possible causes of the syndrome, neither gastrointestinal infection. Hence, causality in the reported cases could not be inferred.

Gasparotto M et al 2023 reported a case series of suspected rheumatic diseases (RDs) following anti-COVID-19 vaccination. These patients were evaluated at first-aid rheumatologic consultancy and at rheumatologic outpatient and inpatient clinic at Padova University Hospital between May and September 2021 presenting with a rheumatic disease (RD) within 30 Days after an anti-COVID-19 vaccine dose. Patients were regularly re-evaluated by telemedicine or face-to-face visit. The case series included 30 cases of RD following vaccination: 24 (80.0%) new onsets and 6 (20.0%) flares. Most of patients (n=23; 76.6%) received the BNT162b2 vaccine and 7 had received VAXZEVRIA (24.4%). The mean time to RD onset/flare was 12±9 Days. Slightly higher incidence of RD was reported in females (53.3%). In general, RD occurred mostly after the second dose (56.7%) and after a mean of 12±9 Days from vaccine administration. The most

common manifestations were inflammatory arthritis (40.0%), rheumatic polymyalgia (33.3%) and adult-onset Still's disease (13.3%). All reports 6 reports with an exacerbation of their underlying RD, were after BNT162b2 vaccine. Seven reports of RD following VAXZEVRIA, 3 of them were reported after dose 1 and 4 of them after dose 2. At the last FU visit (9.6±2.2 months), 83.3% of patients showed complete response to first- or second-line therapy, 13.3% a partial response and one patient (3.3%) was still experiencing an active disease. Authors also discussed potential mechanism of action such as innate immunity through the activation of the same endoscopic and cytoplasmic nucleic acid receptors, however it was concluded that an exact mechanism required further investigations to define whether in susceptible patients could induce the development of autoinflammatory rather than autoimmunity conditions. Overall, the authors reported that the RDs following COVID-19 vaccinations were generally mild, with a benign course with prompt response to therapy.

AstraZeneca comment

The publication identified fewer number of cases of rheumatic disease following COVID-19 vaccination, particularly involving VAXZEVRIA compared to BNT162b2 vaccine (76.6%). Furthermore, limited information on the case reports were noted, such as etiological work-up, diagnosis details, medical history or family history for those with new onset of rheumatic disease. Hence causality in the reported cases could not be inferred. Overall, this article does not provide sufficient evidence of an increased risk of rheumatic disease in vaccinees who received VAXZEVRIA.

Nafilyan et al 2023 assessed the impact of COVID-19 vaccination and positive SARS-CoV-2 tests on the risk of cardiac and all-cause mortality in young people (12 to 29 years) using a self-controlled case series (SCCS) design.

Methods of analysis

Design: A modified SCCS design.

Study population: All deaths among 12 to 29 year-olds in England that occurred between 08 December 2020 and 25 May 2022 and registered by 08 June 2022 with the Office for National Statistics (ONS) and deaths recorded on hospital discharge (Hospital Episode Statistics records) between 08 December 2020 and 31 March 2022.

Data source: ONS and Hospital Episode Statistics for England (HES).

Exposure data on COVID-19 vaccination was from National Immunisation Management Service (NIMS) and a supplementary extract from NHS point of care data provided by NHS-Digital.

SARS-CoV-2 positive test results were obtained from the National testing data from pillar 1 (tests in hospitals) and pillar 2 (tests in the community) recorded between 09 September 2020 and 31 December 2021.

Outcome data on death was derived from ONS and hospital deaths recorded in Hospital Episode Statistics for England (HES).

Outcome: Three outcomes were included: all-cause registered death, cardiac registered death (International Classification of Diseases [ICD]-10 code I30-I52 mentioned on the death certificate), and all-cause hospital death.

Exposure:

- COVID-19 vaccination: (a) 'mRNA' includes the Pfizer BNT162b2 Pfizer-BioNTech and mRNA-1273 Moderna vaccines. (b) 'Not mRNA or unknown' includes the ChAdOx1 Oxford-AstraZeneca vaccine, all other recorded vaccine manufacturers and nonrecorded vaccination manufacturers.
- SARS-CoV-2 positive test.

Duration of FU: 08 December 2020 and 25 May 2022.

Statistical methods: A SCCS approach designed to handle multiple event dependent exposures was used. This specific SCCS approach compares the risk of death during a predefined risk period following exposure (vaccination or positive test for SARS-CoV-2) with a reference period of all time subsequent to the risk period. By comparing time periods within individuals, time-invariant factors such as sex and, in general, age group and comorbidity, were implicitly controlled for; time-varying factors were controlled by the inclusion of unexposed cases in the analysis and by the inclusion of calendar time as a covariate. Analysis was stratified by vaccine type, mRNA vaccines included Pfizer BNT162b2 and mRNA-1273 Moderna vaccine and non-mRNA included VAXZEVRIA and all other recorded vaccine manufacturers and nonrecorded vaccination manufacturers.

Key findings: There were 3807 deaths recorded for 12 to 29 year olds in England that occurred between 08 December 2020 and 25 May 2022 and were registered by 08 June 2022. Of these 791 (21%) were within 12 weeks after COVID-19 vaccination, and the relative incidence (incidence rate ratio [IRR]) was 0.88 (95% confidence interval (CI): 0.80 – 0.97) for all-cause registered death, all doses in the risk period as a whole (1-12 weeks), compared to all time subsequent to the risk period. The IRR for all-cause registered deaths was 0.84 (0.75 – 0.95) for mRNA vaccines and 0.86 (0.75 – 0.99) for non-mRNA vaccines. The relative incidence of cardiac registered deaths for all doses was 0.84 (0.61 – 1.15) for mRNA vaccinated and 1.71 (1.20 – 2.45) for non-mRNA vaccinated including other and non-specified vaccines. Stratified by sex, dose, and vaccine vector, the relative incidence of cardiac registered deaths for combined 12- week post vaccination period 3.52 (1.71 – 7.26) for females after first dose non-mRNA

vaccination, which corresponds to one additional cardiac death for every 16,486 females aged 12-29 who received a first dose of non-mRNA vaccine. However, this estimate is based on 15 cardiac registered deaths in women that received a first dose of a non mRNA or unknown vaccine vector. There was also a non-significant risk for cardiac deaths post dose two of mRNA vaccines in males (IRR 1.70; CI: 0.98-2.97), which, if valid, would correspond to one additional cardiac death for every 359,294 males aged 12-29 who received a second dose of an mRNA vaccine.

Strengths: The study used high-quality data sources that included the whole population of England.

The SCCS use an intra-individual comparison where a person acts as their own control, and thereby adjusting for confounders that do not vary over time. Additionally, the investigators applied a modified SCCS method for event-dependent exposures since occurrence of the event (death in this case) will inevitably preclude subsequent exposures.

Author's interpretation:

The authors concluded they found minimal evidence of an increased incidence of cardiac or all-cause mortality overall in the twelve weeks following COVID-19 vaccination for all vaccine vectors combined.

The authors also stated that they found evidence of an increased risk of cardiac death after a first dose of a non-mRNA vaccine among females of this age group.

AstraZeneca comment:

Authors recognize some restrictions in their analysis, however during our assessment; a number of additional limitations were noted:

- The authors have grouped all non-mRNA vaccines together, including all other recorded vaccine manufacturers and nonrecorded vaccination manufacturers. According to MHRA, three COVID-19 vaccines - the monovalent COVID-19 Vaccine Pfizer/BioNTech, VAXZEVRIA and monovalent COVID-19 Vaccine Moderna – were used in the primary and booster vaccination campaigns up to the end of August 2022 (<https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting>). Based on this we could assume the vast majority of the non-mRNA vaccines were VAXZEVRIA. However, including other, and nonrecorded vaccine manufacturers in this category may lead to mRNA vaccines being misclassified as non-mRNA vaccines.
- Even though the study used a large sample including the whole population of England, there were multiple sub-analyses per outcome strata without clarity on how multiplicity was handled and low event count per strata affecting precision. Fifteen cardiac deaths occurred in women after first dose of non-mRNA vaccination and CIs were wide (IRR:3.52 [CI: 1.71 –

7.26]). The authors report: “Between 8 December 2020 and 25 May 2022, there were 4,012,520 females aged 12 to 29 who received at least one dose of a COVID-19 vaccine between these dates, of which 177,042 received a first dose of a non mRNA or unknown vaccine vector. There were 25 cardiac registered deaths of females within 12 weeks of receiving the first dose of a COVID-19 vaccination, of which 15 had received a first dose of a non mRNA or unknown vaccine vector.”

- The study used a risk period of 12 weeks, for which the authors provided no reasoning. This is longer than the recommended RW for cardiac adverse events of special interests (for example, 1-28 Days for myocardial infarction or 1-42 Days for Myocarditis/Pericarditis where Day 0 is the day of vaccination (FDA Guideline), (Kuntz et al 2018). Including a twice as long FU than recommended may lead to deaths occurring after the true RW being attributed to vaccination, when it is not biologically plausible. In fact, sensitivity analyses with varying lengths of risk periods all COVID-19 vaccines remained below or not significantly different to 1, particularly in the range <12 weeks. In contrast, analyses of deaths after a positive SARS-CoV-2 test for those unvaccinated at time of testing showed the risk of all-cause death was greater for shorter risk period definitions, particularly for hospital deaths. Last, the results in this study are conflicting with another SCCS study from the US where the risk period was set at 28 Days (see below).
- There is lack of detail regarding the cause of death registrations included, the authors included deaths with a cardiac diagnosis mentioned on the death certificate, rather than including the main cause of death. This may have led to misclassification. Moreover, cardiac deaths included only ICD codes I130 to I152, the authors give no reason for including only these codes.
- The authors did not take COVID-19 infection into consideration in the analysis of COVID-19 vaccination and death, even though the study periods overlapped. It is possible that individuals change behaviour after COVID-19 vaccination, increasing social contacts, and as a consequence, being at an increased risk of COVID-19 infection after vaccination. Moreover, as a large proportion of the study population are expected to be healthcare workers based on the vaccination roll out, they would be at high risk of COVID-19 infection. Specifically, the interaction between vaccination and infection was not explored. The distribution of events over calendar time post positive test result clearly shows a modal value close to day 0 which means a high proportion of deaths can be attributable to the infection. Observations post dose are not dissimilar but, the model value has shifted to 20 weeks for dose 1 and further for dose two making any inference of direct relationship more challenging. An understanding of any synergistic effect is needed for a more comprehensive understanding of risk. Of note, in the US SCCS study cited by the authors (Ladapo et al 2022), where post-vaccination positive tests for SARS-CoV-2 were excluded, no increased risk of cardiac deaths post non-mRNA vaccination was observed as compared to post mRNA vaccination – particularly among males (see below for more details).
- The authors provided no explanation for the biological basis underlying their key result of a possible sex difference in the rates of deaths following non-mRNA vaccination, with significant risk thereof in young females. Moreover, these results are inconsistent with studies published to date. For example, in the SCCS study from the US Ladapo et al 2022 where the risk period was set at 28 Days, there was an increased risk of cardiac deaths in males receiving mRNA vaccines (RI 1.11, CI: 1.05-1.18) while males who received non-

mRNA vaccines had lower risk (IR 0.75, CI: 0.58-0.98). Notably, similar pattern was observed among females, and among the subgroups evaluated, males aged 18-39 had the highest risk (RI 1.97, CI: 1.16 - 3.35). Although the two studies may not be directly comparable with respect to non-mRNA vaccines, given that VAXZEVRIA was not used in the US, results from mRNA analyses provide valuable insights with expected reproducibility across different geographies.

- The roll-out VAXZEVRIA in this age group was limited to health care workers and people who were clinically extremely vulnerable. Therefore, these results cannot be generalised to the population as a whole. The data available for analyses in this study lacked the means to characterise potentially impactful differences across the study sub-groups, specifically those who received non-mRNA vaccines as compared to those who received mRNA vaccines. Given the design inherent limitation of lacking the capacity to construct direct, matched comparisons between the two groups, the indirect contrast set forth by the authors should have been provided with a word of caution – that is the lack of incomparability between the two groups as a result of major shifts in COVID-19 vaccination policy during the study period.

In this study, the authors reported no significant increase in cardiac or all-cause mortality in the 12 weeks following COVID-19 vaccination compared to more than 12 weeks after any dose. However, they reported an increase in cardiac death in women aged 12-29 years after a first dose of non-mRNA vaccines. In summary, several limitations were identified after reviewing the study design and methods, including low precision; methodological uncertainties including the choice of RW in main analyses; conflicting results with published literature; lack of characterisation of/comparability between study sub-groups; and combining VAXZEVRIA with unknown and “other” vaccinations. These methodological concerns limit the inferences that can be drawn from this study.

12 OTHER PERIODIC REPORTS

There have been no significant findings from other periodic reports provided by other parties during the reporting period.

13 LACK OF EFFICACY IN CONTROLLED CLINICAL TRIALS

Immune response against Omicron variant

The results of assessments on immunogenicity of VAXZEVRIA (formerly COVID-19 Vaccine AstraZeneca) and convalescent serum from SARS-CoV-2-infected donors against the Alpha, Beta, and Gamma SARS-CoV-2 variants of concern as well as select variants of interest in a pseudovirus neutralisation assay (the assays were validated subsequently to the specimen testing) are presented in this section. Additional data have been provided on homologous and heterologous booster doses of AZD1222 against the Omicron variant (including subvariants BA.1, BA.2, BQ.1, BQ.1.1, XBB.1.5). The recently emerged Omicron subvariants such as BA.2.86, FL.1.5.1, EG.5, and HV.1 (CDC 2023) were not in scope of the project.

In order to further characterise the neutralising antibody (nAb) response induced by a primary series vaccination of AZD1222 and as part of an ongoing commitment to evaluate immunogenicity of AZD1222 against emerging variants, 21 pools of serum from 210 AZD1222 vaccinees have been assessed in validated pseudovirus neutralisation assays for the Alpha, Beta, Gamma, Delta, Lambda, Mu and Omicron variants of concern (including subvariants BA.2, and BA.4/5). Additionally, given the importance of booster vaccines on the effectiveness of COVID-19 vaccines against SARS-CoV-2 Omicron variants, 10 pools of 10 vaccinees receiving 3 doses of AZD1222 were also evaluated against Alpha, Beta, Gamma, Delta, and Omicron variants (including subvariants BA.1, BA.2, BQ.1, BQ.1.1, XBB.1.5). Finally, a comparative analysis of nAb responses for primary series, 3rd dose boosters, and 4th dose boosters was performed against the ancestral strain, Omicron BA.5, and Omicron XBB.1.5 variants.

The VAXZEVRIA 2-dose primary series vaccination has modest but statistically significant reductions in nAb potency against the Alpha, Gamma, and Delta variants of concern. More substantial reductions in nAb titers were observed against the Beta, Mu, and Omicron (BA.1, BA.2, and BA.4/5) variants. A homologous booster dose of VAXZEVRIA afforded higher levels of nAb titers against Omicron subvariants BA.1, BA.2, BA.4/5, BQ.1, and BQ.1.1. While no neutralising responses against the Omicron XBB.1.5 were observed with a third dose booster, neutralising activity was detected in half of the relatively small sample size of evaluated participants (n = 20) following a fourth dose (currently not approved) in the COV003 sub-study. However, while the nAb responses were similar to observations from other vaccine platforms showing lower immunogenicity to Omicron XBB, these results should be interpreted with caution due to the higher proportion of the population with hybrid immunity (immunity provided by a combination of vaccination and SARS-CoV-2 infection) globally.

The three fundamental components of the adaptive immune system are B cells (the source of antibodies), CD4+ T cells, and CD8+ T cells. Swanson et al 2021 provided a comprehensive assessment of the T cell response to VAXZEVRIA vaccination. VAXZEVRIA vaccination elicited a robust and polyfunctional TH1-dominated T cell response to the SARS-CoV-2 spike protein with a spike protein-specific CD8+ T cell response across all age groups. These responses may be critical in reducing the clinical symptoms associated with COVID-19 disease, as evidenced by longitudinal FU of patients with SARS-CoV-2 infection, where rapid CD4+ T cell responses in acute COVID-19 were shown to be associated with mild disease and accelerated viral clearance, and early appearance of SARS-CoV-2-specific T cells was associated with shorter duration of infection. Also, there is evidence with some vaccinations, such as influenza, that T cell-mediated immunity may be a reliable correlate of protection against severe disease in older adults. The VAXZEVRIA-primed T cell responses that formed across all age groups may provide critical protection from severe illness due to COVID-19, as seen in vaccinated participants in these trials. Efficacy of VAXZEVRIA against SARS-CoV-2 variants B.1.351 and B.1.1.7 investigated in Syrian hamsters showed that, despite an observed reduction in nAb titers against B.1.351 in VAXZEVRIA-vaccinated hamsters compared with

those against B.1.1.7, there was evidence of protection in the lower respiratory tract against both variants after vaccination (Swanson et al 2021) .

Correlates of protection against COVID-19 are currently undetermined; however, cellular immunity (T cell responses) are associated with less severe disease. While studies show a possible correlation between nAb levels and VE against symptomatic SARS-CoV-2 infection at a population level, what this means to an individual in terms of their specific level of protection remains unclear (Khoury et al 2021) A similar correlation with VE against severe disease has not been demonstrated. With previous variants (Beta and Delta), VE against severe disease, including hospitalisation and death, has been higher and has been retained for a longer period than VE against mild disease (Abu-Raddad et al 2021, Andrews et al 2022a).

Omicron is reported to escape nAbs elicited by COVID-19 vaccination (with vaccines developed against the ancestral SARS-CoV-2 strain) or natural infection; however, T cell responses are somewhat conserved across variants (including Omicron XBB). While correlation between humoral responses and degree of protection against symptomatic disease have been described at a population level, T-cell responses likely play a more central role in the pathogenesis of severe disease. Recovery from an episode of severe disease is likely a combination of viral clearance and the downregulation of host driven non-infectious inflammatory responses, where T-cell responses are known to be important (Shrotri et al 2021). This may explain the protection against severe disease still afforded by the original vaccine, despite the significantly lower humoral immune responses against these most distant variants (ICMRA 2023, Choi et al 2022, and Meyer et al 2023)

In conclusion, nAbs were not detected against Omicron XBB with a third booster dose in a study performed before XBB emergence; however, following a fourth dose, hybrid immunity driven nAb responses to XBB were observed in approximately 50% of a small sample of study participants. It is unknown how the level of immune response against different variants correlates with clinical outcome. Real world VE data for VAXZEVRIA against the Omicron variant is limited with no available data for Omicron XBB. While there were no nAbs against XBB following a third booster dose, VE was maintained over time against severe disease from Omicron as T cell epitopes are somewhat conserved across variants including XBB descendants which would explain the protection against severe disease offered by vaccines developed against the ancestral SARS-CoV-2 strain.

14 LATE-BREAKING INFORMATION

No potentially important safety or efficacy/effectiveness findings arose after the DLP. Of note, due to the evolving new COVID variants and vaccines landscape there was decreased administration of VAXZEVRIA, and the safety data is limited during this reporting period.

15 OVERVIEW OF SIGNALS (NEW, ONGOING OR CLOSED)

15.1 Overview of Validated Signals (New, Ongoing or Closed)

AstraZeneca are required to carry out pharmacovigilance on a routine basis according to the legislation. Routine pharmacovigilance is described in the pharmacovigilance system master file. However, a summary of signal identification is provided below.

Signals may be identified during:

- Review of individual case safety reports (ICSRs) arising from marketed use of the medicinal product or during clinical trials.
- Regular analysis of aggregate ICSR data, including statistics of disproportionate reporting applied to the AstraZeneca global safety database and, as appropriate, publicly available databases of AEs (the US Food and Drug Administration Adverse Event Reporting System, the World Health Organisation Vigibase and the Eudravigilance Data Analysis System databases).
- Regular review of published biomedical articles and conference abstracts.
- Review of results arising from AstraZeneca-sponsored trials and externally-sponsored scientific research (previously referred to as investigator-sponsored trials).
- Review of reports from the product complaints management system (ie, product quality complaints).

Safety-related enquiries from Health Authorities, healthcare professionals (HCPs), and consumers are also considered a source of signals. Relevant findings from preclinical trials and new safety information on products with the same or similar modes of action to the medicinal product are also considered.

The above are considered the most likely sources of signals, however relevant information from other sources is not excluded from consideration.

In the analysis of aggregate ICSRs arising from marketed use of AstraZeneca products, qualitative and pre-defined quantitative criteria are applied to the data in order to identify signals for evaluation. Quantitative analysis includes the use of algorithms to generate statistics of disproportionate reporting, including significant changes in these statistics over time. The initial evaluation of identified signals may lead to a more detailed evaluation and if a potential new risk is identified, a detailed review is undertaken by a scientific and medical forum.

A tabulation of **validated** signals that were ongoing or closed during the reporting period is presented in Appendix 3.

During the reporting interval, two signals were evaluated and closed. For details on the closed signals: “Decreased appetite” and “Potential Vaccination Failure/Lack of Efficacy against Emerging Variants (including Omicron XBB)” see section 16.2.5.

15.2 Health Authority requests

AstraZeneca received the following requests from PRAC in the Assessment Report (AR) for PBRER (Procedure no.: EMEA/H/C/PSUSA/00010912/202212; period 29 June 2022 to 28 December 2022) and from Therapeutic Goods Administration (TGA) to present the following topics to be addressed in the next Periodic Safety Update Report (PSUR). The topics in question are presented in Table 20.

Table 20 List of Health Authority requests

Topics	Section of the PBRER where additional details is provided	Procedure Number/ Health authority
Estimated exposure of other countries like African countries	Section 5.2.1.1	EMA/H/C/PSUSA/00010912/202212/ EMA
Pemphigus and Pemphigoid	Section 15.2.1	EMA/H/C/PSUSA/00010912/202212/ EMA Note: Pemphigus- also requested by SFDA
Myositis-in specific Dermatomyositis	Section 15.2.2 (Dermatomyositis) Myositis described in Appendix 12	EMA/H/C/PSUSA/00010912/202212/ EMA Note: Myositis also requested by SFDA
SCARs (literature case reports) specifically-Erythema multiforme a cumulative review	SCARs: Section 15.2.3	EMA/H/C/PSUSA/00010912/202212/ EMA
Menstrual disorder (literature review)	Section 15.2.4	EMA/H/C/PSUSA/00010912/202212/ EMA
Hearing loss	Section 15.2.5	TGA
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) described within GBS	Section 15.2.6	SFDA
Thrombosis with thrombocytopenia syndrome: Risk of very rare events after a booster dose	Section 16.3.2.1	EMA/H/C/PSUSA/00010912/202212/ EMA

CIDP Chronic inflammatory demyelinating polyradiculoneuropathy; EMA: European Medical agency; EMEA: Europe, Middle East, and Africa; GBS Guillain-Barre Syndrome; PBRER Periodic Benefit Risk Evaluation Report; PRAC: Pharmacovigilance Risk Assessment Committee; SCAR: Severe Cutaneous Adverse Reactions; SFDA: The Saudi Food and Drug Authority; TGA: Therapeutic Goods Administration.

15.2.1 Pemphigus and Pemphigoid

On 02 December 2022, AstraZeneca received the European Medicines Agency (EMA) PRAC Signal Assessment Report (19858) on pemphigus and pemphigoid with COVID-19 Vaccine (ChAdOx1-5 [recombinant]) -VAXZEVRIA (Vaccines, other viral vaccines) (dated 01 December 2022). Based on the request AstraZeneca performed a cumulative review and considered that there was insufficient evidence to suggest a causal association between pemphigus/pemphigoid and VAXZEVRIA. The PRAC rapporteur agreed with AstraZeneca's assessment on causal association (EMA/H/C/PSUSA/00010912/202212) and requested MAH to continue to monitor the topic in PSUR. On 08 January 2024, SFDA has also requested us to evaluate "Pemphigus" with VAXZEVRIA.

Clinical Trial

A search was conducted in the AstraZeneca Clinical database for AE reports of pemphigus and pemphigoid following use of VAXZEVRIA reported from the completed clinical studies (Final data cut-off of 31 December 2021 for the Oxford pooled studies and 21 March 2023 for Study D8110C00001). The search utilised the following MedDRA PTs:

"Acquired epidermolysis bullosa, Autoimmune blistering disease, Benign familial pemphigus, Dermatitis herpetiformis, Herpes gestationis, Lichen planus pemphigoides, Linear IgA disease, Mucous membrane pemphigoid, Ocular pemphigoid, Paraneoplastic pemphigus, Pemphigoid, Pemphigus, Pemphigus disease area index"

There were no pemphigus and pemphigoid events reported in the Oxford pooled studies (COV001, COV002, COV003, and COV005). From the US study (D8110C00001), one non-serious Pemphigus (Pemphigus Vulgaris) was reported with AZD1222 arm (not related to treatment medication as per investigator) and one non-serious ocular pemphigoid case was reported with placebo.

Global Patient Safety Database

A search was conducted in AstraZeneca Global Safety Database using the above-mentioned search strategy (Search terms included under clinical trial section). During the reporting interval (29 December 2022 to 28 December 2023), 27 cases retrieved, and 4 cases were considered as duplicates (excluded from analysis). Of the remaining 23 cases, 7 cases were related to Pemphigus (Pemphigus vulgaris =2, Pemphigus foliaceus =2 and pemphigus =3), 15 cases related to Pemphigoid (Bullous Pemphigoid=13, Linear IgA disease and Pemphigoid=1, each) and 1 case reported autoimmune blistering disease. A detailed description of these cases is included in Table 21.

Pemphigus cases (n=7 cases)

These 7 Pemphigus cases (5 Literature, 1 Regulatory and Spontaneous each) were MC, and 5 cases reported in female vaccinees and 2 cases in male vaccinees. The vaccinees age ranged between 52-65 years. The median age group of the vaccinees was 62 years and time to onset of the event ranged between 3 Days to 91 Days (median of 10 Days). In two cases, recurrence of pemphigus (new onset with no medical history) was noted with both doses (Dose 1 and Dose 2), in one case there was worsening of the pre-existing condition with dose 2 (no information available with dose 1), in four cases new onset of pemphigus was noted (Dose 2= 2; Dose 1 and Dose 4= 1 case, each). The RW for this topic was considered within 28 Days as recommended by PRAC and in 6 (86%) cases, the TTO was within the RW.

Of the 7 cases, 6 cases (85.7%) were diagnostically confirmed by histopathological examination with immunofluorescence (IF) and serological markers: direct immunofluorescence (DIF) and enzyme-linked immunoassay (ELISA) and skin antibody test. Information on treatment was reported in all cases. Most of them were treatment with topical steroids or oral steroids (prednisolone, methylprednisolone, rituximab, prednisone, mycophenolic acid and doxycycline). The outcome of the event was reported as recovering in 4 cases, in 2 cases outcome was unknown and in 1 cases event was still ongoing.

None of these cases were considered as causally related with VAXZEVRIA. In one case, vaccinee, experienced pemphigus after 90 Days (20 Days after receiving second dose of mRNA vaccine) and in this case the event was assessed as unlikely as the temporal relationship was implausible. The remaining 6 cases had limited information pertaining to latency, concomitant medications, medical history, etiological work-up and clinical course of the events for a comprehensive causality assessment.

The individual case details along with the causality assessments is included in the Table below.

Table 21 Pemphigus cases with histopathological findings and WHO-UMC

Case ID, Country, Source, Age (years), Gender (F/M)	Dose#/ TTO in Days	AE PT (LLT)/ Co-reported PTs	Relevant Investigations	Confounders, risk factors	Recurrence/ relapse	Seriousness, Outcome	Treatment	WHO-UMC causality assessment
Spontaneous, 52, M	Dose 2/ 25	Pemphigus/ Critical illness; Impaired work ability; Suicidal ideation; Joint destruction; General physical health deterioration; Blister; Gait disturbance; Photosensitivity reaction; Autoimmune disorder; Blood pressure abnormal	Unknown	Unknown	New onset	Medically Significant/ Disability, Unknown	Steroids	Possible with limited information
AstraZeneca comment: AE of pemphigus in a 52-year-old male with no medical history. No information on dermatologist or biopsy confirmation. It is unclear if patient experienced any event with Dose 1 and with dose 2, patient reported Pemphigus on Day 25. TTO of 25 Days is reasonable, however, there was insufficient information on biopsy, clinical status of pre-existing pemphigus, any treatment for pre-existing pemphigus and etiological workup.								
Literature, 53, F Pham et al 2023	Dose 4/ 21	Pemphigus/ None	Several erosions had thick crusts, and Nikolsky's sign positive. Histopathology revealed acantholysis above the	Hypertension/ Amlodipine	New onset	Hospitalization, Recovering	Oral methylprednisolone no response after 10 Days initiation. Changed treatment with	Possible with limited information

			stratum basalis and lymphocyte and neutrophil infiltration in the dermis. DIF: IgG and C3 epidermal reticular deposition and absence of IgM, IgA, and fibrinogen.				rituximab (good response)	
AstraZeneca comment: There was insufficient information on concomitant use of anti-hypertensive medications. Clinical course following vaccine dose 1, dose 2 and dose 3. Family history, etiological work-up is missing.								
Literature, 62, F Almasi-Nasrabadi et al 2023	Dose 1/ 7 Dose 2/ 2	Pemphigus	Physical examination demonstrated large erosive annular erythematous plaques on her face, trunk and limbs. No muscular involvement. Histology demonstrated subcorneal acantholysis and a blister filled with neutrophils. acantholysis with suprabasal	No pre-existing AIBD, no family history and no medications	Recurrence-new onset	Medically important/ Recovering	Prednisolone	Possible with limited information

			blistering in PV and subcorneal blistering in PF. DIF: intercellular IgG in the C3 epidermal depositions in a [REDACTED] pattern Biopsy: confirmed Pemphigus					
AstraZeneca comment: The diagnostic certainty of PF with biopsy and spreading of the rash (with dose 1) following the second vaccine dose could be a possible exacerbation, however due to insufficient information on exact chronologic clinical course and any corrective therapy for initial rash, an exacerbation cannot be comprehensively confirmed, although temporal relationship is reasonable. Although there is reported absence of any relevant medical history or concomitant medications, there is limited etiologic and geographical information, limited work-up done for possible triggers including viral exposure and the exclusion of malignancies (hematologic malignancies, solid malignancies (oesophageal and laryngeal cancer), other autoimmune diseases (Sjögren's disease, systemic lupus erythematosus (SLE), and alopecia areata), psoriasis, and neurologic diseases (dementia, Parkinson disease, and epilepsy) which have been related to the appearance of the disease, Limited information on the exposure to concomitant drugs after the first vaccination such as NSAIDs.								
AE Adverse Event; AIBD Autoimmune Skin Blistering Diseases; F Female; IgG Immunoglobulin G; LLT Lowest Level Terms; M Male; PF Pemphigus Foliaceus; PT Preferred Term; PV Pemphigus Vulgaris SLE Systemic Lupus Erythematosus UMC Uppsala Monitoring Centre; WHO World Health Organization								

██████████ Literature, 63, F Corra et al 2023	Dose 1/28 Dose 2/4	Pemphigus	Acantholysis on histology DIF: intercellular deposition of IgG and C3. Serological investigation supported the diagnosis of PV (preferred term: Pemphigus) showing intercellular deposition of IgG and positive staining for anti-DSG1 and anti-DSG3. ELISA was positive for anti-DSG1 and anti-DSG3 antibodies, with titers of 62.2 IU/mL and 157.3 IU/mL, respectively.	Hypertension/ systemic therapy, No medical history of AIBD	Recurrence- new onset	Medically important/ Recovering	Prednisone and rituximab	Possible with limited information
AstraZeneca comment: The diagnostic certainty of PV with biopsy and spreading of the rash (with dose 1) following the second vaccine dose could be a possible exacerbation, however due to insufficient information on exact chronologic clinical course and any corrective therapy for initial rash, an exacerbation cannot be comprehensively confirmed, although temporal relationship is reasonable. Although there is limited etiological and geographical information, limited work-up done for possible triggers including viral exposure and the exclusion of malignancies (hematologic malignancies, solid malignancies (oesophageal and laryngeal cancer), other autoimmune diseases (Sjögren's disease, SLE, and alopecia areata), psoriasis, and neurologic diseases (dementia, Parkinson disease, and epilepsy) which have been related to the appearance of the disease, Limited information on the exposure to concomitant drugs after the first vaccination such as NSAIDs.								

[REDACTED] Literature, 64, M Lansang et al 2023,	Dose 1/90	Pemphigus; Interchange of vaccine products	Punch biopsy showed a spongiotic inflammatory process with eosinophils on the left lower leg and acantholytic dermatosis on the back. DIF: Epidermal intercellular fluorescence for IgG, IgA, and C3 in keeping with IgA pemphigus.	Unknown	New onset	Medically important/ Recovering	Topical 0.25% menthol and 0.25% camphor in 0.1% betamethasone valerate and oral rupatadine to manage his pruritus.	Unlikely
AstraZeneca comment: Vaccinee received Dose 1 of the Vaxzevria and experienced event within 20 Days of Dose 2 with mRNA vaccine. Even when the event is biopsy confirmed, there is insufficient information on exact chronologic clinical course of the events. It is not clear if vaccinee experienced any event post Dose 1 and the event is reported 90 Days after Vaxzevria administration and hence, considered the event “pemphigus” as not related to Vaxzevria.								
[REDACTED] Literature, 65, F Zhou et al 2022	Dose 2/3	Pemphigus	Histopathology: suprabasal acantholysis and a linear palisade of intact basal keratinocytes with a [REDACTED] appearance. DIF: IgG intercellular deposition	No history of autoimmune disorder	New onset	Medically important/ Unknown	Prednisone and mycophenolic acid	Possible with limited information

AstraZeneca comment: Clinical features of pemphigus in a 65-year-old female vaccinee with no history of any autoimmune disorder. TTO of 2-3 Days is reasonable. Insufficient information on any clinical course of the event.								
	Dose 2/ 28	Skin disorder; Muscle twitching; Productive cough; Nasal abscess; Tooth abscess; Abscess oral; Skin weeping; Peripheral swelling; Loss of control of legs; Arthropathy; Muscle disorder; Mouth ulceration; Eye pain; Pemphigus; Monoplegia; Muscle atrophy; Tongue biting; Oropharyngeal pain; Joint stiffness; Musculoskeletal stiffness; Blister; Oral herpes; Loss of consciousness; Swelling; Feeling abnormal; Malaise; Myalgia; Headache; Arthralgia; Influenza like illness; Fatigue; Pain in extremity; Pain in extremity;	Unknown	Unknown	Worsening	Disability/ Unknown	Topical doxycycline	Possible with limited information
Regulatory, F								

		Pain; Rash; Swollen tongue; Pruritus						
AstraZeneca comment: Vaccinee's baseline information like medical history, underlying medical condition, lab values, biopsy details missing, etiologic work-up is missing, information leading up to the events are not clear. Event observed with dose 1 is missing.								

DIF: Direct immunofluorescence; ELISA: Enzyme-linked immunosorbent assay; F: female; IIF: Indirect immunofluorescence; M: Male; MH: Medical History; PT: Preferred Term; Unk: Unknown; NA: Not applicable; SmPC: Summary of product characteristics; SSS: Salt-split skin.

Pemphigoid cases including 1 autoimmune blistering disease case (n=16 cases)

Of 16 Pemphigoid cases (13 Literature and 3 regulatory) 13 were MC and 3 cases were consumer reports. 8 cases were reported for female vaccinees and 8 for male vaccinees. The vaccinees age ranged between 49-86 years. The median age group of the vaccinee was 72 years. The time-to-onset of the event ranged between 3-294 Days (median of 7 Days).

In 3 cases, recurrence of Pemphigoid (new onset with no medical history) was noted with both doses (Dose 1 and Dose 2), in one case there was worsening of the pre-existing condition with Dose 1, in nine cases new onset of pemphigus was noted (Dose 1=2, Dose 2= 4; Dose 3= 1 and Dose unknown n=2). In 3 cases, there was a relapse of the underlying condition with Dose 1 by 7-14 Days. The RW for this topic was considered within 28 Days as recommended by PRAC and in 14 (75%) cases, the TTO was within the RW.

Of the 16 cases, 10 cases (62.5%) were diagnostically confirmed by histopathological examination with immunofluorescence (IF) and serological markers: DIF and enzyme-linked immunoassay (ELISA), Salt-split skin (SSS) and skin antibody test. Information on treatment was reported in all cases. Most of them were treatment with topical steroids or oral steroids (Dapsone, prednisolone, methylprednisolone, azathioprine, prednisone, mycophenolic acid and doxycycline). The outcome of the event was reported as recovering in 2 cases, in 7 cases outcome was unknown, in 6 cases outcome was reported as recovered and recovered with sequelae and in 1 case outcome was reported with fatal outcome. The cause of death of an elderly vaccinee was atrial fibrillation, acute kidney injury, and methicillin-sensitive *Staphylococcus aureus* sepsis.

None of these cases were considered as causally related with VAXZEVRIA. In 2 cases, vaccinee, experienced pemphigoid after 90 Days and these cases were assessed as unlikely as the temporal relationship was implausible. In one case, relapse of the event was noted with Dose 1 (underlying condition IBD especially Ulcerative colitis [UC]) and four cases were confounded by underlying medical condition or concomitant medications. The remaining 9 cases had limited information pertaining to latency, concomitant medications, medical history, etiological work-up and clinical course of the events for a comprehensive causality assessment.

The individual case details along with the causality assessments is included in the Table below.

Table 22 Pemphigoid cases with histopathological findings and WHO-UMC

Case ID, Country, Source, Age (years), Gender (F/M)	Dose#/ TTO in Days	AE PT (LLT)/ Co-reported PTs	Relevant Investigations	Confounders, risk factors	Recurrence/ relapse	Seriousness, Outcome	Treatment	WHO-UMC causality assessment
Literature, 72, F, Maronese et al 2022	Dose 1 (AZ vaccine) and Dose 2 (mRNA vaccine) / TTO unknown	Pemphigoid (Bullous pemphigoid)/ Off label use; Interchange of vaccine products	Biopsy confirmed.	Acetylsalicylic acid, amlodipine maleate, levothyroxine, perindopril erbumine and simvastatin. Baseline BPDAI score is 15.	Recurrence-new onset	Medically confirmed, Unknown	Systemic corticosteroids and Dapsone	Possible with Confounders
AstraZeneca comment: Vaccinee is over 60 years and at baseline, BPDAI score is 15. Patient was receiving treatment with amlodipine (latency unknown) and Pemphigoid is histopathological confirmed. Baseline line etiological work up, medical history, underlying medical condition, lab values, biopsy details missing, information leading up to the events are not clear. However, considering the elderly age group, patient was on concomitant Amlodipine and simvastatin (which has Pemphigoid listed as an ADR as per SmPC) and hence considered as possible with confounded).								
Literature, 77, F Maronese et al 2022	Dose 1/ 3	Pemphigoid (Bullous pemphigoid)/ None	Biopsy confirmed. DIF: Linear C3 deposits along with dermal-epidermal junctions. IIF: IgG along with DEJ SSS:roof ELISA: 52.9 anti-BPI 80 (U/mL);	Baseline BPDAI score 42 and ABSIS 60 Amlodipine, bisoprolol, furosemide, ramipril, sertraline.	Worsening	Medically confirmed, Resolved	Methotrexate	Possible with Confounders

Table 22 Pemphigoid cases with histopathological findings and WHO-UMC

Case ID, Country, Source, Age (years), Gender (F/M)	Dose#/TTO in Days	AE PT (LLT)/ Co-reported PTs	Relevant Investigations	Confounders, risk factors	Recurrence/ relapse	Seriousness, Outcome	Treatment	WHO-UMC causality assessment
			22.2 anti-BP230 (U/mL)					
AstraZeneca comment: Patient had a moderate disease at baseline (BPDAI score is 42 (ABSIS 60) and there as a worsening of the underlying condition noted within 3 Days of first dose of Vaxzevria. This elderly vaccinee receiving concomitant treatment with amlodipine, furosemide, ramipril and simvastatin (Latency unknown). Based on the temporal association, the event is considered as possible with confounders (Pemphigoid listed as an ADR as per SmPC of amlodipine, furosemide, ramipril and simvastatin).								
Literature, 86, M, Lai et al 2022	Dose 1/ 14	Pemphigoid (Bullous pemphigoid)/ None	Bullous pemphigoid with Pemphigoid Nodularis (PN). There were some tense bullae with some flattened erythematous nodules on his back with excoriation.	Prurigo nodularis, Diabetes using Gliptins (DPP-4 inhibitor)	Relapse	Medically confirmed, Resolved	Systemic steroid treatment (methylprednisolone 4--32 mg/day), doxycycline (100 mg twice daily), topical clobetasol 0.05 ointment, and systemic antihistamines were administered as adjuvant to dupilumab.	Possible with confounders
AstraZeneca comment: Patient was recovering from Prurigo nodularis with treatment of dupilumab. However, multiple blisters on the trunk and limbs appeared within 2 weeks after the first injection of the AstraZeneca COVID-19 vaccine. Gliptins were stopped and treatment with systemic steroid treatment (methylprednisolone 4-32 mg/day), doxycycline (100 mg twice daily), topical clobetasol 0.05 ointment, and systemic antihistamines were administered as adjuvant therapy in addition to the dupilumab. Patient reported nearly complete resolution of the pruritus, and he remained free of blisters and PN for 10 months after dupilumab monotherapy. However, when we attempted to prolong the dosing interval to every 3 weeks, the bullous lesions recurred. The subject								

Table 22 Pemphigoid cases with histopathological findings and WHO-UMC

Case ID, Country, Source, Age (years), Gender (F/M)	Dose#/TTO in Days	AE PT (LLT)/ Co-reported PTs	Relevant Investigations	Confounders, risk factors	Recurrence/ relapse	Seriousness, Outcome	Treatment	WHO-UMC causality assessment
has medical history of diabetes and use of DPP-4 inhibitor, as per the article this drug was stop and with treatment with dupilumab the patient recovered. The article also reported that the subject has multiple relapses a year since 2011. The case is considered possible with cofounders due medical history of PN and use of gliptins (DPP-4 inhibitors).								
Literature, 49, F Chao et al 2022	Dose 1/ 1 day Dose 2/ 5 Days	Pemphigoid (Bullous pemphigoid)/ Rash pruritic	Sub-epidermal blister and a perivascular infiltrate of eosinophils and lymphocytes in the dermis. DIC: linear deposition of IgG at dermal-epidermal junction F revealed negative anti-intercellular substance antibody, but positive anti-basement membrane zone antibody with titer 1:40. Note: other infectious factors were excluded.	Denied history of skin disorders	Recurrence-new onset	Medically important/ Recovering	Methylprednisolone and Azithroprine	Possible with limited information

Table 22 Pemphigoid cases with histopathological findings and WHO-UMC

Case ID, Country, Source, Age (years), Gender (F/M)	Dose#/TTO in Days	AE PT (LLT)/Co-reported PTs	Relevant Investigations	Confounders, risk factors	Recurrence/relapse	Seriousness, Outcome	Treatment	WHO-UMC causality assessment
AstraZeneca comment: The diagnostic certainty of PF with biopsy and spreading of the rash (bullous eruption, recovered-no treatment reported) following the second vaccine dose could be a possible exacerbation, however due to insufficient information on exact chronologic clinical course and any corrective therapy for initial bullous eruption, an exacerbation cannot be comprehensively confirmed, although temporal relationship is reasonable. Although there is reported absence of any relevant medical history or concomitant medications, there is limited etiological work-up done for possible triggers (environmental or genetic) considering the reporting country of Tunisia wherein PF is endemic. In addition to the above comments, most vaccine related cases tend to happen after 10-14 Days post immunisations, secondary to the production of IgG, there is limited information on concomitant medications including diabetic medication such as gliptins, in this case medical history is missing in relation to non-skin disorders (malignancies, comorbidities secondary to overweight as seen in the pictures presented in the literature article here reported) which could provide insight on other possible concomitant medications (Gliptins, PD-1/PD-L1 inhibitors, Loop diuretics, penicillin's, NSAIDs, Thiazides). For this reason, the causality as per WHO is possible with limited information.								
Literature, 51, M, Hali et al 2022	Dose 3/7	Pemphigoid (Bullous pemphigoid)	Subepidermal split with a superficial perivascular inflammatory infiltrate and predominant eosinophils. Nikolsky positive DIF: Linear C3 pattern at the basement membrane zone. IIF: salt-split normal human skin substrate: detected circulating immunoglobulin G	None	New onset	Medically important/Recovered	Prednisone	Possible with limited information

Table 22 Pemphigoid cases with histopathological findings and WHO-UMC

Case ID, Country, Source, Age (years), Gender (F/M)	Dose#/TTO in Days	AE PT (LLT)/ Co-reported PTs	Relevant Investigations	Confounders, risk factors	Recurrence/relapse	Seriousness, Outcome	Treatment	WHO-UMC causality assessment
			(IgG) (BP180 antibodies)					
AstraZeneca comment: Etiological work-up, clinical course following vaccine dose 1 and dose 2 was not available, concomitant medications, medical history is missing. Based on the temporality, the event is considered as possible with limited information								
Literature, 54, F, Hali et al 2022	Dose 1/ 3	Pemphigoid (Bullous pemphigoid)	Nikolsky positive, subepidermal split with a superficial perivascular inflammatory infiltrate and predominant eosinophils. DIF and IIF are positive with linear IgG and C3, consistent with BP. Eosinophil count of 2200/mm ³ .	Unknown	New onset	Medically Significant, Unknown	topical steroids with clobetasol propionate	Possible with limited information
AstraZeneca comment: Etiological work-up, clinical course following vaccination, concomitant medications, medical history is missing. Based on the temporality, the event is considered as possible with limited information								
Literature, 60, F,	Dose 2/ 5	Pemphigoid (Bullous pemphigoid)	BPDAI/PDAI score 5	No pre-existing AIBD	New onset	Medically important/ Unknown	Unknown	Possible with limited information

Table 22 Pemphigoid cases with histopathological findings and WHO-UMC

Case ID, Country, Source, Age (years), Gender (F/M)	Dose#/TTO in Days	AE PT (LLT)/ Co-reported PTs	Relevant Investigations	Confounders, risk factors	Recurrence/ relapse	Seriousness, Outcome	Treatment	WHO-UMC causality assessment
Cowan et al 2023								
AstraZeneca comment: Etiological work-up, clinical course following vaccine dose 1 is not available, concomitant medications, medical history is missing. Based on the temporality, the event is considered as possible with limited information								
Literature, 68, M, Hali et al 2022	Dose 1/ 14 Dose 3 (within 3 weeks of Dose 1)/ 7	Pemphigoid (Bullous pemphigoid)	Tense bullae and bullous eruption on an erythematous base measuring 3-10 cm in diameter on trunk and limbs, with a positive Nikolsky sign. Erosions on the oral and genital mucosa were also observed	Hypercholeste rolemia	Recurrence/ new onset	Medically important/ Recovered with sequelae	oral corticosteroid therapy	Possible with limited information
AstraZeneca comment: Etiological work-up, clinical course following vaccine dose 1 is not available, concomitant medications, medical history is missing. Based on the temporality, the event is considered as possible with limited information								
Literature, 71, M Cowan et al 2023	Dose 2	Pemphigoid (Bullous pemphigoid)	BPDAI/PDAI score 78	Unknown	New onset	Medically important/ Unknown	Yes, but unknown	Possible with limited information

Table 22 Pemphigoid cases with histopathological findings and WHO-UMC

Case ID, Country, Source, Age (years), Gender (F/M)	Dose#/TTO in Days	AE PT (LLT)/ Co-reported PTs	Relevant Investigations	Confounders, risk factors	Recurrence/ relapse	Seriousness, Outcome	Treatment	WHO-UMC causality assessment
AstraZeneca comment: Patient received both the doses (not clear as per the article). Also, events with dose 1 and clinical course of events. Baseline information is missing and no pre-existing AIBD, relevant clinical features and histopathological findings are missing.								
Regulatory, 71, F	Dose 2/4	Pemphigoid (Bullous pemphigoid)	None	Unknown	New onset	Life-threatening/ Recovered with sequelae	Unknown	Possible with limited information
AstraZeneca comment: Patient received both the doses, but the clinical course of events with dose 1, baseline information and no pre-existing AIBD, relevant clinical features and histopathological findings are missing.								
Belgium, Literature, 75, M Happaerts et al 2022	Dose 1/ Unknown	Pemphigoid (Bullous pemphigoid)/ Acquired haemophilia;	Large ecchymosis on his right arm and left buttock, with multiple new bullae.	Bullous Pemphigoid (BP) (probably a year ago), COVID-19 pneumonia, chronic kidney disease stage 3b, arterial hypertension, and insulin-dependent diabetes mellitus,	Relapse	Fatal/ Death (not due to BP)	Methylprednisolone	Possible with confounder

Table 22 Pemphigoid cases with histopathological findings and WHO-UMC

Case ID, Country, Source, Age (years), Gender (F/M)	Dose#/TTO in Days	AE PT (LLT)/ Co-reported PTs	Relevant Investigations	Confounders, risk factors	Recurrence/relapse	Seriousness, Outcome	Treatment	WHO-UMC causality assessment
				complicated with polyneuropathy and a chronic foot ulcer.				
AstraZeneca comment: Patient with a prior history of bullous pemphigoid develops AHA and noted multiple new bullae within 10 Days of vaccination. Patient with multiple co-morbidities developed new atrial fibrillation, acute kidney injury and methicillin-sensitive staphylococcus aureus sepsis and his clinical condition deteriorated. This elderly patient received palliative treatment and died after 15 Days of hospitalization due to atrial fibrillation, acute kidney injury and methicillin-sensitive Staphylococcus aureus sepsis. Based on the available information, the event pemphigoid is confounded by elderly age and medical history of bullous pemphigoid.								
Literature, 83, F Jmor et al 2022	Dose 1/ 10	Pemphigoid (Bullous pemphigoid)	Biopsy confirmed. Itchy erythema with tense blisters throughout her limbs and trunk	Unknown	New onset	Medically important/ Recovering	Prednisolone, doxycycline, and ultra-high potency topical corticosteroids	Possible with limited information
AstraZeneca comment: Etiological work-up, clinical course following vaccine dose 1 is not available, concomitant medications, medical history is missing. Based on the temporality, the event is considered as possible with limited information.								
Regulatory, 82, M	Dose unknown	Pemphigoid (Pemphigoid)	None	Unknown	New onset	Medically important/ unknown	Unknown	Unassessable/unclassifiable with limited information
AstraZeneca comment: Etiological work-up, clinical course following vaccination, concomitant medications, medical history is missing. Hence, the causality of the event with Vaxzevria is Unassessable/unclassifiable as the dose related information and event onset date is unknown.								

Table 22 Pemphigoid cases with histopathological findings and WHO-UMC

Case ID, Country, Source, Age (years), Gender (F/M)	Dose#/TTO in Days	AE PT (LLT)/ Co-reported PTs	Relevant Investigations	Confounders, risk factors	Recurrence/ relapse	Seriousness, Outcome	Treatment	WHO-UMC causality assessment
Regulatory, 63, F	Dose unknown/ 294	Pemphigoid (Bullous pemphigoid) Dermatitis artefacta; Linear IgA disease	None	Allergy, Asthma	New onset	Medically Significant/D isability, Unknown	Unknown	Unlikely
AstraZeneca comment: Etiological work-up, clinical course following vaccination, concomitant medications, medical history is missing. However, event occurred beyond the risk window and hence considered as unlikely with Vaxzevria.								
Literature, 76, M, Hou et al 2022	Dose 1/ 7	Pemphigoid (Pemphigoid)/ Pyostomatitis vegetans (PSV) and autoimmune blistering disease	Biopsy: superficial ulcers covered with purulent crust, epidermal hyperplasia with mild spongiosis, some necrotic basal keratinocytes, and focal dermoepidermal junction separation but without acantholysis. DIF: granular to linear staining of IgG and C3 along	Inflammatory bowel diseases (IBD) particularly Ulcerative colitis (UC). Flareup of UC 7 months ago.	Relapse	Medically important/ Recovered	0.1% topical tacrolimus	Unlikely

Table 22 Pemphigoid cases with histopathological findings and WHO-UMC

Case ID, Country, Source, Age (years), Gender (F/M)	Dose#/TTO in Days	AE PT (LLT)/Co-reported PTs	Relevant Investigations	Confounders, risk factors	Recurrence/relapse	Seriousness, Outcome	Treatment	WHO-UMC causality assessment
			the dermoepidermal junction. Tzanck's smear revealed negative herpetic cytopathy.					
AstraZeneca comment: PSV developed 1 week after first AstraZeneca vaccination. Though there was temporal relationship, the patient's PSV occurred during UC flare-up. The patient has a known concurrent disease of UC, and the description of the symptoms are in line with a UC flare -up. The events pemphigoid and PSV are due to exacerbation of underlying disease condition post vaccination.								
Literature, 82, M Cowan et al 2023	Dose 2/ 92	Linear IgA disease (Linear IgA disease)	BPDAI/PDAI score 47	Had a mild or pre-existing condition BPDAI/PDAI 14	New onset	Life-threatening/ unknown	Unknown	Unlikely
AstraZeneca comment: As the event occurred beyond the risk window, the event was considered as unlikely. Patient received both the doses. Also, events with dose 1 and clinical course of events, baseline information is missing, relevant clinical features and histopathological findings are missing.								

ABSIS Autoimmune Bullous Skin Disorder Intensity Score; AHA: Acquired Hemophilia; aPTT: Activated partial thromboplastin time; BMI: Body mass index; BPDAI: Bullous Pemphigoid Disease Area Index; DEJ: Dermal-epidermal junction; DH: Dermatitis Herpetiformis; DIF: Direct immunofluorescence; DM: diabetes mellitus; ELISA: Enzyme-linked immunosorbent assay; F: female; IIF: Indirect immunofluorescence; M: Male; MH: Medical History; ; NA: Not applicable; PDAI Pemphigoid Disease Area Index; PT: Preferred Term; SmPC: Summary of product characteristics; SSS: Salt-split skin; Unk Unknown

Literature

A search of medical databases (including Embase and Insight Meme database) up to 28 December 2023 was conducted to obtain information on literature articles about pemphigus and pemphigoid reported in vaccinees' receiving VAXZEVRIA and discussing possible mechanisms/plausible causal association between BP, PV and related blistering conditions and vaccination with VAXZEVRIA.

The following key words were utilized as part of the search strategy:

'epidermolysis bullosa'/exp OR 'acquired epidermolysis bullosa' OR 'autoimmune blistering disease' OR 'hailey hailey disease'/exp OR 'benign familial pemphigus' OR 'dermatitis herpetiformis'/exp OR 'pemphigoid gestationis'/exp OR 'herpes gestationis' OR 'lichen planus pemphigoides' OR 'linear IgA bullous dermatosis'/exp OR 'linear IgA disease' OR 'mucous membrane pemphigoid'/exp OR 'ocular pemphigoid' OR 'paraneoplastic pemphigus'/exp OR 'pemphigoid'/exp OR 'pemphigus'/exp OR 'pemphigus disease area index'

Cumulatively until 30 November 2022, 143 articles were retrieved, and these articles were reviewed and discussed as part of the response submitted 06 February 2023 (Appendix). During the reporting interval, 56 literature articles were retrieved, and 15 cases were case series and these articles were included under the global safety database analysis. The remaining 41 articles did not report any new information or abnormal epidemiologic trends of pemphigus/pemphigoid post COVID-19 vaccination.

Discussion and Conclusion

AstraZeneca performed a cumulative evaluation of available data on pemphigus and pemphigoid from sources including pre-clinical, clinical studies, post-marketing case reports, observed versus expected analysis and published literature.

There were no reports of pemphigus and pemphigoid in the Oxford Studies (COV001, COV002, COV003, and COV005) and from US Study (D8110C00001), one case (PT: Ocular pemphigoid) was reported in the placebo group and one non-serious Pemphigus (Pemphigus Vulgaris) was reported with AZD1222 arm (not related to treatment medication as per investigator).

Within AstraZeneca Global Safety Database, 23 events of interest (7 pemphigus, 16 pemphigoid) were identified. The distribution of cases by age, gender, reporting country, were similar to the BG rates in non-COVID-19 vaccinated population. The trends of fatality and relapse rates were less than the expected trends based on BG data in non-COVID-19 vaccinated population. Overall, majority of the cases had insufficient information for a comprehensive causality assessment. No specific pattern or index case was identified upon a careful assessment of these cases.

Upon review of literature retrieved, no abnormal epidemiologic trends of pemphigus/pemphigoid post COVID-19 vaccination. In summary, a review of the clinical, post-marketing cases,

literature data did not identify any safety concerns in association of pemphigus and pemphigoid and VAXZEVRIA.

Based on the review of the currently available cumulative data, AstraZeneca considers that there is insufficient evidence to suggest a causal association between pemphigus/pemphigoid and VAXZEVRIA. It is AstraZeneca's opinion that no changes to the CDS or RMP on this topic are warranted at this time. AstraZeneca will continue to monitor pemphigus and pemphigoid as part of routine surveillance activities for VAXZEVRIA.

15.2.2 Myositis-specifically Dermatomyositis

In the assessment report received from the PRAC (procedure number: EMEA/H/C/PSUSA/00010912/202206) for the (review period: 29 December 2022 to 28 December 2023), further information on the topic of Dermatomyositis has been requested as follows:

The MAH is requested to present new cases of dermatomyositis (DM) and as well as new data from the literature.

From SFDA, AstraZeneca also received a request to review Myositis. The topics myositis including Dermatomyositis was monitored as part of the routine surveillance and no new safety concerns were raised. However, as requested by PRAC a review of new literatures and cases of Dermatomyositis were performed and details are summarized below.

Global Patient Safety Database

A search was conducted in AstraZeneca Global Safety Database using the below mentioned search strategy.

Dermatomyositis; Anti-melanoma differentiation-associated protein 5 antibody positive; Anti-Jo-1 antibody; Anti-MDA5 antibody positive

The above-mentioned search retrieved 9 cases, all MC (6 initial and 3 FU cases) during the reporting interval. Most of these cases were from literatures (n=7, 77.8%) and 2 cases (22.2%) were received from regulatory authorities. Most of these cases were received from Taiwan (n=3). Five vaccinees were Female and 4 were male. The age of the vaccinees ranged between 27 to 90 years and the median age is 60 years. The median TTO was 14 Days (range 3 to 21 Days). Of the 9 cases, 8 had TTO within the RW of 28 Days. The dose related information was available in only 7 cases. In 4 cases, event occurred with Dose 2 (n=4) and in 3 cases event occurred post Dose 1. The outcome of the events was reported as recovering in 5 cases, in 1 case reported as Recovered with sequelae and 3 cases the outcome was not reported.

Case classifications based on EULAR/ACR

All 9 cases were assessed and classified according to European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) Idiopathic Inflammatory Myopathies (IIM) classification criteria Lundberg et al 2017 and are presented in Table 23. In most cases, clinical details of the event, relevant laboratory values, muscle biopsy findings, electromyographic study results, and autoantibodies profiles were not provided but a conservative approach was used for classification criteria for both possibility of IIM and subgroup Dermatomyositis.

None of the cases were considered as probable/ definite based on the available information.

Table 23 Summary of Dermatomyositis cases received during the PBRER period

Sr. No.	AZ Case ID / Country / Serious (S/NS)/ HCP (Y/N)/ source	Age (y) / Sex	PT/ Event Outcome EULAR/ACR IIM assessment	TTO ^a / Vaccine dose	WHO-UMC Causality AZ assessment	AstraZeneca comment
1	[REDACTED] S/Y/Regulatory	62/M	Dermatomyositis/ Recovered with sequelae/	3 Days/Dose 1	Possible with limited information	The case has limited information on baseline health and does mention that the patient has myasthenia gravis (no clear info when it started) which could also explain the symptoms described in the case and may be a differential diagnosis as myasthenia gravis and Lambert-Eaton syndrome has been known to mimic dermatomyositis
2	[REDACTED]/S/Y/Lit erature Ajdinaj et al 2022	68/M	Dermatomyositis/ Recovering/	Unk/Unk	Unassessable/uncl assifiable with limited information	Limited information on clinical details and risk factors
3	[REDACTED] S/Y/Literature Guevarra et al 2023	27/M	Dermatomyositis/ Recovering/	Unk/Unk	Unassessable/uncl assifiable with limited information	Limited information on clinical details and risk factors
4	[REDACTED] /Y/Literature Walid et al 2023	60/F	Dermatomyositis/ Recovering/	5 Days/Unk	Possible with limited information	Limited information on clinical details and risk factors. There was no MH of rash or drug intake prior to the event but other details are not provided

Table 23 Summary of Dermatomyositis cases received during the PBRER period

Sr. No.	AZ Case ID / Country / Serious (S/NS)/ HCP (Y/N)/ source	Age (y) / Sex	PT/ Event Outcome EULAR/ACR IIM assessment	TTO ^a / Vaccine dose	WHO-UMC Causality AZ assessment	AstraZeneca comment
5	[REDACTED] N/Y/Li terature Suparna et al 2023	45/F	Dermatomyositis/ Recovering/	21 days (3 weeks) /Unk	Possible with limited information	TTO within RW (0-28 Days). The case has limited information, no aetiology workup, physical examination or laboratory testing was provided in the case to exclude other causes or know risk factors such as other systemic rheumatic diseases, metabolic, infectious, malignant disorders, causes of photosensitive or pruritic cutaneous eruptions.
6	[REDACTED] NS/ Y/ Literature Chiang et al 2023	79/F	Dermatomyositis/ Recovering/	7 days (1 week)/Unk	Possible with limited information	TTO within RW (0-28 Days). Limited information on baseline health status, medical history and concomitant medications
7	[REDACTED] NS/ Y/Literature Chao et al 2022	41/M	Dermatomyositis/ Recovering/	3 weeks/Unk	Possible with limited information	TTO within RW (0-28 Days). Limited information on baseline health status, medical history, and concomitant medications
8	[REDACTED] S/ Y/Regulatory	53/F	Dermatomyositis/ Not recovered/	Unk/Unk	Unassessable/Unclassifiable - limited information	Limited information on clinical details and risk factors, baseline health, etiology workup.

Table 23 Summary of Dermatomyositis cases received during the PBRER period

Sr. No.	AZ Case ID / Country / Serious (S/NS)/ HCP (Y/N)/ source	Age (y) / Sex	PT/ Event Outcome EULAR/ACR IIM assessment	TTO ^a / Vaccine dose	WHO-UMC Causality AZ assessment	AstraZeneca comment
9	[REDACTED] S/Y/ Literature Wu CF et al 2023	90/F	Dermatomyositis/ Unknown/	3 weeks (21 days)/Unk	Possible with limited information	Event with dose 1 is missing TTO within RW (0-28 Days) for 2nd dose. Etiology workup was not completed to exclude other know causes, overlap syndrome, and baseline line health, the case does not provide clear information on all the medical history of the patient and concomitant medications which may cause drug induce myopathy.

^a Shortest

AZ AstraZeneca; DM Dermatomyositis; EULAR/ACR European Alliance of Associations for Rheumatology/American College of Rheumatology; F Female; HCP Healthcare Professional; ID Identifier; IIM = Idiopathic Inflammatory Myopathies; M Male; N No; NS Non-Serious; PT Preferred Term; RW Risk Window; S Serious; Sr No Serial Number; TTO Time To Onset; Unk Unknown; WHO-UMC World Health Organization- Uppsala Monitoring Centre; Y Yes.

Literature

A search of medical databases (including Embase and Insight Meme database) up to 28 December 2023 was conducted to obtain information on literature articles about Dermatomyositis reported in vaccinees' receiving VAXZEVRIA and discussing possible mechanisms/plausible causal association between Dermatomyositis and vaccination with VAXZEVRIA.

During the reporting interval 190 new literatures were retrieved, 31 were related to VAXZEVRIA and the remaining 159 articles were related to other COVID-19 vaccines. Five articles speaking about case series (6 case reports) were reviewed as part of the global safety database analysis and the review remaining 25 literatures with VAXZEVRIA neither suggested a causal association nor mechanism by which Dermatomyositis is caused post vaccination.

Discussion and Conclusion

During the reporting interval, 9 new cases were retrieved within AstraZeneca Global Safety Database. Most of these cases were literature case reports. The cases were assessed and classified according to the EULAR/ACR IIM criteria. None of these cases probable/ definite based on the available information. Overall, majority of the cases had insufficient information for a comprehensive causality assessment. No specific trend or pattern was identified.

Upon review of literature retrieved, no abnormal epidemiologic trends of dermatomyositis post COVID-19 vaccination. In summary, a review of the clinical, post-marketing cases, literature data did not identify any safety concerns in association of dermatomyositis and VAXZEVRIA. Based on the review of the cumulative data, AstraZeneca has concluded that there is insufficient evidence to suggest a causal association between dermatomyositis and VAXZEVRIA. No changes to the CDS or RMP are recommended for myositis specifically for dermatomyositis and the topic will continue to be monitored as part of ASTRAZENECA's ongoing safety surveillance activities for VAXZEVRIA.

15.2.3 SCARs in particularly erythema multiforme

15.2.3.1 SCARs (Literature case reports)

In the assessment report (EMA/H/C/PSUSA/00010912/202212) of the previous PBRER DLP 28 December 2022, PRAC has requested MAH to present all the literature cases reports (including the ones discussed in previous reporting interval along with new literature case reports).

SCAR cases: The MAH is requested to review and discuss all available literature cases (ie. cases that might have been discussed in the previous PSUR together with any new literature cases).

Background: Based on the PRAC request, in the current PBRER all literature case reports on SCARs are presented below. Additionally, a detailed review on Erythema multiforme is included in Section 15.2.3.2 (Erythema multiforme).

Global Patient Safety Database

A search of the AstraZeneca Global Safety database for the reporting interval using the SMQ (narrow, MedDRA 26.1): Severe cutaneous adverse reactions (excluding the PT: Cutaneous vasculitis) retrieved around 21 cases reporting the following 22 events.

Table 24 **Distribution of SCARs events by MedDRA PTs with VAXZEVRIA during the reporting interval**

MedDRA PT	Number of events
Acute generalized exanthematous pustulosis	1
Dermatitis bullous	5
Erythema multiforme	6
Stevens-Johnson syndrome	6
Toxic epidermal necrolysis	4
Total	22

MedDRA Medical Dictionary for Regulatory Activities; PT Preferred Term

Of the 21 cases, 6 cases of erythema multiforme is included in Section 15.2.3. Of the remaining 15 cases, 8 cases are literature reports, and they are summarized in the table below as per the PRAC request received.

Of the remaining 7 cases reported from other sources, 4 cases are related to Dermatitis bullous, 2 Stevens-Johnson syndrome (SJS) and 1 Toxic epidermal necrolysis (TEN) cases. Of these 7 cases one TEN case was reported with fatal outcome. In this case, a 74-year-old male patient with a medical history of diabetes mellitus and hypertension reported TEN with Dose 2 of vaccination (dose 1 no events reported). Patient experienced an aggressive skin reaction, which began with the appearance of diffuse red dots evolved into a chicken vesicle, on more than 60% of the cutaneous surface (Lyell's syndrome) and this patient died on an unknown date. It was unknown if the autopsy was performed. This case has limited information pertaining to clinical course of events with Dose 1 and concomitant medications.

The remaining 6 cases had limited information pertaining to clinical features of the event, confirmatory tests (biopsy) and etiological features.

Based on the PRAC request all literature case reports of SCARS retrieved cumulatively are presented below. Cumulatively there were 29 literature cases reports and 8 cases reported EM and they are summarized in Section 15.2.3 The remaining 21 case reports are summarized below.

Table 25 Summary of all literature case reports on SCARs with VAXZEVRIA

Authors / Case ID / Age / Gender / Country	Clinical features	Final diagnosis	Time to onset (in Days) / Dose number	New onset / Relapse / Worsening / Recurrence	Previous history	Outcome	AZ Assessment as per WHO-UMC scale
Acute generalized exanthematous pustulosis (AGEP)							
Guégan et al 2021 / [REDACTED] / 43 / F / [REDACTED]	Diffuse maculopapular pustular exanthema (>80% of BSA)	Acute generalized exanthematous pustulosis	3 / Dose 1	New onset	[REDACTED] Adrenal insufficiency, Cytomegalovirus (CMV) colitis, Oesophageal candidiasis, and Vaginal infection	Recovered	Possible with confounders
Treatment: Topical corticosteroids							
Laboratory data: not reported Histopathology: Lichenoid interface dermatitis, intracorneal pustules, lymphocytic infiltrate with numerous eosinophils							
AstraZeneca Comment: Time to onset of 3 Days after Dose 1 of Vaxzevria, suggested a plausible time relationship. Medical history included [REDACTED] adrenal insufficiency, osteonecrosis, [REDACTED] CMV colitis, vaginal infection, esophageal thrush and abdominal infection which are considered confounders; hence causality assessment is considered as Possible with confounders.							
Wantavornprasert et al 2021 / [REDACTED] / 32 / F / [REDACTED]	Not reported	Acute generalized exanthematous pustulosis	21 / Dose 1	New onset	Unknown	Recovered	Possible with limited information
Treatment: Systemic corticosteroids							
Laboratory data: leukocytosis with neutrophilia Histopathology: not reported							
AstraZeneca Comment: Time to onset of 21 Days after Dose 1 of Vaxzevria, suggested a plausible time relationship. Limited information on baseline health condition before vaccination, relevant family and medical history, concurrent disease, concomitant medications, risk factors							

Table 25 Summary of all literature case reports on SCARs with VAXZEVRIA

Authors / Case ID / Age / Gender / Country	Clinical features	Final diagnosis	Time to onset (in Days) / Dose number	New onset / Relapse / Worsening / Recurrence	Previous history	Outcome	AZ Assessment as per WHO-UMC scale
	(allergy, smoking, alcohol, autoimmune diseases), detailed etiological and diagnostic workup (dermatological examination, infection work up, skin biopsy), hence, WHO-UMC causality assessment was considered as Possible with limited information.						
Kang et al 2021 / [REDACTED] 32 / F	Generalized pruritic rash and feverish sensation.	Acute generalized exanthematous pustulosis	21 / Dose 1	New onset	None	Recovered	Possible with limited information
	Treatment: Oral antihistamine and high-potency topical corticosteroids, as well systemic corticosteroid.						
	Clinical observation: pustular eruptions atop erythematous areas that started in the axillary regions and rapidly progressed to the upper and lower extremities, where various sizes of erythematous lesions containing numerous pinhead-sized pustules. Laboratory data: white blood cell count of $12.72 \times 10^3/\text{mm}^3$ with 89.0% neutrophils Histopathology: not performed						
	AstraZeneca Comment: TTO 21 Days; limited information on the baseline health characteristics of the patient before vaccination and further clarification of the event, circumstances leading to the event, relevant medical and family history of the patient, concurrent diseases (Hypersensitivity disorder, Immunocompromised state, Autoimmune disease, Degenerative disease, Pre-existing Bacterial or Viral infection), concomitant medications, risk factors (lifestyle, diet, stress), etiological and complete diagnostic work-up (allergy panel test, peripheral blood smear, immunoglobulin titer, CRP, ESR, blood panel test, blood culture)						
Heo et al 2023 / [REDACTED] / 73 / F	Acute lesion in the left lower extremity, and fine pustules on the left thigh along with overall erythema of both lower extremities.	Acute generalized exanthematous pustulosis	6 / Dose 1	New onset	Hypertension, diabetes, and acute coronary syndrome	Recovered	Possible with limited information
	Treatment: 16 mg/d of methylprednisolone for the first week, then reduced to 12 mg/d for the next week, and an oral antihistamine and an external steroid were prescribed together. From the 2nd week, dapsone 50 mg/d was additionally prescribed.						

Table 25 Summary of all literature case reports on SCARs with VAXZEVRIA

Authors / Case ID / Age /Gender/ Country	Clinical features	Final diagnosis	Time to onset (in Days) / Dose number	New onset / Relapse / Worsening / Recurrence	Previous history	Outcome	AZ Assessment as per WHO-UMC scale
	Laboratory data: slight increase to 480/uL (6.4%), white blood cells (7,500/uL) and neutrophils (4,790/uL) were within the normal range. Histopathology: sub corneal pustule was observed. Infiltration of inflammatory cells including neutrophils and eosinophils was observed inside the pustules. Papillary dermis edema was observed around the pustules, and infiltration of inflammatory cells was observed around blood vessels in the upper dermis. AstraZeneca Comment: A 73-year-old female patient with a history of hypertension, diabetes, and acute coronary syndrome reported an onset of acute lesion in the lower extremities (left) and fine pustules were observed on the left thigh along with overall erythema of both lower extremities. Histopathological findings confirmed acute localized exanthematous pustulosis. Treatment with steroids and improved gradually without recurrence. Insufficient information on COVID-19 test, family history, etiologies other than viral infection not ruled out (autoimmune/bacterial infection). The temporal plausibility of Acute localized exanthematous pustulosis (ALEP) after 6 Days following first dose of COVID-19 vaccination is considered.						
Bullous Lesions							
Wantavornprasert et al 2021-1/ ██████████ 74 / M / ██████████	Abrupt erythematous lesions in trunk.	Generalized bullous fix ed drug eruption	1 / Dose 1	New onset	Allergy to penicillin	Resolved	Possible with limited information
	Treatment: Topical 0.25% desoximethasone cream						
	Clinical observation: multiple, well-defined, round to oval, erythematous to violaceous plaques with central dusky appearance and bullous formation on the trunk and both extremities, with no mucosal involvement. Laboratory data: no definite internal organ involvement Histopathology: subepidermal separation with superficial and deep perivascular mixed inflammatory cells infiltration composing lymphohistiocytes and numerous eosinophils, melanophages were seen in the upper dermis IFN-γ ELISpot assay: negative for polysorbate 80.						
	AstraZeneca Comment: Time to onset of 1 day after Dose 1 of Vaxzevria, suggested a plausible time relationship. Medical history reported penicillin allergy. Due to limited information on concurrent conditions, concomitant medications, other risk factors, baseline health and performance status, further diagnostic workup (including immunological workup); a causal relationship between the event and AZD1222 is considered Possible with limited information.						

Table 25 Summary of all literature case reports on SCARs with VAXZEVRIA

Authors / Case ID / Age /Gender/ Country	Clinical features	Final diagnosis	Time to onset (in Days) / Dose number	New onset / Relapse / Worsening / Recurrence	Previous history	Outcome	AZ Assessment as per WHO- UMC scale
Ben Salem et al 2022/ [REDACTED] / 41 / F / [REDACTED]	Well-defined pruritic erythematous, painful plaque on the left shoulder	Generalized bullous fixed drug eruption	3 / Dose 1	New onset	None	Recovered	Possible with limited information
	Treatment: Topical corticosteroids and hydroxyzine						
	Clinical observation: bullous erythematous plaque surrounding the injection site on the upper and lower lumns, no evidence of mucosal involvement. Laboratory data: COVID-19 test negative. Histopathology: Biopsy of the lesion reported epidermal necrosis leading to bullae formation with superficial and deep perivascular mixed infiltrate of lymphocytes, neutrophils and eosinophils, in addition to dermal melanophages. Direct and indirect immunofluorescence were negative.						
	AstraZeneca Comment: Time to onset of 3 Days after Dose 1 of Vaxzevria, suggested a plausible time relationship. The patient had no known allergies to medications, or vaccines, and reported no insect bites, trauma or burns to the area. Due to limited information on the further clarification of the event, patient's baseline health condition before vaccination, relevant family history, concurrent diseases, concomitant medications, and etiologic workup. The causality was assessed as possible, with limited information based on the temporality.						
	Drug reaction with eosinophilia and systemic symptoms (DRESS)						
O'Connor et al 2022 / [REDACTED] / 45 / F / [REDACTED]	Gradually worsening rash consisting of red papules on the face, trunk, and extremities.	Drug reaction with eosinophilia and systemic symptoms	7 weeks / Dose 1	New onset	Unknown	Recovering	Unlikely
	Treatment: Intravenous hydrocortisone on admission, switched to oral prednisolone.						

Table 25 Summary of all literature case reports on SCARs with VAXZEVRIA

Authors / Case ID / Age /Gender/ Country	Clinical features	Final diagnosis	Time to onset (in Days) / Dose number	New onset / Relapse / Worsening / Recurrence	Previous history	Outcome	AZ Assessment as per WHO-UMC scale
	Clinical observation: erythema and edema of the eyelids and lips, and multiple pink papules and plaques on the face, trunk, and extremities, some with superficial scale, along with small pustules on the upper lip. Edema of the arms and legs with coalescent erythema. Violaceous patches on the feet, with some targetoid lesions and some central erosion. There was conjunctivitis, erythema of the pharynx, and cervical lymphadenopathy. Laboratory data: Blood test results on admission showed an elevated eosinophil count of 1.48*10⁹/L (normal range 0.02-0.5*10⁹/L), CRP 32.3 (normal range <5.0), normal liver function tests, COVID-19 IgG weakly positive, COVID-19 polymerase chain reaction (PCR) tests negative *2, negative respiratory panel, and negative serology for Mycoplasma pneumoniae, CMV, Epstein-Barr virus, and human herpes virus. Chest computed tomography showed serositis with mild fluid in the pleural and peritoneal cavities. Histopathology: Skin biopsy showed diffuse marked spongiosis with patchy vacuolar interface change and occasional dyskeratotic cells. There was a patchy lichenoid band of lymphocytes with perivascular lymphocytes and abundant eosinophil AstraZeneca Comment: Event experienced 7 weeks after dose 1. Patient who after initial Treatment with IV hydrocortisone and oral prednisone, experienced a relapse, including conjunctivitis, generalized erythema and edema (Laboratory data reported elevated eosinophil count, along with elevated AST/ALT); requiring Treatment with IV methylprednisolone for 3 Days, providing improvement in skin conditions, and reduction in eosinophilic count and liver enzymes. Follow-up after 3 weeks, reported edema of the face, arms, and legs with normal liver enzymes and very mild increase in eosinophilic count. Considering the event occurred outside the risk window, causality is assessed as Unlikely.						
Dermatitis Bullous							
Saleem et al 2022/ [REDACTED] / 69 / F	Generalized, pruritic, scaly, painless, erythematous rash, developing a macular rash in her inframammary region, progressing to her thighs, and becoming painful, non-pruritic,	Dermatitis bullous	0 / Booster dose	New onset	Unknown	Unknown	Possible with limited information

Table 25 Summary of all literature case reports on SCARs with VAXZEVRIA

Authors / Case ID / Age /Gender/ Country	Clinical features	Final diagnosis	Time to onset (in Days) / Dose number	New onset / Relapse / Worsening / Recurrence	Previous history	Outcome	AZ Assessment as per WHO-UMC scale
	plaques, non-blanching papules.						
	Treatment: Oral doxycycline						
	Laboratory data: worsening inflammatory markers, liver function test, and hyponatremia. Histopathology: Skin biopsy demonstrated sub-epidermal blistering with negative immunofluorescence not keeping with an immuno-bullous disease. Biopsy reported as with direct immunofluorescence showed accentuation of the junction with immunoglobulin (Ig)G and IgA, but no bright or above- BG staining. IgM and C3 were negative. Punch biopsy of skin demonstrated extensive neutrophils in the surface epithelium, below the keratin layer. There was subepidermal oedema and splitting and subepidermal vesicle formation which contains scattered chronic inflammatory cells. Within the dermis, there was a mixed perivascular inflammatory infiltrate. Eosinophils were inconspicuous. Fungal stain was negative. The frozen section H&E showed superficial pustules, acute inflammation in the epidermis and oedema at the dermo-epidermal junction with incipient splitting.						
	AstraZeneca Comment: Event was experienced 36 hours after Vaxzevria booster, however, information regarding inflammatory reactions with dose 1 and dose 2 is lacking. Due to limited information on relevant medical history (autoimmune disorders, infection, collagen diseases, blood disorders), risk factors, family history, past history of similar episodes if any, and concomitant medications, causal relationship between the event and AZD1222 was considered Possible with limited information.						
SJS-TEN							
Da Cruz et al 2022 / / 40 / F	Vesicles over confluent erythematous macules, disseminated	Stevens-Johnson syndrome	2 / Dose 1	New onset	Unknown	Unknown	Possible with limited information

Table 25 Summary of all literature case reports on SCARs with VAXZEVRIA

Authors / Case ID / Age /Gender/ Country	Clinical features	Final diagnosis	Time to onset (in Days) / Dose number	New onset / Relapse / Worsening / Recurrence	Previous history	Outcome	AZ Assessment as per WHO-UMC scale
	throughout the body, and atypical target lesions on the palms and soles of the feet, along with oral mucosal lesions.						
	Treatment: Prednisone						
	Laboratory data: routine test was normal, except for inflammation markers such as high CRP and ESR. Serology for arboviruses, Epstein-Barr virus, HIV, HTLV, viral hepatitis, syphilis, toxoplasmosis, CMV, were negative for acute phase. Histopathology: Skin biopsy showed keratinocyte necrosis with a detachment of the epidermis and mild lymphocytic interface dermatitis.						
	AstraZeneca Comment: A 40-year-old black female presented with 48-hour progressive worsening of the skin rash to a widespread pattern two Days after first dose of the ChAdOx1. She denied taking any medication in the past few weeks as well as having any previous drug reaction or erythema multiforme. Skin biopsy results suggestive of SJS. Serology test provided negative results. Treatment with prednisone was initiated. On the fifth day, she was discharged from the hospital with epidermal detachment <10% body surface area (BSA). Patient's ethnicity could be a risk factor (Asians or Black patients are at an increased risk for SJS). Insufficient information on COVID-19 test, family history, etiologies other than viral infection not ruled out (autoimmune/bacterial infection). The temporal plausibility of SJS after 2 Days following first dose of COVID-19 vaccination, suggest a causality assessment for Possible with limited information.						
Kherlopian et al 2022/ [REDACTED] / 48 / F [REDACTED]	Vesicles over confluent erythematous macules, disseminated throughout the body, and atypical target lesions on the palms and soles of	Toxic epidermal necrolysis	14 / Dose 1	New onset	None	Recovered	Possible with limited information

Table 25 Summary of all literature case reports on SCARs with VAXZEVRIA

Authors / Case ID / Age /Gender/ Country	Clinical features	Final diagnosis	Time to onset (in Days) / Dose number	New onset / Relapse / Worsening / Recurrence	Previous history	Outcome	AZ Assessment as per WHO-UMC scale
	the feet, along with oral mucosal lesions.						
	Treatment: Betametasone valerate 20.02% cream, fexofenadine 180 mg daily. Adalimumab and human IgG1 monoclonal antibody Tumor Necrosis Factor-alpha (TNF-a) 80 mg via subcutaneous injection Clinical observation: Confluent erythematous maculopapular eruption with a positive Nikolsky sign and orogenital mucosal involvement. Laboratory data: Serology for <i>Mycoplasma pneumoniae</i>, herpes simplex virus or adenovirus, HIV, hepatitis B, hepatitis C, tuberculosis and Strongyloides was negative. Mildly increased liver transaminases, blood differential and chemistry were within normal limits. Histopathology: Skin biopsies reported full-thickness epidermal necrosis, pauci inflammatory dermis, and negative direct immunofluorescence. AstraZeneca Comment: This 48-year-old patient was diagnosed with TEN (SCORTEN score 2 at the time of admission, and more than 10% BSA of epidermal detachment progressing to 90% of BSA) 14 Days after Vaxzevria Dose 1. Due to limited information on baseline health condition before vaccination, relevant family history, concurrent diseases, details and circumstances surrounding the event, possible risk factors, a causality assessment following WHO-UMC is considered possible with limited information						
Dash et al 2021 [REDACTED] / 60 / M / [REDACTED]	Oral ulceration and generalized skin rash	Stevens-Johnson syndrome	3 / Dose 1	New onset	Hypertension , diabetes Amlodipine	Recovered	Possible with confounders
	Treatment: Oral cyclosporine 300 mg.						

Table 25 Summary of all literature case reports on SCARs with VAXZEVRIA

Authors / Case ID / Age /Gender/ Country	Clinical features	Final diagnosis	Time to onset (in Days) / Dose number	New onset / Relapse / Worsening / Recurrence	Previous history	Outcome	AZ Assessment as per WHO-UMC scale
	Clinical observation: multiple purpuric macules all over the body with perilesional erythema. The lesions coalesced to form large sheets of necrosed skin over the front and back of the trunk, with a few areas showing bullae. Mucosal involvement was present in the form of oral erosions, hemorrhagic crusting over the lips, redness of a slight discharge from the eyes, and erosions on the glans. Laboratory data: not reported. Histopathology: Orthokeratosis with epidermal atrophy, moderate intraepidermal infiltration of lymphocytes and neutrophils with moderate spongiosis, scattered degenerated apoptotic keratinocytes, patchy areas of basal cell degeneration and interface dermatitis, perivascular and peri adnexal inflammatory cell infiltrate, and extravasation of erythrocytes in the dermis. AstraZeneca Comment: Time to onset of 3 Days after Dose 1 of Vaxzevria, suggested a plausible time relationship. Concomitant medication included amlodipine which in its SmPC mention SJS as listed, hence causality assessment is considered as Possible with confounders.						
Aimo et al 2022, [REDACTED] 65 / M / [REDACTED]	Mucocutaneous eruption.	Stevens-Johnson syndrome	10 / Dose 2	New onset	None	Recovered	Possible with limited information
	Treatment: Prednisone 1 mg/Kg/daily Clinical observation: multiple, round-to-oval erythematous patches were observed, with ill-defined borders and purpuric centres giving the lesions an atypical targetoid appearance. The patches were widely distributed on face, trunk and limbs, sparing the scalp, palms and soles with an approximate BSA involved of 9%. Mucosal involvement was also presented with erosions and vesicles affecting both superior and inferior labial mucosae and glans penis. Laboratory data: neutrophilia and low platelets along with elevated CRP (9.21 mg/dL), LDH (319 U/L) and fibrinogen (>700). Subsequently, an increase in CRP (14.73), creatine-kinase (299 U/L), LDH (345 U/L) and D-dimer (from 1984 to 2256 lg/mL) were noted with fibrinogen consumption, PT and aPTT within normal values. Cranial CT angiography revealed a superior sagittal sinus thrombosis. Histopathology: Skin biopsy evidenced hyper-orto-parakeratosis with focal vacuolar degeneration of the basal layer and scattered apoptotic keratinocytes.						

Table 25 Summary of all literature case reports on SCARs with VAXZEVRIA

Authors / Case ID / Age /Gender/ Country	Clinical features	Final diagnosis	Time to onset (in Days) / Dose number	New onset / Relapse / Worsening / Recurrence	Previous history	Outcome	AZ Assessment as per WHO-UMC scale
AstraZeneca Comment: Time to onset of 10 Days after Dose 2 of Vaxzevria, suggested a plausible time relationship. No events were reported with Dose 1. Nevertheless, due to limited information on circumstances leading to event, concurrent conditions, concomitant medications, other risk factors, baseline health and performance status, further diagnostic workup (including immunological workup); a causal relationship between the event and AZD1222 is considered Possible with limited information.							
Singh et al 2022 [REDACTED] 62 / F / [REDACTED]	Whole-body eruptions, including hemorrhagic crusting at the mucosa. Mild local erythema was observed on the trunk and both arms	Stevens-Johnson syndrome	6 months / Booster dose	New onset	Unknown	Recovering	Unlikely
Treatment: Steroid and supportive therapy							
Laboratory data: not reported-							
AstraZeneca Comment: A 62-year-old female patient had an episode of SJS 6 months booster dose and was hospitalized for a month. Treated with steroids and supportive therapy. Post the systemic therapy, she complained about redness, decreased vision in both her eyes, and ocular discomfort. Vaccinee developed fungal keratitis in the right eye (6 months later) and was treated with topical antifungal agents (natamycin and voriconazole, ketoconazole). The patient was scheduled for a therapeutic keratoplasty for her right eye. Due to limited information on circumstances leading to event, clinical course, predisposing risk factors, relevant medical history (prior allergy and medication reactions), family history, concurrent conditions, concomitant medications, diagnostic and etiologic workup; events reported with dose 1 and dose 2, the evaluation. The causality is considered as unlikely as the event occurred beyond the risk window.							
Kherlopian et al 2022 [REDACTED] / 48 / [REDACTED]	Unknown	Toxic epidermal necrolysis	Unknown / Unknown	New onset	Intermittent migraines	Recovered	Unassessable with limited information
Treatment: Adalimumab, Cephalexin							

Table 25 Summary of all literature case reports on SCARs with VAXZEVRIA

Authors / Case ID / Age /Gender/ Country	Clinical features	Final diagnosis	Time to onset (in Days) / Dose number	New onset / Relapse / Worsening / Recurrence	Previous history	Outcome	AZ Assessment as per WHO-UMC scale
	Histopatology: Skin biopsy revealed Partial-to-full thickness epidermal necrosis, paucicellular dermis, direct immunofluorescence was negative. AstraZeneca Comment: Vaccinee experienced impetigo due to S. aureus complication, which was resolved after antibiotic therapy .Limited information regarding clinical feature or laboratory data, however SCORTEN score Day 0 and Day 3; was reported to be 3% of mortality prognostication. Considering the lack of information related to time to onset, clinical course of the event, triggering risk factors, relevant medical history, existing allergies, concurrent conditions (hypersensitivity reaction or immune diseases), concomitant medications, detailed diagnostic, and etiologic workup (complete blood counts, toxicology report); the WHO-UMC causality assessment was considered as Unassessable/Unclassified with limited information.						
Lee HJ et al 2023 / [REDACTED] / 59 / F / [REDACTED]	Bullae on the trunk and both extremities.	Stevens-Johnson syndrome	21 / Dose 1	New onset	Unknown	Recovered	Possible with limited information
	Treatment: Triamcinolone 4 mg, prednisolone 2.5 mg, and methylprednisolone 0.1% cream Clinical observation: multiple, variable-sized, erythematous patches and hemorrhagic bullae were located on the lips, dorsum of the right hand, trunk and extremities. Laboratory data: normal, however slightly elevated ESR and CRP. Histopathology: Skin biopsy showed subepidermal blister, full thickness epidermal necrosis, and diffuse intraepidermal deposition of immune reactants on direct immunofluorescence. AstraZeneca Comment: Timeframe reported between vaccination and symptoms is considered plausible. Nevertheless, following the limited information other circumstances surrounding the event, etiological and diagnostic workup (infectious and autoimmune work up), further concurrent conditions and status of underlying comorbidities, concomitant medications, the causal assessment is considered Possible with limited information						
Pollozhani et al 2023 / [REDACTED] / 69 / F / [REDACTED]	Innumerable confluent erythematosis and purpuric macules with superficial	Toxic epidermal necrolysis	21 / Dose 1	New onset	Unknown	Unknown	Possible with limited information

Table 25 Summary of all literature case reports on SCARs with VAXZEVRIA

Authors / Case ID / Age /Gender/ Country	Clinical features	Final diagnosis	Time to onset (in Days) / Dose number	New onset / Relapse / Worsening / Recurrence	Previous history	Outcome	AZ Assessment as per WHO-UMC scale
	erosions and blisters.						
	Treatment: Unknown						
	Laboratory data: elevation of ANA, anti-Ro and Anti-La antibodies Histopathology: Vacuolar interface dermatitis, and also showed numerous necrotic keratinocytes as well as focally extensive epidermal necrosis.						
	AstraZeneca Comment: Timeframe reported between vaccination and symptoms is considered plausible. However, considering the limited information related to medical history, risk factors (allergy to drugs) concurrent diseases, concomitant medications, complete etiologic and diagnostic workup, and treatment provided; the WHO-UMC causality assessment is noted as Possible with limited information.						
Others							
Seque et al 2022-1/ [REDACTED] / 66 / M / [REDACTED]	Erythroderma	Dermatitis exfoliative generalized	2 / Dose 1	New onset	Hypertension, diabetes, and acute coronary syndrome	Unknown	Possible with limited information
	Treatment: Systemic corticoid						
	Laboratory: no reported Histopathology: Spongy dermatitis						
	AstraZeneca Comment: Time to onset of 2 Days after Dose 1 of Vaxzevria, suggested a plausible time relationship. Due to limited information on circumstances leading to event, concurrent conditions, concomitant medications, other risk factors, baseline health and performance status, further diagnostic workup (including immunological workup); a causal relationship between the event and AZD1222 is considered Possible with limited information.						
Seque et al 2022-2/ [REDACTED] / 85 / M / [REDACTED]	Erythroderma	Dermatitis exfoliative generalized	1 / Dose 1	New onset	Chronic renal disease	Unknown	Possible with limited information

Table 25 Summary of all literature case reports on SCARs with VAXZEVRIA

Authors / Case ID / Age /Gender/ Country	Clinical features	Final diagnosis	Time to onset (in Days) / Dose number	New onset / Relapse / Worsening / Recurrence	Previous history	Outcome	AZ Assessment as per WHO-UMC scale
Ramessur et al 2021/ [REDACTED] / 73 / M / [REDACTED]	Treatment: Systemic corticoid						
	Laboratory: no reported Histopathology: Spongy dermatitis with superficial perivascular infiltrate						
	AstraZeneca Comment: Time to onset of 1 day after Dose 1 of Vaxzevria, suggested a plausible time relationship. Due to limited information on circumstances leading to event, concurrent conditions, concomitant medications, other risk factors, baseline health and performance status, further diagnostic workup (including immunological workup); a causal relationship between the event and AZD1222 is considered Possible with limited information.						
	Left shin erythema and blistering ulcerations	Skin necrosis	14 / Dose 1	New onset	Atrial fibrillation with Ischemic cardiomyopathy	Recovering	Possible with limited information
	Treatment: Topical clobetasol propionate 0.05%, neomycin sulphate and nystatin ointment, and compression bandaging Treatment.						
	Clinical observation: 2 superficial ulcers with a necrotic base and a violaceous edge, which measured approximately 20*30 mm, on the lateral aspect of his left shin. Laboratory data: Full blood count (FBC) showed a normal white cell differential count and mild thrombocytopenia (platelets 112 9 109 /L; normal range: 150–450 9 109/L), normal liver and renal function test with normal levels for ANA, activated partial thromboplastin time, fibrinogen and D-dimer. Histopathology: Skin biopsy showing epidermal necrosis with underlying proliferation of blood vessels, many of which show the presence of microthrombi. Fat necrosis also evident in the subcutaneous tissue.						
	AstraZeneca Comment: Time to onset of 14 Days after Dose 1 of Vaxzevria, suggested a plausible time relationship. The patient's advanced age could be considered a contributory risk factor. Limited information on circumstances surrounding the events, relevant medical history, other concurrent conditions, concomitant medications, risk factors (injury, inflammation, abnormal immune response, smoking, immobility, malignancy, blood clot disorder), detailed etiological and etiology work-up; hence causality assessment is considered as Possible with limited information.						

AGEP Acute generalized exanthematous pustulosis; ALEP Acute Localized Exanthematous Pustulosis; ALT Alanine Aminotransferase; ANA Antinuclear Antibodies; AST Aspartate Aminotransferase; AZ AstraZeneca; BSA Body Surface Area; CMV Cytomegalovirus; COVID-2019 Coronavirus Disease Of 2019; CRP C-Reactive Protein; CT Computed tomography; DRESS Drug Reaction with Eosinophilia and Systemic Symptoms; HIV Human Immunodeficiency Virus; HTLV human T-cell leukemia Virus; ID Identifier; IFN Interferon; IV Intravenous; LDH Lactate dehydrogenase; PT Preferred Term; SCORTEN SCORE of Toxic Epidermal Necrosis; SJS Stevens-Johnson syndrome; TEN toxic epidermal necrolysis; TNF Tumor Necrosis Factor; TTO Time To Onset; UMC Uppsala Monitoring Centre; WHO World Health Organization

Discussion and Conclusion

AstraZeneca performed a cumulative review to identified 29 literature case reports (including 19 presented in the previous reporting interval). Upon review of the cases, none of them were considered as probable as per the WHO-UMC causality assessment. Overall, majority of the cases (17/21, 81%) had insufficient information for a comprehensive causality assessment, 2 cases were confounded by underlying medical condition and in 2 cases event occurred beyond the risk window. No specific trend or pattern was identified upon a careful assessment of these cases.

Based on the review of the currently available cumulative data, AstraZeneca considers that there is insufficient evidence to suggest a causal association between SCARs and VAXZEVRIA. It will continue to be monitored as part of routine surveillance activities for VAXZEVRIA.

15.2.3.2 Erythema Multiforme (EM)

In the assessment report (EMA/H/C/PSUSA/00010912/202212) of the previous PBRER DLP 28 December 2022, PRAC has requested MAH to present the topic of Erythema Multiforme (EM) and the request is as follows: *“The MAH should present:*

- a cumulative review of erythema multiforme (at PT level) based on data from all available sources;*
- a causality assessment of the cases (using the WHO-UMC causality assessment) and discuss the cases assessed as WHO Possible, Probable or Certain;*
- relevant literature data;*
- a discussion on the need for updating product information and/or risk management plan (RMP), and submit proposal as required. [Request for the next PBRER]”*

Pre-Clinical Data

There is no pre-clinical data on erythema multiforme with VAXZEVRIA.

Clinical Study Data

There were no EM cases reported from clinical trials.

Global Patient Safety Database

A cumulative search till 28 December 2023 of the AstraZeneca Global Safety Database for Erythema Multiforme with VAXZEVRIA was performed using MedDRA version 26.1. The search strategy included PT ‘Erythema Multiforme’.

The search retrieved a total of 128 events of Erythema multiforme in 128 case reports. All AEs were serious with reported seriousness criteria as follows: 79 (61.7 %) medically important event, 19 (14.8%) hospitalization and 7 (5.5%) life threatening.

The breakdown and overview of these 128 cases with 128 events is presented in the Table 26

Table 26 Overview of Events/Cases (Cumulatively)

Parameter	Category	Values (%)
Event Count	Total	128
	Serious	128 (100)
Case count	Medically confirmed	79 (61.7)
Case Report Source	Interventional Clinical study	0 (0)
	Non-interventional study	3 (2.3)
	Spontaneous	29 (22.7)
	Literature	6 (4.7)
	Regulatory	90 (70.3)
Sex	Female N (%)	77 (60.2)
	Male N (%)	41 (32)
	Unknown/not reported N (%)	10 (7.8)
Age Group	0-49	51 (39.8)
	50-59	20 (15.6)
	60-69	22 (17.2)
	70-79	14 (10.9)
	80+	2 (1.6)
	Unk	19 (14.8)
	Median age (range)	51.9 (1 month to 87 years)
Event occurrence with dose	Dose 1 (%)	29 (22.7)
	Dose 2 (%)	10 (7.8)
	Dose 3 (%)	0
	Dose 4 (%)	0
	Dose unspecified	89 (69.5)
Case level -TTO (days) ^a	0-2	37 (38.1)
	3-14	31 (32)
	15-28	15 (15.5)
	29-42	5 (5.2)
	43 and above	9 (9.3)
	Unknown	31
	Median TTO in Days (range)	7 ((0-229)
Event Seriousness criteria ^b	Medically important	110 (85.9)
	Disability	4 (3.1)

Table 26 Overview of Events/Cases (Cumulatively)

Parameter	Category	Values (%)
	Hospitalization	19 (14.8)
	Congenital anomaly	0
	Life-threatening	7 (5.5)
	Death	0
AE Outcome	Recovered	27 (21.1)
	Recovering	28 (21.9)
	Recovered with sequelae	4 (3.1)
	Not recovered	35 (27.3)
	Fatal	0
	Unknown	34 (26.6)
Duration of recovered/recovered with sequelae events	Range (days)	3 to 77
	Mean (days)	29.3
	Unknown duration (number of events)	111 (86.7)

^a TTO was reported for 97 case reports (total number of cases) used to calculate the percentage.

^b In few cases, there was more than 1 seriousness criteria reported.

^c AE: Adverse Event, Unk: Unknown, TTO: Time to onset

The events most commonly co-reported with Erythema multiforme cumulatively are presented in Table 27.

Table 27 Distribution of most frequently co-reported events (≥ 5) in case reports for Erythema multiforme, cumulatively

Adverse events (PT) ^a	Number of events	Percentage (%)
Pyrexia	17	5.1
Rash	17	5.1
Myalgia	11	3.3
Headache	11	3.3
Arthralgia	10	3
Chills	9	2.7
Pruritus	9	2.7
Malaise	7	2.1
Fatigue	7	2.1
Blister	6	1.8
Urticaria	6	1.8
Hypersensitivity	5	1.5

Table 27 Distribution of most frequently co-reported events (≥ 5) in case reports for Erythema multiforme, cumulatively

Adverse events (PT) ^a	Number of events	Percentage (%)
Nausea	5	1.5

^a There was a total of 331 co-reported PTs identified.

PT Preferred Term

WHO -UMC causality Assessment

WHO-UMC causality assessment performed for Erythema Multiforme case reports presented in Table 28.

Table 28 Overview of WHO-UMC Causality Assessments for Erythema Multiforme Case Reports with VAXZEVRIA reported Cumulatively through 28 December 2023

WHO-UMC Causality category	WHO-UMC Causality assessment scale (AZ adapted)	Number of Cases (Percentage)
Certain	Certain	0
Probable/Likely	Probable-Likely	2 (1.6%)
Possible	Possible with risk factors/confounders ^a	25 (19.5%)
	Possible with limited information	61 (47.7%)
Unassessable/Unclassifiable	Unassessable/Unclassifiable with risk factors/confounders ^a	3 (2.3%)
	Unassessable/Unclassifiable with limited information	28 (21.9%)
Unlikely	Unlikely	9 (7%)
Conditional/Unclassified	Conditional/Unclassified	-
Total		128

^a Cases were considered to have “risk factors/confounders” where the event could also be explained by the vaccinee’s diseases, where relevant risk factors were present, or concomitant medications that could potentially contribute to the development of the event were reported.

AZ AstraZeneca; UMC Uppsala Monitoring Centre; WHO World Health Organization

One case reported about recurrence of event with both doses is described below.

Table 29 Summary of recurrence Erythema multiforme Case Reports as per WHO-UMC causality criteria Cumulatively through 28 December 2023

Case ID / Country / Medically confirmed (Y/N) / Source / Serious (Y/N)	Age (Years) / Gender (M/F)	Medical History / Concomitant medications	TTO (days) from AZ vaccine / Dose Information	Preferred Term / AE Outcome	AstraZeneca Comment
[REDACTED] / NO / Regulatory / Y	47 / F	Not reported / Not Reported	1 and Unk / Dose 1 and Dose 2	Erythema Multiforme / Recovering	TTO within risk window. This case has limited information on underlying medical condition such as infections like HSV type, Cytomegalovirus, Epstein-Barr virus, Influenza virus, Vulvovaginal candidiasis, SARS-CoV-2, Histoplasmosis, and other conditions like Inflammatory bowel disease, Hepatitis C, Leukaemia, Lymphoma, Solid organ cancer malignancy. The clinical course of erythema multiforme with Dose 1 and outcome of the event was not clear. It was not reported if the event recovered with treatment or not. In this case, it was reported that erythema polymorphed recurred with re-administration of the vaccine and event was improving. The case was assessed as 'Possible' with limited information based on the WHO-UMC criteria based on the temporal relationship.

F Female; FBC Full Blood Count; HBV Hepatitis B Virus; HSV Herpes Simplex Virus; LFT, Liver Function; M Male; PCR Polymerase Chain Reaction; S Serious; TTO, Time to Onset; Unk, Unknown; WHO, World Health Organization; Y Yes

Amongst 128 cases for Erythema Multiforme, 32 (25.0%) were identified with relevant risk/confounding factors (Roujeau et al 2012, Huff et al 1983, Leclerc et al 2021 presented in Table 30 as below. These are categorized as risk/confounding factors in descending order of frequency.

Table 30 Relevant Risk factors/Confounders identified for Erythema Multiforme Case Reports Cumulatively through 28 December 2023

Relevant Risk factors/ Confounders	Count
Concomitant medications (Such as NSAIDs, Statins, Antidepressant, Antibacterial medications, Antibiotics, Proton-Pump inhibitors, Calcium channel blocker, ACE inhibitor etc.)	24 ^a
Chronic conditions (such as Diabetes Mellitus, Immunodeficiency, Raynaud's phenomenon, Systemic Lupus Erythematosus, Dermatitis Herpetiformis etc.)	8 ^a
History of viral Infections (Such as, Herpes Simplex, Varicella, Oral herpes, Chikungunya virus infection etc.)	4 ^a
Previous history of Erythema Multiforme	3 ^a
Neoplasms (Such as Metastatic non-small cell lung cancer, Colon cancer, Breast cancer)	3 ^a

Cases may contain more than 1 risk factor.

ACE angiotensin-converting enzyme; NSAIDs Non-steroidal anti-inflammatory drugs

In the 97 (75.7%) case reports, there was insufficient information with respect to either TTO, medical history/co-morbidities, concomitant medication details or clinical course for a comprehensive causal assessment.

Literature review

In line with PRAC's request, a cumulative literature search for the approved COVID-19 vaccines, in the databases - Embase, InsightMeme and PubMed was conducted using the search terms 'Erythema multiforme'.

Search results:

The cumulative search for literature case reports published in peer-reviewed journals with special focus to Adeno-vectored vaccines was done and identified a total of 196 relevant abstracts, of these:

- 7 published case reports for VAXZEVRIA, presented in the Table 31 below.

- Remaining 189 articles did not have adequate relevant information to require further review.

Medicinal product no longer authorised

Table 31 Erythema multiforme cases from literature articles

Authors / Case ID / Age / Gender / Country	Clinical features	Final diagnosis	Time to onset (in Days) / Dose number	New onset / Relapse / Worsening / Recurrence	Previous history	Outcome	AZ Assessment as per WHO-UMC scale
Goodarzi et al 2021 / [REDACTED] / Unk / F / [REDACTED]	Erythema multiform-like lesions and extensive erosive mucosal lesions	Erythema multiforme	Unknown / Unknown dose	New onset	Unknown history	Unknown	Unassessable / Unclassified with limited information
	Laboratory data: no information regarding Laboratory data , or histological study						
	Treatment: unknown						
Charfi et al 2022 / [REDACTED] / 32 / F / [REDACTED]	Targetoid lesion within erythema multiforme and urticaria	Erythema multiforme	20 / Dose 1	New onset	Unknown history	Recovering	Possible with limited information
	Laboratory data: WBC reported as 10100, AST 79, ALT 139, ESR 49 and CRP negative						
	Treatment: prednisolone, topical clobetasol						
Charfi et al 2022 / [REDACTED] / 57 / F / [REDACTED]	Targetoid skin lesions over the trunk, ear, upper and lower members. Oral and genital mucosal ulcerations	Erythema multiforme	Unknown / Unknown dose	New onset	Hypertension and anxiety disorder	Unknown	Unassessable / Unclassified with limited information
	Laboratory data: no reported						
	Treatment: unknown						
AstraZeneca Comment: The absence of information regarding event time to onset, previous medical history, concomitant medication, clinical course following dose 1 of VAXZEVRIA, as well as a complete diagnostic workup to confirm diagnosis or etiology workup to consider other possible causes, WHO-UMC causality assessment is considered as Unassessable / Unclassified with limited information							
Kobyashi et al 2022 / [REDACTED] / Unk / [REDACTED]	"Erythema multiforme"	Erythema multiforme	Unknown / Unknown dose	New onset	Unknown history	Unknown	Unassessable / Unclassified with limited information

Authors / Case ID / Age / Gender / Country	Clinical features	Final diagnosis	Time to onset (in Days) / Dose number	New onset / Relapse / Worsening / Recurrence	Previous history	Outcome	AZ Assessment as per WHO-UMC scale
	Laboratory data: no reported Treatment: unknown AstraZeneca Comment: The absence of information regarding event time to onset, other related medical history, concomitant medication, clinical course following VAXZEVRIA, as well as a complete diagnostic workup to confirm diagnosis or etiology workup to consider other possible causes, WHO-UMC causality assessment is considered as Unassessable / Unclassified with limited information						
Awokoya et al 2022 [REDACTED] / 44 / M [REDACTED]	Maculopapular rash associated with purpura and targetoid lesions affecting his distal extremities, trunk, and mucous membranes. Crusting and ulceration of his oral and genital mucosal areas	Erythema multiforme	6 / Dose 1	New onset	Unknown history	Unknown	Possible with limited information
	Laboratory data: Histology revealed parakeratotic scale with interface dermatitis comprising basal layer vacuolation and lymphocyte exocytosis. The epidermis showed prominent dyskeratotic keratinocytes scattered throughout the epidermis. The papillary dermis showed a mild perivascular lymphocytic infiltrate including eosinophils and melanophages. Blood test reported: leucocytosis (12×10^9 L-1), high eosinophils (0.9×10^9 L-1), raised liver enzymes with alkaline phosphatase 159 U L-1 and alanine aminotransferase 172 U L-1. A full infection screen, including herpes simplex virus, SARS-CoV-2 and atypical viral infection, was negative Treatment: topical steroids and emollients AstraZeneca Comment: Time to onset is considered reasonable, although insufficient information such as medical history details, family history, concomitant medications, is missing. Laboratory data suggested a "full infection screenings including atypical viral infection was negative" however, a detailed report of the complete infectious screens was limited in author's article, hence, it's not feasible to rule out any other risk factor which could lead to the event.						
Agrawal et al 2023 [REDACTED] / 44 / F / [REDACTED]	Systemic symptoms (fever, malaise and generalised), and target-like, pruritic lesions in lips, arms, legs and trunk, with central bullae.	Erythema multiforme	1 / Dose 1	New onset	[REDACTED]	Unknown	Possible with limited information
	Laboratory data: no reported Treatment: steroids AstraZeneca Comment: Time to onset is considered reasonable, however medical history suggesting [REDACTED] can be considered as risk factor. Nevertheless, the lack of information regarding past or current infectious disease, other concomitant medication, a complete diagnostic workup to confirm diagnosis or etiology workup to consider other possible causes, WHO-UMC causality assessment is considered as Possible with limited information						

Authors / Case ID / Age / Gender/ Country	Clinical features	Final diagnosis	Time to onset (in Days) / Dose number	New onset / Relapse / Worsening / Recurrence	Previous history	Outcome	AZ Assessment as per WHO-UMC scale
Mehta et al 2022 [REDACTED] / 54 / F / [REDACTED]	Genital and oral ulcers with haemorrhagic crusting and painful erythematous targetoid papules over bilateral palms and soles	Erythema multiforme	10 / Dose 2	New onset	Unknown history	Recovered	Possible with limited information
	Laboratory data: Tzanck smear, and routine hematological and biochemical investigations were normal. Biopsy from a targetoid papule showed extensive necrosis of the epidermis with epidermal regeneration, papillary dermal fibrosis, and mild perivascular lymphocytic infiltrate suggestive of resolving erythema multiforme (EM)						
	Treatment: oral prednisolone (0.75 mg/kg) for 7 Days						
AstraZeneca Comment: Time to onset is considered reasonable, although is noted with interest the absence of similar lesions in the past or after VAXZEVRIA dose 1. However, there is insufficient information including medical history, family history, concomitant medications, etiology workup to ruled out any possible causes, which leads to the WHO-UMC causality assessment of Possible with limited information.							

ALT Alanine Aminotransferase; AST Aspartate aminotransferase; AZ AstraZeneca; CRPC-Reactive Protein; EM Erythema Multiforme; ESR Erythrocyte Sedimentation Rate; [REDACTED] ID Identifier, SARS Severe acute respiratory syndrome; UMC Uppsala Monitoring Centre; WBC White Blood Cell; WHO World Health Organization

Summary

In the assessment report received from the PRAC (EMEA/H/C/PSUSA/00010912/202112) for the VAXZEVRIA PBRER (review period: 29 June 2022 to 28 December 2022), the PRAC requested a review of Erythema multiforme in this PBRER. Cumulatively, a total of 430 SCARs cases concerning 414 events were reported in AstraZeneca's global Safety database. Cases were assessed by age, sex, type of event and outcome. A female (63.3%) prevalence versus male (32.6%) was expressed. The median age was 55 years. The majority (44.7%) of events were reported after Dose 1. In 1 case, Erythema Multiforme occurred after Dose 1 and subsequently reappeared after Dose 2 of the vaccination. The recurrence case was assessed against the WHO-UMC causality criteria as 'Probable', due to temporal relationship, and considering recurrence, and the fact that it is not likely that any other confounder was present during both occurrences and absent in between.

All Erythema Multiforme case reports (N=128) were serious and none of the cases was reported with fatal outcome, 61 (46.2%) events had favourable outcome (either 'resolving' 'recovered' or 'recovered with sequelae'). The time to onset (TTO) was available in 97 (75.7%) case reports and ranged from 0 Days to 229 (median: 7 Days) of which 83 (85.5%) case reports were within range of 0-28 Days. Amongst 128 cases, 2 (1.6%) cases met WHO-UMC causality criteria for 'Probable/Likely' (PT: Erythema Multiforme) and 86 (67%) were considered as 'Possible', of which 25 (19.5%) were identified with relevant risk/confounding factors. The remaining cases had limited information to perform a comprehensive causality assessment.

Conclusion

Based on the review of cumulative information from clinical, post-marketing and literature articles, AstraZeneca has concluded that there is insufficient evidence to suggest a causal association between Erythema Multiforme and VAXZEVRIA. No changes to the CDS or RMP are recommended for Erythema Multiforme. Erythema Multiforme will continue to be monitored as part of AstraZeneca's routine safety surveillance activities for VAXZEVRIA.

15.2.4 Menstrual disorder (literature review)

In the PBRER DLP 28 December 2022, AstraZeneca presented a cumulative summary of all literature and serious menstrual disorder cases which required hospitalization, cases resulting in death. Based on the available data, PRAC (Procedure number: EMEA/H/C/PSUSA/00010912/202212), suggested to present updated literatures in the upcoming PSUR.

Based on the request, AstraZeneca performed literature review of the articles received during the reporting interval. Based on the review of 60 articles, the following 2 articles with updated information is summarized below.

Ljung et al 2023 performed a nationwide, register-based cohort study conducted in Sweden aimed to evaluate the risk of menstrual disturbance and bleeding following SARS-CoV-2 vaccination in women who are premenopausal or postmenopausal. The study included 2,946,448 Swedish women aged 12-74 years, with exclusions for pregnant women, those living in nursing homes and individuals with specific medical histories.

The interventions involved SARS-CoV-2 vaccination with ChAdOx1-S, Ad26.COV2-S, BNT162b2, and mRNA-1273. Two-time windows were considered for assessment: 1 to 7 Days (considering the control period), and 8-90 Days after vaccination.

Key findings revealed weak but consistent associations for postmenopausal bleeding, with higher risk observed after the third dose, particularly in the 1-7 Days and 8-90 Days post risk windows. BNT162b2 and mRNA-1273 showed 23-33% increased risk after 8-90 Days post the third dose, while the association with ChAdOx1-S, as per authors, was less clear. For menstrual disturbance, weak association were observed, but adjustments for covariates attenuated risk estimates. Only a weak association remained after the first dose in 1-7 Days risk window for women aged 12-49. Associations for premenopausal bleeding were imprecise, and adjustment for covariates almost completely removed weak associations noted in crude analyses.

Comparative results indicated that postmenopausal bleeding suggested increased risk after the third dose with mRNA vaccines, but the association with ChAdOx1-S was uncertain. Adjustments for covariates removed most association, suggesting potential confounding factors.

As conclusion, authors agreed on weak findings and inconsistent association between SARS-CoV-2 vaccination and postmenopausal bleeding and even less evidence connection for menstrual disturbance bleeding before menopause.

AstraZeneca Comments: This is a post-marketing surveillance study, authors used data from various national and regional registers, including vaccination registers to assess the risk of menstrual disturbance and bleeding following SARS-CoV-2 vaccination in women, before and after menopause. Some limitations noted included the possible underestimation on number of cases, considering the healthcare contacts for outcome ascertainment may introduce bias, some events which didn't result in medical attention could not get captured by the system. There is lack of information related to body mass index, smoking history, each patient medical history, previous infections, hormone disorder, concomitant medication, which could be considered as well as potential confounders.

Duijster et al 2023 performed a comprehensive study conducted in the Netherlands, the impact of COVID-19 vaccination on menstrual abnormalities was investigated using both spontaneous reporting and a prospective cohort event monitoring (CEM) study. The analysis

covered data from 01 February 2021 to 29 March 2022, and included 4 vaccines: Comirnaty, VAXZEVRIA, Spikevax and Jcovden.

A total of 24,090 spontaneous case reports were included, out of which Comirnaty was prominently associated with menstrual abnormalities, reporting 34.6% (19,079) of the cases, followed by Spikevax (11.3%, N=2,727), Jcovden (6.8%, N=1,647) and VAXZEVRIA (2.6%, N=317). An elevated number of events were reported to occur after dose 2 of vaccination than dose 1. Overall, most case reports originated from the age group of 25–34 years (37.6%) and the age group of 35–44 years (27.9%). The majority of women had a BMI of 18.0–24.9 kg/m² (60.2%). Amenorrhoea/oligomenorrhoea was the most reported menstrual abnormality (33.3%), followed by heavy menstrual bleeding (29.4%) and irregular blood loss (22.7%) with no substantial differences between vaccines.

Amenorrhoea/oligomenorrhoea and heavy menstrual bleeding were the most reported abnormalities, collectively accounting for about half of the cases. Altogether, 4,065 reports were included in the amenorrhoea/oligomenorrhoea, majority reported after Comirnaty (80.5%), and less common after VAXZEVRIA (2.7%). Information on abnormal cycles, for vaccinees reporting amenorrhoea/oligomenorrhoea, was collected from 84 women, 91.7% of them stated that their first menstruation after vaccination was absent, meanwhile the remaining women reported that their first menstrual cycle following vaccination was normal, but menstruation was absent in the subsequent cycle. In other hand, a total of 7,068 females reported a heavy menstrual bleeding, commonly reported after Comirnaty (78%) and less frequent for VAXZEVRIA (2.5%). Most of the women were aged 25-34 years (33.9%), followed by 35-44 years (31.4%), which is in line with the overall age of women who reported the menstrual abnormalities. Out of 246 women, 222 (70.6%) experienced abnormal menstrual cycles in the first cycle following vaccination. And, among 422 females who provided information on the extent of menstrual blood loss changes, 298 (71%) reported an increase of “more than twice as much”, 100 (23.7%) reported “twice as much”, and 24 (5.7%) reported “little more”.

The CEM study involved 16,969 female vaccinees aged 16 years and older, with 80.2% under the age of 65. Of these, 432 women reported 1 or more menstrual abnormalities, resulting in incidence of 31.8 per 1,000 women under 65 and 4.1 per 1,000 women aged 54 or younger. Notably, Comirnaty showed the highest incidence of menstrual abnormalities. Authors also found significant association between other COVID-19 vaccines and menstrual abnormalities, with increased odds for Jcovden, Spikevax and VAXZEVRIA, particularly in women aged 54 or younger. Most abnormalities occurred after the second vaccine dose, with a median time to resolution of 7 Days. Burden perception varied, with dysmenorrhea and heavy menstrual bleeding reported as more burdensome for the vaccinees. Menstrual abnormalities were frequently documented alongside other adverse reactions, predominantly after the dose 1.

The reporting rate per age group were highest for Jcovden with one dose 523.0 per 100 000 vaccinations, but in general, the rates were high (>150 reports per 100 000 vaccinations) for the other COVID-19 vaccines, for all first and second doses in the age groups younger than 45 years.

Authors concluded that a relationship between COVID-19 vaccination and the occurrence of menstrual disorders seems plausible, considering the results from CEM study which found an incidence of menstrual disorders of 41.4 per 1,000 female participants aged ≤54 years, sharing congruency with the spontaneous analysis results.

AstraZeneca Comments:

Using CEM and spontaneous data, authors suggested a likely causal relationship between menstrual abnormalities and COVID-19 vaccines, including VAXZEVRIA, giving the highest concern to Comirnaty and Jcovden vaccinees. Associations were identified between menstrual abnormalities other possible factors associated with menstrual abnormalities, including age, body mass index (BMI), comorbidities, and hormonal contraceptive use, reporting a significantly increased ORs for those women who indicated presence of underlying psychological disorders, especially for intermenstrual blood loss (OR 3.01; 95% CI 1.50–5.50), followed by irregular blood loss (OR 2.41; 95% CI 1.28–4.17) and amenorrhoea/oligomenorrhoea (OR 2.08; 95% CI 1.14–3.50). Some limitations were noted, as mentioned by authors, the extensive media coverage on potential AEs of COVID-19 vaccination could have influenced the reporting patterns in both: spontaneous reporting system and the CEM study, in addition a detailed clinical information about menstrual abnormalities in most case report was lacking, including the use of hormonal contraceptives which was underreported in both data sources, as well, considering a limited documentation in regards the BG incidence of menstrual abnormalities in the Dutch population, which can challenge the estimating magnitude of excess menstrual abnormalities in vaccinated women.

Conclusion

Based on the review of the updated literature review, no new significant information to suggest an association between menstrual disorders and VAXZEVRIA was observed. Therefore, AstraZeneca does not consider any changes to the CDS or RMP on this topic to be warranted at this time. AstraZeneca will continue to monitor menstrual disorders as part of routine surveillance activities for VAXZEVRIA.

15.2.5 Hearing loss

AstraZeneca received the request from TGA to provide an updated signal analysis on hearing loss cases including age stratified and age specific observed versus expected analyses, in the next PSUR to further evaluation of this signal.

AZ Response:

A cumulative search until DLP (28 December 2023) of the AstraZeneca Global Safety Database for Hearing loss with VAXZEVRIA was performed using MedDRA version 26.1 with the High Level Term (HLT): Hearing losses. The search retrieved a total of 1993 events of Hearing loss in 1866 case reports cumulatively, (1297 initial and 569 FU).

The case source distribution for Hearing loss cumulatively through DLP 28 December 2023 is presented in Table 32.

Table 32 Hearing loss case reports received with VAXZEVRIA cumulatively through DLP 28 December 2023 by reporting source and seriousness

Classification of case report source	Non-serious cases	Serious cases	Grand Total
Clinical trial	0	2	2
Spontaneous ^a	403	1410	1813
Literature	2	11	13
Non-interventional/post-marketing study	27	11	38
Grand Total	432	1434	1866

^a Of the 1813 Spontaneous case reports, 1616 (89.1%) were from Regulatory source.

These case reports for Hearing loss were reported most frequently in the following countries: UK 859 (50%), Germany 195 (11.3%), Australia 97 (5.6%), France 62 (3.6%) and Brazil 57 (3.3%) and 317 (17%) case reports were MC.

- Vaccinee age was reported in 1661 case reports and ranged from 18 to 99 years (mean: 53 years; median: 54 years). 1281 (68.6%) vaccinees were between age group of 18-<65 years of age (Adult), 380 (20.4%) vaccinees were >65 years (Elderly) of age, 1 (0.1%) vaccinee was pediatric (unclear if this case refers to pediatric vaccinee as age is reported incorrectly) and in 204 (10.9%) vaccinees the age was unknown.
- Vaccinee gender was reported in 1803 case reports. Of these 1803 case reports, 37.1% (669) were male vaccinees and 62.9% (1134) were female vaccinees.
- Of the total 1866 case reports, the time to onset (TTO) of Hearing loss from VAXZEVRIA administration was reported in 1319 case reports and ranged from 0 Days to 854 Days (mean: 96.5 Days; median: 58.5 Days)

The age stratification for Hearing loss cases cumulatively through DLP 28 December 2023 is presented in Table 33.

Table 33 Hearing Loss Cases with Age Grouping

Age Group (Years)	Total Number of Cases ^a	Number of Cases from Australia
0-24	41	1

Table 33 Hearing Loss Cases with Age Grouping

Age Group (Years)	Total Number of Cases ^a	Number of Cases from Australia
25-34	150	1
35-44	296	8
45-54	358	13
55-64	437	30
65 and above	380	36

^a Age was not reported in 204 cases.

Table 34 Hearing Loss Cases – Age group with Time to Onset

Age Group (Years)	Total Number of Cases with TTO (days)					Number of Cases from Australia with TTO (days)				
	0-21	22-28	29-42	>42	Unk	0-21	22-28	29-42	>42	Unk
0-24	32	0	1	2	6	0	0	0	0	1
25-34	103	3	5	6	33	0	0	0	0	1
35-44	199	8	12	10	67	0	0	0	0	8
45-54	224	8	13	26	87	0	0	0	0	13
55-64	240	12	17	35	133	0	0	0	0	30
≥65	219	16	11	29	105	2	1	0	0	33
Unk	69	4	4	10	117	1	0	0	0	14
Total	1086	51	63	118	548	3	1	0	0	100

TTO Time To Onset; Unk Unknown

Observed versus expected analysis

Observed to-expected analyses (O/E) was performed using the risk window of 21 days, based on the suggestion received from TGA. The OE analysis was also performed with the risk window of 28 days. In the general population, incidence is 309.86 estimated per 100,000 PY (Truven market scan). Overall, the observed cases were significantly less than expected.

Table 35 O/E analysis of global reports of hearing loss

AEs	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
All cases all ages RW	21	309.86	448306152	1138	79868.99	0.01 (0.01 - 0.02)	Observed significantly < expected

AEs	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
All cases all ages RW Unk	21	309.86	448306152	1688	79868.99	0.02 (0.02 - 0.02)	Observed significantly < expected
All cases all ages RW	28	309.86	448306152	1138	106491.99	0.01 (0.01 - 0.01)	Observed significantly < expected
All cases all ages RW Unk	28	309.86	448306152	1688	106491.99	0.02 (0.02 - 0.02)	Observed significantly < expected

BG Background; CI Confidence Interval; O/E Observed To Expected; RW Risk Window; TTO Time To Onset; Unk Unknown

Table 36 O/E analysis of hearing loss cases reports from EU, UK, AU and BZ

AEs	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
0-18	21	106.96	1909134	0	117.41	0 (0 - 0.03)	Observed significantly < expected
18-49	21	151.98	100987434	428	8824.53	0.05 (0.04 - 0.05)	Observed significantly < expected
50-59	21	376.09	56425075	238	12201.18	0.02 (0.02 - 0.02)	Observed significantly < expected
60-69	21	615.27	57182485	254	20228.64	0.01 (0.01 - 0.01)	Observed significantly < expected
Over 70	21	1084.08	31869628	182	19864.44	0.01 (0.01 - 0.01)	Observed significantly < expected
0-18	28	106.96	1909134	0	156.54	0 (0 - 0.02)	Observed significantly < expected

Table 36 O/E analysis of hearing loss cases reports from EU, UK, AU and BZ

AEs	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
18-49	28	151.98	100987434	428	11766.04	0.04 (0.03 - 0.04)	Observed significantly < expected
50-59	28	376.09	56425075	238	16268.24	0.01 (0.01 - 0.02)	Observed significantly < expected
60-69	28	615.27	57182485	254	26971.52	0.01 (0.01 - 0.01)	Observed significantly < expected
Over 70	28	1084.08	31869628	182	26485.92	0.01 (0.01 - 0.01)	Observed significantly < expected

AE Adverse Event; AU Australia; BZ Brazil; CI Confidence Interval; EU European Union; UK United Kingdom.

Table 37 O/E analysis of hearing loss cases reports from UK

AEs	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
18-34 UK	21	90.31	3379886	51	175.5	0.29 (0.22 - 0.38)	Observed significantly < expected
35-54 UK	21	239.57	16892266	234	2326.8	0.1 (0.09 - 0.11)	Observed significantly < expected
55-64 UK	21	492.86	11908856	101	3374.67	0.03 (0.02 - 0.04)	Observed significantly < expected
65-74 UK	21	889.02	13406479	79	6852.74	0.01 (0.01 - 0.01)	Observed significantly < expected

Table 37 O/E analysis of hearing loss cases reports from UK

AEs	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
>75 UK	21	1101.55	5580432	69	3534.35	0.02 (0.02 - 0.02)	Observed significantly < expected
18-34 UK (UNK TTO)	21	90.31	3379886	68	175.5	0.39 (0.3 - 0.49)	Observed significantly < expected
35-54 UK (UNK TTO)	21	239.57	16892266	328	2326.8	0.14 (0.13 - 0.16)	Observed significantly < expected
55-64 UK (UNK TTO)	21	492.86	11908856	164	3374.67	0.05 (0.04 - 0.06)	Observed significantly < expected
65-74 UK (UNK TTO)	21	889.02	13406479	108	6852.74	0.02 (0.01 - 0.02)	Observed significantly < expected
>75 UK (UNK TTO)	21	1101.55	5580432	149	3534.35	0.04 (0.04 - 0.05)	Observed significantly < expected

AE Adverse Event; CI Confidence Interval; O/E Observed To Expected; TTO Time To Onset; UK United Kingdom

Overall, no difference was noted in reporting pattern between the age groups (young adults and elderly) and gender. When a qualitative review was conducted for these case reports, there were limited information on medical history or concomitant medications, precluding a proper assessment to determine causal relationship. The O/E analysis does not account for potential confounders that could provide an alternative explanation. Also, when stratified by age/sex, the numbers of cases in each stratification are small, which should be considered when interpreting the significance of the results.

Conclusion

Based on currently available data, AstraZeneca has concluded that there is insufficient evidence to suggest a causal association between hearing loss and VAXZEVRIA. This review did not find evidence of a new or emerging signal for hearing loss to suggest a need to update the VAXZEVRIA product information or RMP. Hearing loss will be monitored through routine pharmacovigilance and ongoing surveillance activities.

15.2.6 Guillain Barre syndrome (GBS) including cases of Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

Review of Cases – reporting interval (29 December 2022 – 28 December 2023)

An in-period search of the AstraZeneca Global Patient Safety Database was conducted using the following MedDRA (v26.1) narrow SMQ: GBS (PTs: *Acute motor axonal neuropathy; Acute motor-sensory axonal neuropathy; Chronic inflammatory demyelinating polyradiculoneuropathy; Demyelinating polyneuropathy; Guillain-Barre syndrome; Miller Fisher syndrome; Subacute inflammatory demyelinating polyneuropathy; Zika virus associated Guillain Barre syndrome; Bickerstaff's encephalitis; Ascending flaccid paralysis*).

The search retrieved a total of 171 events of GBS in 163 case reports (98 were initial reports and 65 were FU reports). These cases were reported most frequently in the following countries during the reporting period: Brazil (n = 50, 30.7%); UK (n = 28, 17.2%); India (n = 27, 16.6%); Germany (n = 13, 8%) and Australia, Egypt and Sweden (n = 5, 3.1 %, each).

All cases related to Guillain-Barre syndrome

Of the 163 serious cases, in 140 cases were reported as Guillain-Barre syndrome (GBS). The distribution of events by PT is as follow: CIDP (14), Demyelinating polyneuropathy (7), Acute motor axonal neuropathy (3), Miller Fisher syndrome and Subacute inflammatory demyelinating polyneuropathy (n=2, each), Acute motor-sensory axonal neuropathy, Ascending flaccid paralysis and Bickerstaff's encephalitis (n=1, each). The slight predominance was noted in male (n=89) than the female vaccinees (n=66).

Review of cases after receiving Dose 3

Of the 3 case reports, reporting GBS after Dose 3 none reported use of heterologous booster dose. Two (66.7%) case reports were MC and 1 (33.3%) was non-medically confirmed. The vaccinee demographics were 56 years male from [REDACTED], 64 years male from [REDACTED] and male of unspecified age from [REDACTED]. Of the 3 case reports, TTO identified from VAXZEVRIA administration to the event of interest was reported in 2 case reports with TTO 329 and 145.

On review of the 3 cases, the causality was assessed as 'Unassessable/Unclassifiable with limited information' (1) and as 'Unlikely' (2).

Review of cases using BCC and causality assessment using WHO-UMC Criteria

Out of the 163 cases, 33 of the cases fulfilled BCC 1 level criteria, 21 of the cases fulfilled BCC 2 level criteria, 6 of the cases fulfilled BCC 3 level criteria, 101 of the cases fulfilled BCC 4 level criteria and two of the cases fulfilled BCC 5 level criteria.

The causality assessment according to WHO-UMC criteria for the reporting interval are given in Table 38 below. Case reports assessed as 'Possible with limited information' had limited information on other aetiologies, medical history, concomitant medications etc. Cases were considered to have risk factors/confounders where the event could also be explained by the vaccinee's diseases, relevant risk factors that were present, or concomitant medications that could potentially contribute to the development of the event.:

Table 38 Overview of WHO-UMC Causality Assessment for case reports of GBS with VAXZEVRIA reported during the reporting period (29 December 2022 – 28 December 2023) for cases of diagnostic certainty (BCC levels 1, 2, and 3)

WHO-UMC Causality category	WHO-UMC Causality assessment scale (AZ adapted)	BCC 1	BCC 2	BCC 3	Number of Cases
Certain	Certain	0	0	0	0
Probable-Likely	Probable-Likely	0	0	0	0
Possible	Possible with risk factors/confounders ^a	0	2	1	4
	Possible with Limited information	32	14	4	50
Unlikely	Unlikely	1	3	1	5
Conditional / Unclassified	Conditional / Unclassified	0	0	0	0
Unassessable/Unclassifiable	Unassessable/Unclassifiable with risk factors/confounders ^a	0	0	0	0
	Unassessable/Unclassifiable with limited information	0	3	0	
Total		33	21	6	60

^a Cases were considered to have "risk factors/confounders" where the event could also be explained by the vaccinee's diseases, or where relevant risk factors were present, or concomitant medications that could potentially contribute to the development of the event were reported.

BCC Brighton Collaboration Classification; GBS Guillain-Barre Syndrome; WHO UMC World Health Organization-Uppsala Monitoring Centre

BCC Level 1

Thirty three of 163 case reports fulfilled BCC 1 level criteria. The cases fulfil this classification by clinical course, examination features, and confirmatory cerebrospinal fluid (CSF) and nerve conduction study (NCS) test results indicative of GBS. Out of these 33 cases, 11 of the vaccinees were female, and 22 were males. The age range was 20-79 years. The median age was 40 years.

In 3 of the 19 cases, risk factors/confounding factors, and relevant co-morbidities were noted, such as: Male above 50 from EEA/UK (2) Law B 2021 [A]; Medical history of Suspected COVID-19 (1); and Crohn's disease (1).

Three of the cases reported the event occurring after receiving the second dose. None of the cases reported a positive rechallenge. None of the cases reported the event occurring after receiving the booster dose.

Using the WHO-UMC criteria for causality assessment, out of the 33 cases fulfilling BCC level 1: 32 of the case reports were assessed as 'Possible with Limited information' and 1 of the case reports were assessed as 'Unlikely'.

BCC Level 2

Twenty one out of 163 case reports fulfilled BCC 2 level criteria. The cases fulfil this classification by clinical course, examination features, and confirmatory CSF and NCS test results indicative of GBS. Out of these 21 cases, 09 of the vaccinees were female and 12 of the vaccinees were male. The age range was 23-74 years. The median age was 51 years.

In 4 of the 18 cases, risk factors/confounding factors, and relevant co-morbidities were noted, such as: Male above 50 from EEA/UK (1); Polyradiculitis (1); Herpes zoster ophthalmicus (1), Graves-basedow disease (1), Swine flu (1), Breast cancer (1), and Arterial hypertension (1).

Three of the cases reported the event occurring after receiving the second dose. None of the cases reported a positive rechallenge.

None of the cases reported the event occurring after receiving the booster dose.

Using the WHO-UMC criteria for causality assessment, out of the 21 cases fulfilling BCC level 2: 2 of the case reports were assessed as 'Possible with risk factors/confounders', 14 of the case reports were assessed as 'Possible with Limited information', 3 of the case reports were assessed as 'Unlikely' and 2 of the case reports were assessed as 'Unassessable/Unclassifiable with limited information'.

BCC Level 3

Five out of 105 case reports fulfilled BCC 3 level criteria. The cases fulfil this classification by clinical course, examination features, and confirmatory CSF and NCS test results indicative of GBS. Out of these 5 cases, 1 of the vaccinees were female and 4 of the vaccinees were male. The age range was 34-69 years. The median age was 59 years.

In 1 of the 4 cases, risk factors/confounding factors, and relevant co-morbidities were noted, such as: Male above 50 from EEA/UK (1), Respiratory (1), and Hepatitis C (1).

None of the cases reported the event occurring after receiving the second dose. None of the cases reported a positive rechallenge.

One of the cases reported the event occurring after receiving the booster dose.

Using the WHO-UMC criteria for causality assessment, out of the 5 cases fulfilling BCC level 3: 1 of the case reports were assessed as 'Possible with risk factors/confounders', 1 of the case reports were assessed as 'Possible with Limited information' and 2 of the case reports were assessed as 'Unlikely'.

BCC Level 4

Based on the review, 101 out of the 163 case reports fulfilled BCC 4 level criteria. These cases did not fulfil criteria for a level 3, 2, or 1 certainty as there was insufficient information to confirm the diagnosis or medical assessment of the case.

Out of the 103, 09 of the cases reported the event occurring after receiving the second dose and 2 of the cases reported the event occurring after a booster dose, as discussed above

([REDACTED]).

BCC Level 5

Based on the review, 2 cases of 163 case reports fulfilled BCC 5 level criteria (ie, GBS excluded due to an alternative diagnosis).

Summary BCC level 1-3

Out of the 163 cases, 60 met the BCC level 1-3. When the 60 case reports are assessed for causality to VAXZEVRIA according to WHO-UMC classification: 3 of the case reports were assessed as 'Possible with risk factors/confounders'; 50 of the case reports were assessed as 'Possible with Limited information'; 5 of the case reports were assessed as 'Unlikely' and 2 of the case reports were assessed as 'Unassessable/Unclassifiable with limited information'.

Case reports assessed as 'Possible with limited information' had limited information on other aetiologies, medical history, concomitant medications etc. Cases were considered to have risk

factors/confounders where the event could also be explained by the vaccinee's diseases, relevant risk factors that were present, or concomitant medications that could potentially contribute to the development of the event.

Fatal cases (Interval)

During the period covered by this report, 08 cases pertaining to the GBS search criteria have been reported with fatal outcome.

Out of the 8 fatal cases, Guillain-Barré Syndrome (GBS) as an event was reported as the cause of death in 5 cases. Other reported causes of death in these 5 cases were: Paraesthesia (2); Hypersensitivity pneumonitis (1); Quadriparesis (1); Paralysis (1); Arthralgia (1); Respiratory failure (1); Ataxia (1); Acute respiratory failure (1); Muscular weakness (1); Cardiac arrest (1); Pyrexia (1); Cardio-respiratory arrest (1); Shock (1); Chills (1) and Dengue fever (1). In the remaining 3 out of 8 cases, the cause of death was reported as Ischaemic stroke (1) and Death (2).

The assessment for the 5 cases reporting a fatal outcome for GBS are provided in Table 39 below.

Table 39 Summary of GBS cases with fatal outcome with VAXZEVRIA reported during the reporting period [29 December 2022 – 28 December 2023]

Case ID/Country/ Medically confirmed (Y/N)/ Source	Age in years/ Gender (M/F)	Relevant medical History or concomitant medications	Time to Onset of Event of interest (days)	Event of interest	Cause of death	BCC	WHO-UMC Causality Assessment	Additional Comment
/India/YES/Literature Nagdevet al 2022	25/M	Unknown relevant risks/medical history	15	Guillain-Barre syndrome	Guillain-Barre syndrome; Cardiac arrest	BCC 1	Possible with limited information	CSF: normal opening pressure, clear, colourless, and transparent appearance, 99mg/dL of protein, 58 mg/dL of glucose, gram stain – negative, RBC count – occasional. NCS: significant reduction in compound muscle action potential (CMAP) amplitude in all four nerves in the test, and sensory nerve action potential (SNAP) amplitude in the median and ulnar nerves suggestive of sensory-motor axonal polyradiculoneuropathy. Unknown other etiological workup, to determine possible causes such as viral screen, bacterial serology, COVID-19 test.
/Brazil/YES/Spontaneous	64/M	Unknown relevant risks/medical history	1	Guillain-Barre syndrome	Shock; Quadriparesis; Acute respiratory failure; Guillain-Barre syndrome; Arthralgia; Chills	BCC 2	Unlikely	MMII Clinical features included ascending tetraparesis, starting in the LL and progressing to the MMSS. Evaluation by neurology, analysed liquor with a result compatible with acute polyradicular neuritis, laboratory data suggested: CSF: CL 124, GLIC 60, PRT 78, clean liquid, nucleated cells 03, RBCs 12. No details regarding EMG, NCS, or any etiology workup to determine other possible trigger factors.

Table 39 Summary of GBS cases with fatal outcome with VAXZEVRIA reported during the reporting period
[29 December 2022 – 28 December 2023]

Case ID/Country/ Medically confirmed (Y/N)/ Source	Age in years/ Gender (M/F)	Relevant medical History or concomitant medications	Time to Onset of Event of interest (days)	Event of interest	Cause of death	BCC	WHO-UMC Causality Assessment	Additional Comment
/Brazil/YES/S pontaneous	62/F	Unknown relevant risks/medical history	19	Guillain-Barre syndrome	Guillain-Barre syndrome; Cardio-respiratory arrest; Paralysis; Hypersensitivity pneumonitis	BCC 3	Possible with limited information	Clinical features reported, progressive loss of strength, no reflex or sensitivity in upper and lower limbs, progressing to tetraplegia, without patellar reflexes in lower limbs. No details regarding CSF, EMG, NCS, or any etiology workup to determine other possible trigger factors
/Brazil/YES/S pontaneous	69/F	Hepatitis C	14	Guillain-Barre syndrome	Paraesthesia; Hypoaesthesia; Ataxia; Respiratory failure; Guillain-Barre syndrome	BCC 3	Possible with limited information	Clinical features included numbness, gait ataxia, dysphagia, and paresthesias in the MMSS and MMII, flacid paraplegia, along with areflexia and bilateral peripheral palsy. No details regarding CSF, EMG, NCS, or any etiology workup to determine other possible trigger factors.
/Brazil/N/SP	56/M	Unknown relevant risks/medical history	Unknown	Guillain-Barre syndrome	Dengue fever; Guillain-Barre syndrome; Muscular weakness; Pyrexia; Paraesthesia	BCC4	Unassessable/Uncl assifiable with limited information	Clinical features of fever, weakness in the lower limbs with difficulty walking, paraesthesia in the hands and feet reported concurrently with hematemesis. Dengue fever could be a confounder for GBS and fatality. No details on clinical course of Dengue and GBS, time to fatal event, etiological and diagnostic workup.

^a The article was published in 30th Brazilian Congress on Neurology - Brazilian Academy of Neurology (ABN). The report concerns a male patient of Unknown ethnic origin. However, the patient is captured as male from United States due to author being of American origin.

AIDP Acute Inflammatory Demyelinating Polyneuropathy; BCC Brighton Collaboration Classification; CMAP Compound Muscle Action Potential; CSF Cerebrospinal fluid; F Female; FVC Forced Vital Capacity; M Male; MMII Multimodal Image Integration; N No; NCS Nerve Conduction Study; RBC Red Blood Cell; SNAP Sensory Nerve Action Potential; SP Spontaneous; WBC White Blood Cells; WHO UMC World Health Organization-Uppsala Monitoring Centre; Y Yes

Pattern and variant of GBS

As requested by PRAC, the cases were reviewed for the pattern of GBS observed after vaccination with VAXZEVRIA.

AstraZeneca is actively monitoring cases for the variant of bifacial weakness with paraesthesia by narrative review. Out of 163 cases reported during the period covered by this report, 4 case reports of GBS had facial diplegia/bifacial weakness as symptoms. Three of the cases reported GBS variant of interest (ie, Facial Diplegia & GBS as defined by Brighton definition & Muscular weakness/Asthenia & cranial nerves/brainstem involvement). In addition, all the reported cases had facial diplegia along with other symptoms of GBS as well. Out of the 4 reports, none of the cases were from the literature and none were reported with fatal outcome. None of these cases were diagnostically confirmed (all categorized as BCC level 4) and these cases had limited information on medical history, baseline conditions, previous infections, COVID-19 exposure, or concomitant medications or laboratory data, no evidence of NCS, CSF, EMG are provided. Neither information regarding etiological workup, to identify other possible triggering factors are available.

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

A total of 14 CIDP cases were retrieved during the reporting interval. All these 14 cases were reported as serious and the vaccinees age was reported in 11 cases. The age ranged between 31-67 years (median n=46 years). Most of the cases were reported in males (n=7) and 4 cases in female vaccinees.

GBS presents more acutely and reaches to its most severe state in less than 4 weeks. CIDP is chronic autoimmune neuropathy which presents slowly and reaches to severe state typically in over 8 weeks. Three or more relapses in the first eight weeks is highly suggestive of acute onset CIDP. Based on this risk window for CIDP was considered as 5-56 Days. The TTO of the event was available in only 6 cases (43%) and it ranged between 7-106 Days (median: 23 Days). Most of the frequently co-reported AE with are hypoesthesia, paraesthesia, dysaesthesia, paresis, facial paresis, and Guillain-Barre syndrome. None of these cases were reported with fatal outcome and none of the cases were considered as probable/certain as per the WHO-UMC criteria.

Only 2 cases were considered as diagnostically confirmed as per the BCC criteria as BCC level 2. These 2 cases had limited information on cerebrospinal diagnosis, nerve conduction velocity measurement, electroneuromyography test showing sensory-motor polyneuropathy and etiologic workup. Based on the TTO of event, these cases are acute immune-mediated neuropathies (reported within 15 and 24 Days of vaccination and were assessed as Unlikely as per the WHO-UMC criteria. The remaining 12 cases were not diagnostically confirmed (BCC level 4).

Relevant Literature data review of reporting period

Lehmann et al (2023) aimed to determine (i) whether there were excess GBS cases following administration of any of the four vaccines in Germany and (ii) whether these cases many have a different clinical presentation, ie bifacial paresis or facial diplegia with paraesthesia (FDP).

The investigators analysed AE safety surveillance data associated with vaccination as reported to the German national competent authority between 27 December 2020 and 31 August 2021. GBS case definition was based on the following MedDRA Terminology (MedDRA) coding terms: Standardized MedDRA Queries (SMQ) 'Guillain-Barre' Syndrome (narrow) and the PTs: 'axonal and demyelinating polyneuropathy', 'autoimmune demyelinating disease', 'acute polyneuropathy', 'Bells phenomenon', 'diplegia', 'facial paralysis' and 'facial paresis'. GBS cases were validated according to Brighton Collaboration (BC) criteria. An observed vs expected (OvE) analyses was conducted on cases fulfilling BC criteria levels 1 to 4 with known time to onset for all four EMA- approved COVID-19 vaccines. COVID-19 exposure data were determined from two sources – the digital immunisation monitoring system (Digitales Impfquotenmonitoring [DIM]) and data from the practice sector supplied by the Robert-Koch Institute. Age specific pre-pandemic BG IRs were obtained from Denmark, as there were no data for Germany of comparable quality and second that the population structures of the two countries were very similar. A negative control was used: GBS cases following EMA approved influenza vaccination (all types) between 01 January 2020 and 31 March 2021, this period overlapping with study period of interest.

Results: During the reporting period, a total of 214 GBS cases after COVID-19 vaccination were reported, of whom 156 Days eligible for further analysis. Standardised morbidity ratio estimates 3-42 days after vaccination were 0.34 (95% CI: 0.25-0.44) for Comirnaty, 0.38 (95% CI: 0.15-0.79) for Spikevax, 3.10 (95% CI: 2.44-3.88) for VAXZEVRIA, 4.16 (95% CI: 2.64-6.24) for COVID-19 Vaccine Janssen and 0.60 (95% CI: 0.35-0.94) for influenza vaccines. Regarding clinical characteristics (phenotype), bilateral facial paresis was reported in 19.7% and 26.1% of the 156 GBS cases following vaccination with VAXZEVRIA and COVID-19 Vaccine Janssen, respectively, and only in 6% of cases exposed to Comirnaty.

The study limitation included the limitations of spontaneous reporting such as underreporting which is a well-known impacting reliability of numerator for IR calculations (this being differential for serious to non-serious events). Furthermore, the denominator is based on drug-event combination reports rather than population estimates.

The authors concluded that 3 to 4 times more GBS cases were observed than expected after vaccination with VAXZEVRIA and COVID-19 Vaccine Janssen, respectively, therefore GBS might be an AE of vector-based vaccines. Bifacial paresis was more common in cases with GBS following vaccination with vector-based than mRNA COVID-19 vaccines.

AstraZeneca comments:

The authors provided a quantitative analysis of GBS surveillance data (passive) of 8 months from Germany.

Pooling exposure data cannot be fully endorsed so misclassification by age group is possible, considering as per article DIM exposure data these were provided up to 31 August 2021, stratified by vaccine and age group. Nevertheless, vaccine exposure data from practice sector were not connected to DIM and did not contain information on age, only vaccines. Therefore, only vaccine stratified aggregate data were available and age was imputed at aggregate level by the investigators by applying the vaccine related age distribution of patients seen by physicians (for all conditions) in the private sector.

The paper by Levison et al 2019 quoted by the investigators to justify this approach describes pooled IRs of GBS over a 30 years period estimated in three of the five regions of Denmark. The conclusion of that Danish study was that the national 30 year GBS IR was stable over time and similar to GBS IRs reported in other European and North American populations. However specific analyses for other countries were not presented nor any comparison with other country population structure. An evaluation of demographics as of July 2021 Levison et al 2019 ports a higher proportion of 15–24-year-olds in Denmark vs Germany and lower proportions of subjects aged 55–64 years; overall the mean age for Germany is 47.8 years and Denmark is 42 years. Furthermore, the outcome of GBS was not based on spontaneous reports but discharge diagnoses for GBS from hospital specialist setting, with some adjacent ICD codes which align with some but not all MedDRA codes for the bifacial paresis and FDP within the study by Lehmann. The use of Danish data for expected rates is not supported following the differences in population demographics and sources of cases and definition of outcome data.

Whilst the rate of GBS in the Danish population may be considered stable during that period the same may not be true for the immediate pre-pandemic period nor peri-pandemic period during which the SARS-COV 2 was in circulation; they may themselves also be underestimated given the association between COVID-19 infection and GBS and absence of data up to release of first vaccine. A more appropriate control (reference) period would include 2019 and 2020.

There is a lack of specificity in this case definition which may result in either under or over estimation of risk of this outcome, since regardless of the appropriate use of SMQ for GBS, the PTs related to bifacial paresis and FDP, are broad and non-specific (given no healthcare physician diagnosed term exists).

Other weaknesses with this type of analysis include that it is not adjusted for any confounders. There is no information presented on the distribution of age by vaccine from German data to be able to then ascertain comparability with the Danish cohort. Standardisation by age group goes some way to improve comparability recognising that age has been imputed for private practice data but absence of information on clinical characteristics including those defining priority groups according to German vaccine policy and restrictions imposed on some but not all vaccines introduce significant residual

confounding. There is also no accounting for differences in calendar time between vaccine availability and the fact that the periods after vaccine restriction was included may also have caused some differential reporting bias, making reporting of adverse effects to German regulators more likely for patients that received VAXZEVRIA or COVID-19 Vaccine Janssen than mRNA vaccines. The use of Danish data for expected rates is not supported because of differences in calendar period during which rates have been estimated. Furthermore, standardisation on age alone and absence of data on other clinical characteristics means that residual confounding is likely and may explain the reported differences.

The authors suggested a signal of increase occurrence in GBS cases following VAXZEVRIA and COVID-19 Vaccine Janssen administration but not to other vaccines. However, these findings were not seen with the subsequent vaccine doses. Also, the sensitivity analysis stratified to BCC1-3 cases showed decreased GBS rates for VAXZEVRIA versus background rates in ages more than 60 years old. The incidence rates for the negative control used in the publication, included the year 2020 where the incidence for GBS was less than during the previous year's Lunn et al 2021, possibly due to home isolation prior to vaccine availability. Including that year can, therefore, provide a suppressed pre-vaccine incidence rate for comparison. The risk-window of 3-42 is not consistent with the recommended RW of 5-42 Days (As per the recommendation from the external neurology expert panel that provided their consultation in the May 2021 monthly safety summary report (mSSR) for VAXZEVRIA) and introduces possibly of overestimation of relative incidence within RW of 3-5 Days. The study period of 27 December 2020 and 31 August 2021 also coincided with the COVID-19 infections peaks and COVID-19 deaths in Germany WHO COVID-19 dashboard which could possibly confound the study findings. The article didn't provide sufficient case details to replicate classification and causality assessment. Also, as there was an unequal distribution of vaccine types in various countries, including introduction of vaccine at different times and to varying background population, a direct comparison may not be appropriate. Although, the authors extrapolated the findings of Patone et al 2021 article, however, in this article COVID-19 infections could not be ruled out as a possibility in the cases included in the study. Also, whilst the authors report similarities of finding with other publications, the methodological concerns, particularly using Danish data as source of expected rates, limit the inferences that can be drawn from this study.

Massari et al 2023 conducted a study aimed to evaluate the risk of GBS after vaccination with anti-COVID-19 vaccines (BNT162b2/Tozinameran; mRNA-1273/Elasomeran, ChAdOx1-S and Ad26.COV2-S) in the population aged ≥ 12 years.

The Investigators conducted a SCCS study using national data on COVID-19 vaccination linked to emergency care/hospital discharge databases. GBS case definition is based ICD-9 CM codes of GBS: 357.0. The outcome was the first diagnosis of GBS between 27 December 2020 and 30 September 2021. Exposure risk period were days 0 (vaccination day) through 42 days following each of the 2 vaccine doses. The remaining periods were considered as not at risk (baseline) period. The SCCS model, adapted to event-dependent

exposures, was fitted using unbiased estimating equations to estimate relative incidences (RIs) and excess of cases (EC) per 100,000 vaccinated by dose and vaccine product. Calendar period was included as time-varying confounder in the model.

The study included 15,986,009 persons who received at least one dose of COVID-19 vaccine. During the 42-day risk interval there were a total of 67 cases of GBS after the first dose and 41 cases after the second dose. In the 42-day risk interval, increased risks were observed after the administration of first dose (RI=6.83; 95% CI 2.14-21.85) and second dose (RI=7.41; 95% CI 2.35-23.38) for mRNA-1273 vaccine, corresponding to 0.4 and 0.3 EC per 100,000 vaccinated, respectively. Increased risk was also observed after the first dose of ChAdOx1-S vaccine (RI=6.52; 95% CI 2.88-14.77), corresponding to 1.0 EC per 100,000 vaccinated. There was no evidence of increased risk of GBS after vaccination with BNT162b2 and Ad26.COV2-S vaccines.

In the subgroup analysis by sex an increased risk of GBS was observed among both males and females after mRNA-1273 vaccine. In males an increased risk was observed after the first dose, with a borderline significance (RI=5.26; 95% CI 0.94-29.42; $p=0.06$) and the second dose (RI=16.50; 95% CI 3.01-90.56) and in females after the first dose (RI=13.44; 95% CI 2.83-63.80). There was also evidence of an increased risk after a first dose of ChAdOx1-S in males (RI=4.94; 95% CI 1.84-13.28) and females (RI=7.14; 95% CI 1.94-26.19).

In the subgroup analysis by age, there was evidence of an increased risk of GBS with mRNA-1273 vaccine among those aged ≥ 60 years after the first (RI=8.03; 95% CI 2.08-31.03) and second dose (RI=7.71; 95% CI 2.38-24.97). After a first dose of ChAdOx1-S there was evidence of an increased risk of GBS in those aged 40-59 (RI=4.50; 95% CI 1.37-14.79) and in those aged ≥ 60 years (RI=6.84; 95% CI 2.56-18.28). There was no evidence of increased risk of GBS after vaccination with BNT162b2 and Ad26.COV2-S vaccines in the subgroup analysis by age and sex. Study limitations include that the outcome was not validated through review of clinical records, the possibility of time-dependent residual confounding and the imprecision of the obtained estimates in the subgroup analysis due to the very low number of events.

The authors concluded that it is important the continuous monitoring of the suspected AEs of the COVID-19 vaccines as key component of any vaccination program. Results from this large SCCS study showed an increased risk of GBS after first and second dose of mRNA-1273 and first dose of ChAdOx1-S. However, these findings were compatible with a small number of EC. They specified that their data are reassuring regarding BNT162b and Ad26.COV2-S vaccines with respect to GBS outcome. No increased risk of GBS was detected following each of BNT162b vaccine dose nor any increased risk after Ad26.COV2-S vaccine dose.

AstraZeneca Comments:

This is an active postmarketing surveillance of effectiveness and safety of COVID-19 vaccines in Italy published as a pre-print.

This case definition is appropriate however, the outcome was not validated through review of clinical records hence misclassification if possible, resulting in either an under or over estimation of risk. In addition, the authors do not refer to the Brighton Collaboration levels of diagnostic certainty 1-5 (level 1 being highest level, level 5 reflecting exclusion). The combined risk-window of 0-42 is not consistent with immunopathogenesis of GBS (As per the recommendation from the external neurology expert panel that provided their consultation in the May 2021 mSSR for VAXZEVRIA).

This SCCS method also requires all cases to be used during the study period, including those unvaccinated, thus all cases of GBS between 27 December 2020 to 30 September 2021 meeting eligibility criteria should have been included, however unvaccinated data were not included, since the surveillance data only collected data on vaccinated cases. There was also no information on when GBS cases occurred over calendar time or after exposure. Thus, an understanding of distribution of number of GBS cases before and after vaccination to explore the requirement for alternative risk window was not evaluated and an overestimation of risk cannot be excluded.

The modified SCCS method did not include all GBS cases as recommended, there is no information on distribution of GBS cases in relation to the exposure, as well there is insufficient information to interpret the findings of the sensitivity analyses and robustness of primary analysis and therefore an overestimation of risk cannot be excluded. In the study, whilst the source population has been selected appropriately, the categorisation by vaccine received has not taken into account heterologous regimens and thus misclassification of exposure is possible.

The authors report that this SCCS study, covering about 16 million people, found evidence of an increased risk of GBS after administration of first and second dose of mRNA-1273 and first dose of ChAdOx1-S in the risk period of 0-42 Days. However, an increased risk of GBS was not observed following first and second dose of BNT162b nor Ad26.COV2-S vaccination.

This pre-print has not been peer-reviewed therefore any results must be interpreted with caution. A similar paper using the identical methodology but assessing a different safety concern has been published and there are some unexpected differences that cannot be explained. The strengths of this study pertain mostly in relation to the large source population which spans 5 regions within Italy representing 44% of patients aged 12+ years, the availability of data on COVID-19 vaccinations and outcomes and selection of the SCCS to address this research question. However, despite reporting similarities of finding with other publications, the methodological concerns relating to the SCCS adapted design, particularly the choice of risk window limit the inferences that can be drawn from this study.

It is reported in the literature up to 50% of GBS cases can either present with or have early predominance of facial diplegia as a clinical symptoms (Hozumi et al 1999, Keane 1994) the reported cases reviewed from the AstraZeneca safety database showed about 4.2% (9 out of 216) with facial diplegia noted, without the specific subtype of facial diplegia, hyporeflexia

and paraesthesia. Because the cranial nerve involvement is not systematically queried or reported into the various health authorities, it is not possible to say with certainty how many patients have either unilateral facial paralysis or facial diplegia in the safety database.

Based on the review of the data from the period covered by this report, the pattern of GBS after vaccination is the usual picture seen in clinical practice with ascending weakness, sensory abnormalities, hyporeflexia, mild to moderate autonomic dysfunction and infrequent cranial nerve involvement. Overall, the pattern of GBS including facial diplegia/bifacial weakness is considered to occur less commonly after vaccination with VAXZEVRIA than would be expected in the general population.

Review of Cases – Cumulative up to 28 December 2023

Cumulatively (up until 28 December 2023), 1976 cases were reported for GBS based on the search mentioned above.

The search retrieved a total of 2057 events of GBS in 1976 case reports. These cases were reported most frequently in the following countries during the reporting period: UK (n = 604, 30.6%); Brazil (n = 223, 11.8%); Australia (n = 225, 11.4%); Germany (n = 193, 9.8%) and India (n = 113, 5.7%).

Out of the 2057 events, 49 (2.5%) AEs had fatal outcome.

Observed Versus Expected Analysis

The observed versus expected analysis for all cases of GBS is presented with different risk windows (14, 30 and 42 Days). As per the recommendation from the external neurology expert panel that provided their consultation in the May 2021 monthly safety summary report (mSSR) for VAXZEVRIA, the risk window should be calculated between 5-42 Days. To account for the mechanism by which GBS is caused, the lower limit of the window should be set conservatively at 5 Days. Events of GBS occurring less than 5 Days from vaccination would be questionable in any causative association and are therefore excluded from the counts of observed cases. This applies to all observed vs expected analyses presented.

The analysis in Table 40 includes all reported cases irrespective of the BCC level. An observed versus expected analysis of cases meeting case definition according to the BCC Level 1, 2 or 3, based on clinical course, examination and no alternative aetiology in the presence or absence of NCS or CSF results are also presented in Table 41 below.

Furthermore, the observed versus expected analysis is presented with stratification by age for the EU-UK-Brazil-Australia regions based on the available exposure. In addition, stratification by age and gender for UK region only based on the available exposure data have also been included. Since this represents data for UK only, the expected number of cases vary when presented by different age group for males and females due to different incident rates in these subgroups.

Conservatively, the exposure for global reports (470543084) is based on doses administered in 13 markets.

Table 40 Observed Versus Expected Analysis for Global GBS cases

AEs	Risk window	BG rates	Exposure ^a	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
GBS	14	4.52	466115644	466	807.57	0.58 (0.53 - 0.63)	Observed significantly < expected
GBS	30	4.52	466115644	916	1730.5	0.53 (0.5 - 0.56)	Observed significantly < expected
GBS	42	4.52	466115644	983	2422.7	0.41 (0.38 - 0.43)	Observed significantly < expected
GBS RW14Unk TTO	14	4.52	466115644	992	807.57	1.23 (1.15 - 1.31)	Observed significantly > expected
GBS RW30Unk TTO	30	4.52	466115644	1442	1730.5	0.83 (0.79 - 0.88)	Observed significantly < expected
GBS RW42Unk TTO	42	4.52	466115644	1509	2422.7	0.62 (0.59 - 0.66)	Observed significantly < expected

^a Exposure until 28 December 2023

AEs Adverse Events; BCC Brighton Collaboration; BG Background; CI Confidence Interval; E Expected; GBS Guillain-Barre syndrome; IR Incidence Rate; O / E Observed to Expected; TTO Time to Onset

Table 41 Observed Versus Expected Analysis for cases meeting the Brighton Criteria Level 1, 2 or 3 (Global reports) within three risk windows

AEs	Risk window	BG rates	Exposure ^a	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
GBS BC 1-3	14	4.52	466115644	164	807.57	0.2 (0.17 - 0.24)	Observed significantly < expected
GBS BC 1-3	30	4.52	466115644	309	1730.5	0.18 (0.16 - 0.2)	Observed significantly < expected
GBS BC 1-3	42	4.52	466115644	329	2422.7	0.14 (0.12 - 0.15)	Observed significantly < expected
GBS BC 1-3 RW14 Unk TTO	14	4.52	466115644	257	807.57	0.32 (0.28 - 0.36)	Observed significantly < expected

Table 41 Observed Versus Expected Analysis for cases meeting the Brighton Criteria Level 1, 2 or 3 (Global reports) within three risk windows

AEs	Risk window	BG rates	Exposure ^a	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
GBS BC 1-3 RW30 Unk TTO	30	4.52	466115644	402	1730.5	0.23 (0.21 - 0.26)	Observed significantly < expected
GBS BC 1-3 RW42 Unk TTO	42	4.52	466115644	422	2422.7	0.17 (0.16 - 0.19)	Observed significantly < expected

^a Exposure until 28 December 2023

AEs Adverse Events; BCC Brighton Collaboration, CI Confidence Interval; E Expected; GBS Guillain-Barre syndrome; IR Incidence Rate; O Observed; TTO Time to onset; Unk Unknown

Table 42 Observed Versus Expected Analysis for cases meeting the Brighton Criteria Level 1, 2 or 3 and stratified by age for EEA/UK/Brazil/Australia regions

AEs	Risk window	BG rates	Exposure ^a	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
GBS BCC 1-3 Age 18-49 EU/UK/Brazil/ Australia	14	3.07	110094983	28	129.55	0.22 (0.14 - 0.31)	Observed significantly < expected
GBS BCC 1-3 Age 18-49 EU/UK/Brazil/ Australia	30	3.07	110094983	55	277.62	0.2 (0.15 - 0.26)	Observed significantly < expected
GBS BCC 1-3 Age 18-49 EU/UK/Brazil/ Australia	42	3.07	110094983	60	388.66	0.15 (0.12 - 0.2)	Observed significantly < expected
GBS BCC 1-3 Age 50-59 EU/UK/Brazil/ Australia	14	4.71	58336094	48	105.32	0.46 (0.34 - 0.6)	Observed significantly < expected
GBS BCC 1-3 Age 50-59 EU/UK/Brazil/ Australia	30	4.71	58336094	90	225.68	0.4 (0.32 - 0.49)	Observed significantly < expected
GBS BCC 1-3 Age 50-59 EU/UK/Brazil/ Australia	42	4.71	58336094	99	315.96	0.31 (0.25 - 0.38)	Observed significantly < expected

Table 42 Observed Versus Expected Analysis for cases meeting the Brighton Criteria Level 1, 2 or 3 and stratified by age for EEA/UK/Brazil/Australia regions

AEs	Risk window	BG rates	Exposure ^a	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
GBS BCC 1-3 Age 60-69 EU/UK/Brazil/ Australia	14	6.29	57960860	34	139.74	0.24 (0.17 - 0.34)	Observed significantly < expected
GBS BCC 1-3 Age 60-69 EU/UK/Brazil/ Australia	30	6.29	57960860	67	299.45	0.22 (0.17 - 0.28)	Observed significantly < expected
GBS BCC 1-3 Age 60-69 EU/UK/Brazil/ Australia	42	6.29	57960860	68	419.23	0.16 (0.13 - 0.21)	Observed significantly < expected
GBS BCC 1-3 Age Over 70 EU/UK/Brazil/ Australia	14	5.96	32376365	18	73.96	0.24 (0.14 - 0.38)	Observed significantly < expected
GBS BCC 1-3 Age Over 70 EU/UK/Brazil/ Australia	30	5.96	32376365	35	158.49	0.22 (0.15 - 0.31)	Observed significantly < expected
GBS BCC 1-3 Age Over 70 EU/UK/Brazil/ Australia	42	5.96	32376365	38	221.89	0.17 (0.12 - 0.24)	Observed significantly < expected

^a Exposure until 28 December 2022

AE Adverse Event; BCC Brighton Collaboration, BG Background; CI Confidence Interval; E Expected; EU European Union; GBS Guillain-Barre syndrome; IR Incidence Rate; O Observed; TTO Time to onset; UK United Kingdom

Table 43 Observed Versus Expected analysis for GBS cases meeting the Brighton Criteria (BC) Level 1, 2 or 3 and stratified by age and gender for UK only

Age and gender	Risk window	BG rates	Exposure ^a	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Age 18-49 Female UK	14	2.22	7414701	6	6.31	0.95 (0.35 - 2.07)	Observed < expected
Age 18-49 Female UK	30	2.22	7414701	12	13.52	0.89 (0.46 - 1.55)	Observed < expected
Age 18-49 Female UK	42	2.22	7414701	13	18.93	0.69 (0.37 - 1.17)	Observed < expected

Table 43 Observed Versus Expected analysis for GBS cases meeting the Brighton Criteria (BC) Level 1, 2 or 3 and stratified by age and gender for UK only

Age and gender	Risk window	BG rates	Exposure ^a	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Age 50-59 Female UK	14	2.68	5944683	12	6.11	1.96 (1.01 - 3.43)	Observed significantly > expected
Age 50-59 Female UK	30	2.68	5944683	19	13.09	1.45 (0.87 - 2.27)	Observed > expected
Age 50-59 Female UK	42	2.68	5944683	21	18.32	1.15 (0.71 - 1.75)	Observed > expected
Age 60-69 Female UK	14	5.47	4783416	5	10.03	0.5 (0.16 - 1.16)	Observed < expected
Age 60-69 Female UK	30	5.47	4783416	10	21.49	0.47 (0.22 - 0.86)	Observed significantly < expected
Age 60-69 Female UK	42	5.47	4783416	10	30.09	0.33 (0.16 - 0.61)	Observed significantly < expected
Age 70-79 Female UK	14	5.45	3475875	7	7.26	0.96 (0.39 - 1.99)	Observed < expected
Age 70-79 Female UK	30	5.45	3475875	9	15.56	0.58 (0.26 - 1.1)	Observed < expected
Age 70-79 Female UK	42	5.45	3475875	9	21.78	0.41 (0.19 - 0.78)	Observed significantly < expected
Age 80 Female UK	14	2.3	1630324	1	1.44	0.69 (0.02 - 3.87)	Observed < expected
Age 80 Female UK	30	2.3	1630324	1	3.08	0.32 (0.01 - 1.81)	Observed < expected
Age 80 Female UK	42	2.3	1630324	2	4.31	0.46 (0.06 - 1.68)	Observed < expected
Age 18-49 Male UK	14	3.59	6766098	6	9.31	0.64 (0.24 - 1.4)	Observed < expected
Age 18-49 Male UK	30	3.59	6766098	12	19.95	0.6 (0.31 - 1.05)	Observed < expected
Age 18-49 Male UK	42	3.59	6766098	14	27.93	0.5 (0.27 - 0.84)	Observed significantly < expected
Age 50-59 Male UK	14	6.05	6510960	14	15.1	0.93 (0.51 - 1.56)	Observed < expected
Age 50-59 Male UK	30	6.05	6510960	24	32.35	0.74 (0.48 - 1.1)	Observed < expected

Table 43 Observed Versus Expected analysis for GBS cases meeting the Brighton Criteria (BC) Level 1, 2 or 3 and stratified by age and gender for UK only

Age and gender	Risk window	BG rates	Exposure ^a	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Age 50-59 Male UK	42	6.05	6510960	28	45.3	0.62 (0.41 - 0.89)	Observed significantly < expected
Age 60-69 Male UK	14	6.66	4934728	8	12.6	0.63 (0.27 - 1.25)	Observed < expected
Age 60-69 Male UK	30	6.66	4934728	20	26.99	0.74 (0.45 - 1.14)	Observed < expected
Age 60-69 Male UK	42	6.66	4934728	20	37.79	0.53 (0.32 - 0.82)	Observed significantly < expected
Age 70-79 Male UK	14	8.17	3137304	3	9.82	0.31 (0.06 - 0.89)	Observed significantly < expected
Age 70-79 Male UK	30	8.17	3137304	6	21.05	0.29 (0.1 - 0.62)	Observed significantly < expected
Age 70-79 Male UK	42	8.17	3137304	7	29.47	0.24 (0.1 - 0.49)	Observed significantly < expected
Age 80 Male UK	14	5.78	1025046	0	2.27	0 (0 - 1.63)	Observed < expected
Age 80 Male UK	30	5.78	1025046	0	4.87	0 (0 - 0.76)	Observed significantly < expected
Age 80 Male UK	42	5.78	1025046	0	6.81	0 (0 - 0.54)	Observed significantly < expected

^b Exposure until 28 December 2022

BCC Brighton Collaboration, BG Background; CI Confidence Interval; E Expected; GBS Guillain-Barre syndrome; IR Incidence Rate; O Observed; TTO Time to Onset; UK United Kingdom

Discussion on O/E Analysis

The observed versus expected analysis of cumulative cases reported with TTO within all risk windows (14 Days, 30 Days and 42 Days) from vaccination suggests that observed cases are significantly less than expected, except when unknown TTO is included for risk window of 14 Days regardless of BCC level 1-3 where the result is observed significantly more than expected.

When cases fulfilling BCC 1-3 from the UK are stratified by age and gender, observed cases are less than expected for all stratifications except for females aged 50–59 years for all risk windows (exception is made for risk window 14, where the cases are significantly more than expected).

Although certain stratifications by age, gender and dose in the UK when all cases are included in the O/E analyses suggest an increased risk of GBS for the adult population, it is important to note that these analyses are sensitive to the IRs used. The rates used in the analysis are conservative, and other sources have shown higher rates for all age groups Li et al 2022. In addition, it is important to note that incident rates includes rates from pre-pandemic times, ie, the effect of COVID-19 in the BG is not accounted for, which several sources suggest temporal association with GBS Patone et al 2021, Li et al 2022. Furthermore, a majority of the reported cases correlate with the period of peak pandemic activity, suggesting a potential role of COVID-19 infection in causing GBS (Coronavirus (COVID-19) in Australia, Coronavirus (COVID-19) in Brazil, Coronavirus (COVID-19) in Canada, Coronavirus (COVID-19) in Europe, Coronavirus (COVID-19) in the UK). Seasonal fluctuations in the incidence of GBS with a higher incidence in winter compared to summer is also a consideration.

Summary

During the period covered by this report (29 December 2022 to 28 December 2023), 105 cases reported, out of which 74 (70.5%) were reported by HCPs (MC).

Out of the 163 cases, 33 of the cases fulfilled BCC 1 level criteria, 21 of the cases fulfilled BCC 2 level criteria and 5 of the cases fulfilled BCC 3 level criteria. When these 60 are assessed according to WHO-UMC causality criteria 2 did not have sufficient information to do a causality assessment and were assessed as “Unassessable/unclassifiable”, 5 were assessed as “Unlikely”, and 53 were assessed as “Possible” causality to VAXZEVRIA.

Out of the 53 cases assessed for WHO-UMC causality deemed as “Possible”, 50 had limited information on other aetiologies, medical history, concomitant medications, etc., and 3 cases had risk factors or confounders. Cases were considered to have “risk factors/confounders” where the event could also be explained by the vaccinee’s diseases, relevant risk factors that were present, or concomitant medications that could potentially contribute to the development of the event.

The review of GBS cases post COVID-19 booster dosing did not show any significant safety concern.

There is high variability in the data for the observed versus expected analysis of cumulative cases reported, making an assessment on causal association not possible. The majority of the stratifications and analysis suggest that the observed cases are less than expected for all three risk windows (14 Days, 30 Days and 42 Days). However, some analysis for global reports, UK and the EU-UK-Brazil-Australia suggest observed cases are more or significantly more

than expected. However, it is important to note that the mainstream of reported cases correlate with the period of peak pandemic activity, suggesting a potential role of COVID-19 infection in causing GBS (Coronavirus (COVID-19) in Australia, Coronavirus (COVID-19) in Brazil, Coronavirus (COVID-19) in Canada, Coronavirus (COVID-19) in Europe, Coronavirus (COVID-19) in the UK). Seasonal fluctuations in the incidence of GBS with a higher incidence in winter compared to summer is also a consideration.

Based on the review of available evidence from literature and from reports in the safety database on the topic of GBS, AstraZeneca considers that there is not sufficient evidence to confirm any particular clinical features associated with vaccination or establish a causal association with VAXZEVRIA.

Conclusion

From the data identified during the reporting period, and also taking into account the cumulative experience, no new information on GBS warrant any changes in the CDS or RMP. The topic of GBS will continue to be closely monitored as part of AstraZeneca's ongoing surveillance efforts for the important potential risk of immune mediated neurological conditions.

16 SIGNAL AND RISK EVALUATION

16.1 Summary of safety concerns

At the beginning of the reporting period, the VAXZEVRIA safety specification (presented in the global AstraZeneca Core RMP, Version no. 8.0, dated 10 November 2022) included the following important identified risks, important potential risks, and missing information (see Table 44):

Table 44 Summary of safety concerns – AstraZeneca Core Risk Management Plan for VAXZEVRIA (Version no.08.0, dated 05 October 2022)

Risk category	Safety concern
Important identified risks	Thrombosis in combination with thrombocytopenia
Important potential risks	Cerebrovascular venous sinus thrombosis without thrombocytopenia
	Immune mediated neurological conditions
Missing information	Use of VAXZEVRIA in pregnant and breastfeeding women
	Use of VAXZEVRIA in subjects with severe immunodeficiency
	Use of VAXZEVRIA in subjects with severe and/or uncontrolled underlying disease

During the reporting period the RMP was updated twice to include the data from the final study analysis of the COV001, COV002, COV003, COV005 pooled analysis (version 9.0) and US study (D8110C00001) and Booster study (D7220C00001) (version 10.0).

16.2 Signal evaluation

Two validated signals were closed during the reporting period. A summary of the signal evaluation is provided below.

16.2.1 Closed and rejected/refuted signals

There were no closed and rejected/refuted signals during the reporting period.

16.2.2 Closed signals categorised as important potential risks.

There were no closed signals categorised as important potential risks during the reporting period.

16.2.3 Closed signals categorised as important identified risks.

There were no closed signals categorised as important identified risks during the reporting period.

16.2.4 Closed signals that are potential risks not categorised as important.

There were no closed signals that are potential risks not categorised as important during the reporting period.

16.2.5 Closed signals that are identified risks not categorised as important.

During the reporting interval, two signal were evaluated and closed. One signal “Decreased appetite” was considered as an identified risk categorised as non-important and CDS would be updated based on the signal “Potential Vaccination Failure/Lack of Efficacy against Emerging Variants (including Omicron XBB)”. For details, refer to Table 45 and Section 13 and Table 46.

16.2.5.1 Decreased appetite

During the reporting period, final pooled analysis data (Data Cut Off [DCO] 3:31 December 2021; COV001, COV002, COV003, COV005) was evaluated and an imbalance between AZD1222 and control groups was observed for the event “Appetite Decreased” (0.6% [58 participants] in the AZD1222 group versus 0.2% [25 participants] in the control group).

Although the frequency of “decreased appetite” was less than 2% in both treatment groups, the imbalance between groups was also observed for events considered related to study treatment: 0.5% (49 participants) in the AZD1222 group versus 0.2% (18 participants) in the control group. It was also noted in COV001, where the frequency was 2.6% in the AZD1222 group (14 participants) and 0 in the control group. Based on review of these data and relevant post-marketing data, AstraZeneca considers there to be a reasonable possibility of a causal relationship between AZD1222 and the event of “Decreased appetite.” AstraZeneca has therefore added “Decreased appetite” in Section 4.8 of the AZD1222 CDS with a frequency of “Uncommon” (0.6%). Decreased appetite is already included in the EU SmPC.

Table 45 Decreased appetite

Characterisation	Summary
Source of the signal	Final pooled analysis of COV studies (COV001, 002, 003 and 005; DCO 3: 31 December 2021)
Date detected	22 December 2022
Date closed	17 January 2023
Reference document(s)	Not applicable
Regulatory Procedure Reference	Not applicable
Search criteria	MedDRA PT: Decreased appetite
Method(s) of evaluation	With a DCO of 31 December 2021, the “DC03” data was derived from the results of AstraZeneca’s final pooled analysis of the safety, durability of efficacy, and immunogenicity of 2-dose primary intramuscular vaccinations with AZD1222, based on data from University of Oxford sponsored studies COV001, COV002, COV003 and COV005.
Outcome of the evaluation	CDS Section 4.8 (undesirable effects) was updated to include Decreased appetite as an ADR (frequency: uncommon).
Conclusions	CDS (Version 22.0; dated 21 February 2023) was updated to include Decreased appetite as ADR in Section 4.8 with frequency of ‘uncommon’.

ADR Adverse Drug Reaction; CDS Core Data Sheet; MedDRA Medical Dictionary for Regulatory Activities; PT Preferred Term.

16.2.5.2 Potential Vaccination Failure/Lack of Efficacy against Emerging Variants (including Omicron XBB)

During the reporting interval, AstraZeneca initiated a review of the effectiveness of VAXZEVRIA against emerging variants (including Omicron XBB). AstraZeneca has updated the CDS to Section 4.4 (Warnings & Precautions) section to remind the health care professionals about Potential Vaccination Failure/Lack of Efficacy against the circulating SARS-CoV-2 viral variants.

Table 46 Potential Vaccination Failure/Lack of Efficacy against Emerging Variants (including Omicron XBB)

Characterisation	Summary
Source of the signal	Updates from immunogenicity study and developments from the International Coalition of Medicines Regulatory Authorities (ICMRA) COVID-19 Omicron variant workshop.
Date detected	21 June 2023
Date closed	21 June 2023
Reference document(s)	Not applicable
Regulatory Procedure Reference	Not applicable
Method(s) of evaluation	Clinical trial and real-world evidence studies including the booster doses of VAXZEVRIA.

Table 46 Potential Vaccination Failure/Lack of Efficacy against Emerging Variants (including Omicron XBB)

Characterisation	Summary
Outcome of the evaluation	AstraZeneca evaluated the benefit-risk profile of VAXZEVRIA against currently circulating variants of concern (Omicron BA.4/5 and XBB; prior to designation of EG.5). Based on available data and structured benefit-risk assessment CDS was updated to ensure that the HCPs are aware that there are no clinical efficacy/VE data available with emerging variants and to remind them to consider the characteristics of circulating SARS-CoV-2 viral variants, including regional or geographical differences when using VAXZEVRIA.
Conclusions	The CDS was updated to include a warning/reminder to the treating physician on potential vaccination failure/lack of efficacy against the circulating variants, including regional or geographical differences.

CDS Core data sheet; HCPs Health care Professionals; ICMRA International Coalition of Medicines Regulatory Authorities; SARS Severe acute respiratory syndrome.

16.3 Evaluation of risks and new information

This section presents data from the AstraZeneca global safety database obtained using search strategies inclusive of all available data in the database. Numbers presented here may differ from those presented in the Appendix 2 summary tabulations (also from the AstraZeneca global safety database), where the search strategies are specific to the requirements for the summary tabulations.

Period data may include case reports which have been received prior to this period but where FU information have been obtained during the reporting period.

16.3.1 New information on important potential risks

All-important potential risks included in Section 16.1 are kept under close surveillance by AstraZeneca.

16.3.1.1 Cerebrovascular venous and sinus thrombosis without thrombocytopenia Global Patient Safety Database

A cumulative search through 28 December 2023 and period search (29 December 2022 to 28 December 2023) of the AstraZeneca Global Patient Safety Database was conducted using the following MedDRA (v26.1) HLT: Cerebrovascular venous and sinus thrombosis (CVST). To identify the cases of CVST without co-reported thrombocytopenia, the following were excluded from the search results: any cases with events from the HLT: Thrombocytopenia, SMQ: Hematopoietic thrombocytopenia (Narrow), or cases with platelet values less than 150,000 per microliter.

Reporting period (29 December 2022 to 28 December 2023)

After applying the above exclusion criteria, 32 cases (12 initial and 20 FU) of CVST without thrombocytopenia were retrieved. The majority of the cases, 10 (31.25%) from Germany and 10 (31.25%), were reported from the UK.

The distribution of the PTs for CVST without co-reported TCP are presented in below in Table 47 descending order of frequency:

Table 47 Distribution of MedDRA PTs (n = 43) pertaining to CVST without co-reported Thrombocytopenia with VAXZEVRIA received during the reporting period

MedDRA PT	Serious	Non-serious	Grand Total
Cerebral venous sinus thrombosis	26	0	26
Cerebral venous thrombosis	9	0	9
Cavernous sinus thrombosis	4	0	4
Transverse sinus thrombosis	2	0	2
Superior sagittal sinus thrombosis	2	0	2
Grand total	43	0	43

CVST Cerebral Venous Sinus Thrombosis; MedDRA Medical Dictionary for Regulatory Activities; PT Preferred Term

The breakdown and overview of these 39 cases reporting 28 events of topic is presented in the Table 48 below.

Table 48 Overview of CVST without co-reported thrombocytopenia Cases (n=32) during the reporting period

Parameter	Break-down	Values (%)
Case Count	Medically confirmed	19 (59)
Case Report Source	Post-marketing study	0 (0)
	Non-interventional study	0 (0)
	Spontaneous	14 (44)
	Literature	7 (22)
	Regulatory	11 (34)
Sex	Female N (%)	16 (51.6)
	Male N (%)	15 (48.4)
	Unknown/not reported N	1
Age Group	18-49	17 (63)
	50-59	7 (26)
	60-69	2 (7.4)
	70-79	1 (3.7)
	80+	0 (0)
	Unk	5
	Median age (range)	46 years (23 to 72)
Event occurrence with dose	Dose 1 (%)	30 (94)
	Dose 2 (%)	2 (6)
	Dose 3 (%)	-

Table 48 Overview of CVST without co-reported thrombocytopenia Cases (n=32) during the reporting period

Parameter	Break-down	Values (%)
	Dose 4 (%)	-
Case level -TTO days) ^a	0-21 days	12 (38)
	0-30 days	13 (41)
	0-42 days	14 (44)
	More than 42 Days	16 (50)
	Unknown	16 (50)
	Median TTO (range)	10 (1 to 480)
Event Seriousness criteria	Medically important	26 (81)
	Disability	8 (25)
	Hospitalization	16 (50)
	Congenital anomaly	0 (0)
	Life-threatening	9 (28)
	Death	4 (13)
AE Outcome	Recovered	3 (13)
	Recovering	4 (17.4)
	Recovered with sequelae	2 (8.7)
	Not recovered	10 (43.5)
	Fatal	4 (17.4)
	Unknown	9

^a TTO was reported for 07 case reports (total number of cases) used to calculate the percentage. Where multiple TTOs are present in a case, the most conservative TTO for the relevant event is chosen. Percentages for all, calculated based on known values.
AE Adverse Event; CVST Cerebral Venous Sinus Thrombosis; TTO Time To Onset; Unk Unknown

Cases with fatal outcome

Of the 32 total events reported, 4 (12.5%) event was reported with a fatal outcome, MC. Summary of this case report with details is presented below.

Case ID [REDACTED]: Spontaneous report from a health care professional in Germany concerning a 38-year-old male patient. Medical history and concomitant medications were unknown. It was reported that, the patient experienced the event of Cerebral venous sinus thrombosis and central regulatory failure (PT: Nervous system disorder) 11 days after VAXZEVRIA vaccination and died from the events on the same day. An autopsy was performed. The cause of death was reported as central regulatory failure (confirmed at autopsy) and venous sinus thrombosis (confirmed at autopsy). No other information was provided.

AstraZeneca comments: The TTO for the event was within in the risk window (11 days). However, the case has limited information on concomitant medication, history of thrombosis/coagulopathy, patient's COVID-19 infection status, hospitalisation details and diagnostic workup. Based on the information available, the case was assessed as possible with limited information.

Case ID [REDACTED]: The spontaneous case concerned 63 years old female patient received from the health professional via an [REDACTED] in Germany. The patient received VAXZEVRIA on 01-Mar-2021 and 07-May-2021. No medical history and concomitant medication reported. On 17-Jun-2021, the patient died from the event of cerebral haemorrhage, Subarachnoid haemorrhage, headache, migraine, arterial rupture, cavernous sinus thrombosis. The cause of death was reported severe headache, migraine, she suspected arterial rupture, cerebral haemorrhage, subarachnoid haemorrhage and suspected cavernous sinus thrombus. It was unknown if an autopsy performed. No other relevant information was provided.

AZ comments: The patient's age could be confounding factor for the events. The TTO was within in the risk window (31 Days) for the safety topic. However, case has insufficient information on circumstances leading to the events, clinical course, concomitant medication, any history of thrombosis/coagulopathy, patient's COVID-19 infection status, hospitalisation details and diagnostic workup. Based on the information available, the case was assessed as possible with limited information.

Case ID [REDACTED]: This literature case concerned a 43 year female patient of unknown ethnic origin. No concomitant medication was reported. It was reported that the patient was admitted with loss of consciousness 10 days after vaccination. The patient was admitted to the hospital with Glasgow Coma Scale (GCS)=8. Her brain CT scan showed intracranial haemorrhagic infarction (preferred term: Haemorrhagic cerebral infarction), and CVST (preferred term: Cerebral venous sinus thrombosis) was confirmed with brain MRI and Magnetic Resonance Venography (MRV). She had no past medical history and history of medication use. Also, testing for TTP, vasculitis disorder, and microangiopathic haemolytic anaemia was negative. She underwent decompressive craniotomy and other medication, but unfortunately, brain death was suspected for her 20 days later. The cause of death was brain dead, cerebral venous sinus thrombosis and intracranial haemorrhagic infarction. It was unknown if an autopsy performed. No other relevant information was provided.

AZ comments: Due to limited information on baseline health condition before vaccination, circumstances leading to the events, further risk factors, if any conditions and diseases reported in medical history, concomitant medications, autopsy report with confirmed diagnosis, detailed aetiological and diagnostic work up, the evaluation did not find evidence to suggest a causal relationship between the events and AZD1222. However based on time to onset causality is assessed as possible with limited information.

Case ID [REDACTED]: This spontaneous report concerned a female patient of unknown age and unknown ethnic origin. The patient's past and current medical history included anticoagulant therapy. On an unknown date, the patient received VAXZEVRIA and Pfizer Vaccine. On an unknown date the patient experienced cerebral venous thrombosis. The patient died from the event during May 2021.

AZ comments: Insufficient information regarding precise type of anticoagulation patient was on and for what indication, any prior history of arterial/venous thrombosis, event onset latency, event details, lab data and autopsy findings; preclude a comprehensive causality assessment.

Recurrence case reports

There were no cases indicating a recurrence.

WHO-UMC causality Assessment

The TTO of the event was reported in 16 (16/32) cases and 14 cases were reported within the risk window of 42 days. Causality assessment of all cases was performed using WHO-UMC causality assessment criteria with a risk window of 42 days.

Table 49 Overview of WHO-UMC Causality Assessments for case reports of CVST without Thrombocytopenia with VAXZEVRIA reported during the reporting period

WHO-UMC causality assessment	Grand Total
Possible with limited information	10
Possible with Confounders	3
Unlikely	1
Total	14

Cases were considered to have “risk factors/confounders” where the event could also be explained by the vaccinee’s diseases, or where relevant risk factors were present, or concomitant medications that could potentially contribute to the development of the event were reported.

UMC Uppsala Monitoring Centre; WHO World Health Organization

None of the cases met WHO-UMC criteria as ‘Certain’, ‘Probable/Likely’, ‘Conditional/Unclassified’ and Unassessable/Unclassifiable with risk factors/confounders.

There was available information on confounding comorbidities, other medical confounders or risk factors and confounding medications reported in 3 (22%) of the 14 cases. Remaining 10 cases had no information on any confounding/risk factor. A single case may have more than one risk/confounding factor.

The confounding factors reported for the cases were concomitant use of tamoxifen citrate and dabigatran, breast cancer, medical history of sinus vein thrombosis, Hashimoto's thyroiditis, family history of portal vein thrombosis, heterozygous prothrombin mutation, pregnancy (hypercoagulable state).

Observed Versus Expected (O/E) Analyses for all cases of CVST without Thrombocytopenia

The observed versus expected analyses for all cases of CVST without thrombocytopenia are carried out cumulatively using IRs from ACCESS: System for Research in Primary Care (SIDIAP) PCHOSP and Truven Market Scan (2019). The observed versus expected analysis for all cases of CVST without thrombocytopenia is presented with different risk windows (21 Days, 30 Days and 42 Days) for all global reports in Table 53 and stratified by age for the EEA, UK, Australia and Brazil regions in Table 53 and by age and gender in UK Global analysis also included cases with an unknown time to onset, as a conservative approach. The IRs used were from SIDIAP_PCHOSP Willame et al 2021 (A) as that rate was used by the EMA, and this would permit a comparison of the O/E analysis conducted by EMA and AstraZeneca.

SIDIAP PCHOSP is a data source containing 5.7 million (80% of the population) in Catalonia and includes General Practitioner (GP) medical records, communication from specialists and hospitalization discharge diagnoses. SIDIAP PCHOSP is representative of the general population in terms of age, sex, and geographic distribution. Since CVST is a very rare event, a larger database was used in addition to SIDIAP PCHOSP. Truven MarketScan (US) was chosen since is a longitudinal database capturing outcomes from in- and outpatient visits and pharmaceuticals and contains almost 230 million unique patients. Moreover, it includes both commercial employer-based insurance and government-based insurance. In addition to its large sample size Truven MarketScan was used for consistency with BG rates for CVST generated using MarketScan.

As a comparison to the above, the same observed versus expected analyses are carried out using IRs from Truven MarketScan. Those analyses for CVST are presented with different risk windows (21 Days, 30 Days and 42 Days) for all global reports in Table 50, stratified by age in the EEA, UK, Australia and Brazil in Table 51 and by age and gender in the UK Table 52.

Table 50 **Observed versus expected analysis for CVST without thrombocytopenia
(using SIDIAP PC HOSP incident rate)**

Concept							
Observed Versus Expected analysis for CVST without TCP cases Overall							
Overall RW21	21	0.72	466115644	299	402	0.74 (0.66 - 0.83)	Observed significantly < expected
Overall (RW21+Unk TTO)	21	0.72	466115644	480	402	1.19 (1.09 - 1.31)	Observed significantly > expected
Overall RW30	30	0.72	466115644	342	574.28	0.6 (0.53 - 0.66)	Observed significantly < expected
Overall (RW30+Unk TTO)	30	0.72	466115644	523	574.28	0.91 (0.83 - 0.99)	Observed significantly < expected
Overall RW42	42	0.72	466115644	390	803.99	0.49 (0.44 - 0.54)	Observed significantly < expected
Overall (RW42+Unk TTO)							
Observed Versus Expected analysis for CVST without TCP cases stratified by age and gender for UK region with Risk Window (21, 30 & 42)							
Male 18-29 UK	21	1.27	808938	2	0.51	3.92 (0.47 - 14.17)	Observed > expected
Male 30-39 UK	21	0	1415003	2	0.56	3.57 (0.43 - 12.9)	Observed > expected
Male 40-49 UK	21	0.72	4542157	5	2.25	2.22 (0.72 - 5.19)	Observed > expected
Male 50-59 UK	21	0.9	6510960	6	3.41	1.76 (0.65 - 3.83)	Observed > expected
Male 60-69 UK	21	2.49	4934728	4	5.45	0.73 (0.2 - 1.88)	Observed < expected
Male 70-79 UK	21	1.68	3137304	3	4.49	0.67 (0.14 - 1.95)	Observed < expected
Male over 80 UK	21	2.81	1025046	1	3.91	0.26 (0.01 - 1.42)	Observed < expected

Table 50 Observed versus expected analysis for CVST without thrombocytopenia (using SIDIAP PC HOSP incident rate)

Concept							
Female 18-29 UK	21	0	1109488	3	1.57	1.91 (0.39 - 5.58)	Observed > expected
Female 30-39 UK	21	0	1892968	4	2.43	1.65 (0.45 - 4.21)	Observed > expected
Female 40-49 UK	21	0.77	4412245	13	4.67	2.78 (1.48 - 4.76)	Observed significantly > expected
Female 50-59 UK	21	0	5944683	6	2.8	2.14 (0.79 - 4.66)	Observed > expected
Female 60-69 UK	21	0	4783416	3	3.88	0.77 (0.16 - 2.26)	Observed < expected
Female 70-79 UK	21	0	3475875	3	1.42	2.11 (0.44 - 6.17)	Observed > expected
Female over 80 UK	21	1.67	1630324	1	8.74	0.11 (0 - 0.64)	Observed significantly < expected
Male 18-29 UK	30	1.27	808938	2	0.73	2.74 (0.33 - 9.9)	Observed > expected
Male 30-39 UK	30	0	1415003	2	0.8	2.5 (0.3 - 9.03)	Observed > expected
Male 40-49 UK	30	0.72	4542157	7	3.21	2.18 (0.88 - 4.49)	Observed > expected
Male 50-59 UK	30	0.9	6510960	8	4.87	1.64 (0.71 - 3.24)	Observed > expected
Male 60-69 UK	30	2.49	4934728	4	7.78	0.51 (0.14 - 1.32)	Observed < expected
Male 70-79 UK	30	1.68	3137304	3	6.42	0.47 (0.1 - 1.37)	Observed < expected
Male over 80 UK	30	2.81	1025046	1	5.59	0.18 (0 - 1)	Observed significantly < expected

Table 50 Observed versus expected analysis for CVST without thrombocytopenia (using SIDIAP PC HOSP incident rate)

Concept							
Female 18-29 UK	30	0	1109488	4	2.24	1.79 (0.49 - 4.57)	Observed > expected
Female 30-39 UK	30	0	1892968	4	3.47	1.15 (0.31 - 2.95)	Observed > expected
Female 40-49 UK	30	0.77	4412245	13	6.67	1.95 (1.04 - 3.33)	Observed significantly > expected
Female 50-59 UK	30	0	5944683	8	4	2 (0.86 - 3.94)	Observed > expected
Female 60-69 UK	30	0	4783416	5	5.54	0.9 (0.29 - 2.11)	Observed < expected
Female 70-79 UK	30	0	3475875	4	2.03	1.97 (0.54 - 5.05)	Observed > expected
Female over 80 UK	30	1.67	1630324	1	12.48	0.08 (0 - 0.45)	Observed significantly < expected
Male 18-29 UK	42	1.27	808938	4	0.73	2.74 (0.33 - 9.9)	Observed > expected
Male 30-39 UK	42	0	1415003	2	0.8	2.5 (0.3 - 9.03)	Observed > expected
Male 40-49 UK	42	0.72	4542157	8	3.21	2.18 (0.88 - 4.49)	Observed > expected
Male 50-59 UK	42	0.9	6510960	12	4.87	1.64 (0.71 - 3.24)	Observed > expected
Male 60-69 UK	42	2.49	4934728	6	7.78	0.51 (0.14 - 1.32)	Observed < expected
Male 70-79 UK	42	1.68	3137304	3	6.42	0.47 (0.1 - 1.37)	Observed < expected
Male over 80 UK	42	2.81	1025046	1	5.59	0.18 (0 - 1)	Observed significantly < expected

Table 50 **Observed versus expected analysis for CVST without thrombocytopenia
(using SIDIAP PC HOSP incident rate)**

Concept							
Female 18-29 UK	42	0	1109488	4	3.14	1.27 (0.35 - 3.26)	Observed > expected
Female 30-39 UK	42	0	1892968	6	4.85	1.24 (0.45 - 2.69)	Observed > expected
Female 40-49 UK	42	0.77	4412245	14	9.34	1.5 (0.82 - 2.51)	Observed > expected
Female 50-59 UK	42	0	5944683	9	5.61	1.6 (0.73 - 3.05)	Observed > expected
Female 60-69 UK	42	0	4783416	6	7.76	0.77 (0.28 - 1.68)	Observed < expected
Female 70-79 UK	42	0	3475875	4	2.84	1.41 (0.38 - 3.61)	Observed > expected
Female over 80 UK							
Observed Versus Expected analysis for CVST without TCP cases stratified by age for EU+UK+Brazil+Australia region with Risk Window (21, 30 & 42)							
18-49 EU+UK+Brazil+Australia	21	0.27	110094983	128	98.12	1.3 (1.09 - 1.55)	Observed significantly > expected
50-59 EU+UK+Brazil+Australia	21	1.57	58336094	56	28.85	1.94 (1.47 - 2.52)	Observed significantly > expected
60-69 EU+UK+Brazil+Australia	21	0.68	57960860	59	54.99	1.07 (0.82 - 1.38)	Observed > expected
Over 70 EU+UK+Brazil+Australia	21	0.34	32376365	35	16.75	2.09 (1.46 - 2.91)	Observed significantly > expected
18-49 EU+UK+Brazil+Australia	30	0.27	110094983	141	140.16	1.01 (0.85 - 1.19)	Observed > expected
50-59 EU+UK+Brazil+Australia	30	1.57	58336094	66	41.21	1.6 (1.24 - 2.04)	Observed significantly > expected
60-69 EU+UK+Brazil+Australia	30	0.68	57960860	66	78.55	0.84 (0.65 - 1.07)	Observed < expected

Table 50 Observed versus expected analysis for CVST without thrombocytopenia (using SIDIAP PC HOSP incident rate)

Concept							
Over 70 EU+UK+Brazil+Australia ^a	30	0.34	32376365	41	23.93	1.71 (1.23 - 2.32)	Observed significantly > expected
18-49 EU+UK+Brazil+Australia ^a	42	0.27	110094983	159	196.23	0.81 (0.69 - 0.95)	Observed significantly < expected
50-59 EU+UK+Brazil+Australia ^a	42	1.57	58336094	74	57.69	1.28 (1.01 - 1.61)	Observed significantly > expected
60-69 EU+UK+Brazil+Australia ^a	42	0.68	57960860	79	109.97	0.72 (0.57 - 0.9)	Observed significantly < expected
Over 70 EU+UK+Brazil+Australia ^a	42	0.34	32376365	46	33.51	1.37 (1.01 - 1.83)	Observed significantly > expected

^a Incidence rate Source : Willame et al 2021 (A) from ES_SIDIAP_PCHOSP

^b Exposure is to DLP 28 December 2023

^c All cases to DLP 28 December 2023.

Only cases observed within 0-21, 0-30 and 0-42 Days were included; Risk window: 21, 30 and 42 Days.

CI Confidence Interval; CVST Cerebral Venous Sinus Thrombosis; E Expected; EEA European economic area; IR Incidence Rate; O Observed; RW Risk Window; SIDIAP Information System for Research in Primary Care; TTO Time to onset; UK United Kingdom

Table 51 Observed versus expected analysis for CVST without thrombocytopenia (using Truven 14 incident rates)

Concept							
Observed Versus Expected analysis for CVST without TCP cases Overall							
Overall	21	1.5	46611564 4	299	402	0.12 (0.09 - 0.16)	Observed significantly < expected
Overall (RW21+Unk TTO)	21	1.5	46611564 4	480	402	0.19 (0.15 - 0.23)	Observed significantly < expected
Overall	30	1.5	46611564 4	342	574.28	0.11 (0.09 - 0.14)	Observed significantly < expected
Overall (RW30+Unk TTO)	30	1.5	46611564 4	523	574.28	0.15 (0.12 - 0.19)	Observed significantly < expected

Table 51 Observed versus expected analysis for CVST without thrombocytopenia (using Truven 14 incident rates)

Concept							
Overall	42	1.5	46611564 4	390	574.28	0.09 (0.07 - 0.12)	Observed significantl y < expected
Overall (RW42+Unk TTO)							
Observed Versus Expected analysis for CVST without TCP cases stratified by age and gender for UK region with Risk Window (21, 30 & 42)							
Female 18 29 UK	21	2.46	1109488	1	1.57	0.64 (0.02 - 3.55)	Observed < expected
Female 30 39 UK	21	2.23	1892968	3	2.43	1.23 (0.25 - 3.61)	Observed > expected
Female 40 49 UK	21	1.84	4412245	4	4.67	0.86 (0.23 - 2.19)	Observed < expected
Female 50 59 UK	21	0.82	5944683	4	2.8	1.43 (0.39 - 3.66)	Observed > expected
Female 60 69 UK	21	1.41	4783416	1	3.88	0.26 (0.01 - 1.44)	Observed < expected
Female 70 79 UK	21	0.71	3475875	2	1.42	1.41 (0.17 - 5.09)	Observed > expected
Female over 80 UK	21	9.32	1630324	0	8.74	0 (0 - 0.42)	Observed significantl y < expected
Male 18 29 UK	21	1.1	808938	1	0.51	1.96 (0.05 - 10.92)	Observed > expected
Male 30 39 UK	21	0.69	1415003	1	0.56	1.79 (0.05 - 9.95)	Observed > expected
Male 40 49 UK	21	0.86	4542157	3	2.25	1.33 (0.27 - 3.9)	Observed > expected
Male 50 59 UK	21	0.91	6510960	5	3.41	1.47 (0.48 - 3.42)	Observed > expected

Table 51 Observed versus expected analysis for CVST without thrombocytopenia (using Truven 14 incident rates)

Concept							
Male 60 69 UK	21	1.92	4934728	2	5.45	0.37 (0.04 - 1.33)	Observed < expected
Male 70 79 UK	21	2.49	3137304	2	4.49	0.45 (0.05 - 1.61)	Observed < expected
Male over 80 UK	21	6.64	1025046	1	3.91	0.26 (0.01 - 1.42)	Observed < expected
Female 18 29 UK	30	2.46	1109488	1	2.24	0.45 (0.01 - 2.49)	Observed < expected
Female 30 39 UK	30	2.23	1892968	3	3.47	0.86 (0.18 - 2.53)	Observed < expected
Female 40 49 UK	30	1.84	4412245	4	6.67	0.6 (0.16 - 1.54)	Observed < expected
Female 50 59 UK	30	0.82	5944683	5	4	1.25 (0.41 - 2.92)	Observed > expected
Female 60 69 UK	30	1.41	4783416	3	5.54	0.54 (0.11 - 1.58)	Observed < expected
Female 70 79 UK	30	0.71	3475875	3	2.03	1.48 (0.3 - 4.32)	Observed > expected
Female over 80 UK	30	9.32	1630324	0	12.48	0 (0 - 0.3)	Observed significantly < expected
Male 18 29 UK	30	1.1	808938	1	0.73	1.37 (0.03 - 7.63)	Observed > expected
Male 30 39 UK	30	0.69	1415003	1	0.8	1.25 (0.03 - 6.96)	Observed > expected
Male 40 49 UK	30	0.86	4542157	4	3.21	1.25 (0.34 - 3.19)	Observed > expected
Male 50 59 UK	30	0.91	6510960	7	4.87	1.44 (0.58 - 2.96)	Observed > expected

Table 51 Observed versus expected analysis for CVST without thrombocytopenia (using Truven 14 incident rates)

Concept							
Male 60 69 UK	30	1.92	4934728	2	7.78	0.26 (0.03 - 0.93)	Observed significantly < expected
Male 70 79 UK	30	2.49	3137304	2	6.42	0.31 (0.04 - 1.13)	Observed < expected
Male over 80 UK	30	6.64	1025046	1	5.59	0.18 (0 - 1)	Observed significantly < expected
Female 18 29 UK	42	2.46	1109488	1	3.14	0.32 (0.01 - 1.77)	Observed < expected
Female 30 39 UK	42	2.23	1892968	3	4.85	0.62 (0.13 - 1.81)	Observed < expected
Female 40 49 UK	42	1.84	4412245	5	9.34	0.54 (0.17 - 1.25)	Observed < expected
Female 50 59 UK	42	0.82	5944683	6	5.61	1.07 (0.39 - 2.33)	Observed > expected
Female 60 69 UK	42	1.41	4783416	4	7.76	0.52 (0.14 - 1.32)	Observed < expected
Female 70 79 UK	42	0.71	3475875	3	2.84	1.06 (0.22 - 3.09)	Observed > expected
Female over 80 UK	42	9.32	1630324	2	17.47	0.11 (0.01 - 0.41)	Observed significantly < expected
Male 18 29 UK	42	1.1	808938	2	1.02	1.96 (0.24 - 7.08)	Observed > expected
Male 30 39 UK	42	0.69	1415003	1	1.12	0.89 (0.02 - 4.97)	Observed < expected
Male 40 49 UK	42	0.86	4542157	4	4.49	0.89 (0.24 - 2.28)	Observed < expected

Table 51 **Observed versus expected analysis for CVST without thrombocytopenia (using Truven 14 incident rates)**

Concept							
Male 50 59 UK	42	0.91	6510960	8	6.81	1.17 (0.51 - 2.31)	Observed > expected
Male 60 69 UK	42	1.92	4934728	3	10.9	0.28 (0.06 - 0.8)	Observed significantly < expected
Male 70 79 UK	42	2.49	3137304	2	8.98	0.22 (0.03 - 0.8)	Observed significantly < expected
Male over 80 UK							
Observed Versus Expected analysis for CVST without TCP cases stratified by age for EU+UK+Brazil+Australia region with Risk Window (21, 30 & 42)							
18-49 EU+UK+Brazil+Australia	21	1.55	14181834	15	12.64	1.19 (0.66 - 1.96)	Observed > expected
50-59 EU+UK+Brazil+Australia	21	0.86	12455887	11	6.16	1.79 (0.89 - 3.2)	Observed > expected
60-69 EU+UK+Brazil+Australia	21	1.65	9718273	5	9.22	0.54 (0.18 - 1.27)	Observed < expected
Over 70 EU+UK+Brazil+Australia	21	0.9	6613249	6	5.82	1.03 (0.38 - 2.24)	Observed > expected
18-49 EU+UK+Brazil+Australia	30	1.55	2655389	3	12.53	0.24 (0.05 - 0.7)	Observed significantly < expected
50-59 EU+UK+Brazil+Australia	30	0.86	14181834	17	18.06	0.94 (0.55 - 1.51)	Observed < expected
60-69 EU+UK+Brazil+Australia	30	1.65	12455887	15	8.8	1.7 (0.95 - 2.81)	Observed > expected
Over 70 EU+UK+Brazil+Australia	30	0.9	9718273	8	13.17	0.61 (0.26 - 1.2)	Observed < expected
18-49 EU+UK+Brazil+Australia	42	1.55	6613249	8	8.31	0.96 (0.42 - 1.9)	Observed < expected

Table 51 Observed versus expected analysis for CVST without thrombocytopenia (using Truven 14 incident rates)

Concept							
50-59 EU+UK+Brazil+Austral ia	42	0.86	2655389	4	17.91	0.22 (0.06 - 0.57)	Observed significantl y < expected
60-69 EU+UK+Brazil+Austral ia	42	1.65	14181834	21	25.28	0.83 (0.51 - 1.27)	Observed < expected
Over 70 EU+UK+Brazil+Austral ia	42	0.9	12455887	19	12.32	1.54 (0.93 - 2.41)	Observed > expected

CI Confidence Interval; CVST Cerebral Venous Sinus Thrombosis; E Expected; EU European Union; O Observed; RW Risk Window; TCP Thrombocytopenia; TTO Time to onset; UK United Kingdom

When an overall rate of 0.72/100,000 PYs from SIDIAP_HOSP is used, observed cases of CVST without thrombocytopenia are significantly more than expected for all risk windows except for risk window of 42 days. Observed cases were significantly more than expected for all risk windows when an unknown time to onset was included.

In comparison, when Truven 14 IR are used, observed cases are significantly less than expected for all the risk windows, when cases with unknown TTO are excluded. When cases with an unknown TTO are included to all risk windows as a conservative approach, observed cases are significantly more than expected for risk window 21 Days, however observed cases were significantly less than expected for 30 and 42 days risk window Table 52.

When the observed versus expected analysis was stratified by age in the EEA, UK, Australia and Brazil region using SIDIAP_HOSP rates, observed cases were less than expected for all age groups except for age over 70 years with a risk window of 21 and 30 Days Table 52.

In comparison, when observed versus expected analysis was stratified by age in the EEA, UK, Australia and Brazil region using Truven 14 IRs, observed cases are more or significantly more than expected in all age groups from 18-69 and over 70 years for risk windows 21 Days. In risk window of 30 Days, observed cases are more or significantly more than expected in age groups from 50-59 and in age group over 70 years and observed cases are less than expected in age group 18-49 and 60-69 years for risk window of 30 Days. For risk window of 42 Days, observed cases were significantly less than expected for age groups of 18-49, 60-69 and observed cases were either more or significantly more than expected for age groups 50-59 and over 70 years Table 53.

When stratified by age and gender in the UK, using Truven 14 IRs, the observed cases divided between males (Table 52) and females (Table 53) as follows:

For females, observed cases were more or significantly more than expected for the age groups 18-59 and 70-79 years and observed cases were less or significantly less than expected for the age groups 60-69 and over 80 for 21 Days risk window. Observed cases were more or significantly more than expected for the age groups 18-29, 40-49, 50-59, 70-79 years and observed cases were less or significantly less than expected for the age groups 30-39, 60-69 and over 80 years for 30 Days risk window. Observed cases were more or significantly more than expected for the age groups 18-59, 70-79 years and observed cases were less or significantly less than expected for the age groups 60-69 and over 80 years for 42 Days risk window.

For males, observed cases were less or significantly less than expected for age groups 60-69, 70-79 and over 80 years age group for all risk windows (21, 30 and 42 Days). For all other age stratifications observed cases were either more or significantly more than expected for all risk windows (21, 30 and 42 Days).

Observed versus expected analyses for CVST without thrombocytopenia (with known normal platelet count)

Information on normal platelets was available in 114 of the 623 cases. In the remaining 509 of the 623 cases the post-vaccination platelet count was unknown, however no thrombocytopenia-related PTs were reported. The 114 cases were used for observed versus expected analysis in order to represent the dataset with known normal thrombocytes.

The observed versus expected analysis for all 114 cases of CVST without thrombocytopenia is presented with different risk windows (21 days, 30 days and 42 days) for global reports in Table 52, stratified by age in the EEA, UK, Australia and Brazil region in Table 52 and age groups in UK Table 06. The IRs used were from SIDIAP PCHOSP.

Willame et al 2021 (A)), as that rate was used by the EMA, and this would permit a comparison of the O/E analysis conducted by EMA and AstraZeneca. All stratifications are provided with and without cases that have an unknown time to onset.

The O/E analysis for CVST without thrombocytopenia (with known normal thrombocytes) showed that the number of observed cases were significantly lower than expected when overall cases were considered. With the stratified O/E analysis by age and gender, there were certain age and gender groups where the observed number was higher than expected. However, when a qualitative review was conducted, many of the cases were missing information such as medical history, concomitant medications, precluding a proper assessment to determine causal relationship.

Table 52 **Observed versus expected analysis for CVST without thrombocytopenia (with known normal platelet count) (using SIDIAP_PC HOSP incident rate)**

Concept							
Observed Versus Expected analysis for CVST without TCP cases Overall							
Overall RW21	21	0.72	466115644	50	192.96	0.26 (0.19 - 0.34)	Observed significantly < expected
Overall (RW21+Unk TTO)	21	0.72	466115644	75	192.96	0.39 (0.31 - 0.49)	Observed significantly < expected
Overall RW30	30	0.72	466115644	64	275.66	0.23 (0.18 - 0.3)	Observed significantly < expected
Overall (RW30+Unk TTO)	30	0.72	466115644	89	275.66	0.32 (0.26 - 0.4)	Observed significantly < expected
Overall RW42	42	0.72	466115644	76	385.92	0.2 (0.16 - 0.25)	Observed significantly < expected
Overall (RW42+Unk TTO)							
Observed Versus Expected analysis for CVST without TCP cases stratified by age for EU+UK+Brazil+Australia region with Risk Window (21, 30 & 42)							
18-49 EU+UK+Brazil+Australia	21	0.27	110094983	20	21.52	0.93 (0.57 - 1.44)	Observed < expected
50-59 EU+UK+Brazil+Australia	21	1.57	58336094	12	52.66	0.23 (0.12 - 0.4)	Observed significantly < expected

Table 52 Observed versus expected analysis for CVST without thrombocytopenia (with known normal platelet count) (using SIDIAP_PC HOSP incident rate)

Concept							
60-69 EU+UK+Brazil+Australia	21	0.68	57960860	6	22.66	0.26 (0.1 - 0.58)	Observed significantly < expected
Over 70 EU+UK+Brazil+Australia	21	0.34	32376365	7	6.33	1.11 (0.44 - 2.28)	Observed > expected
18-49 EU+UK+Brazil+Australia	30	0.27	110094983	22	30.75	0.72 (0.45 - 1.08)	Observed < expected
50-59 EU+UK+Brazil+Australia	30	1.57	58336094	17	75.23	0.23 (0.13 - 0.36)	Observed significantly < expected
60-69 EU+UK+Brazil+Australia	30	0.68	57960860	9	32.37	0.28 (0.13 - 0.53)	Observed significantly < expected
Over 70 EU+UK+Brazil+Australia	30	0.34	32376365	10	9.04	1.11 (0.53 - 2.03)	Observed > expected
18-49 EU+UK+Brazil+Australia	42	0.27	110094983	24	43.04	0.56 (0.36 - 0.83)	Observed significantly < expected
50-59 EU+UK+Brazil+Australia	42	1.57	58336094	19	105.32	0.18 (0.11 - 0.28)	Observed significantly < expected
60-69 EU+UK+Brazil+Australia	42	0.68	57960860	12	45.32	0.26 (0.14 - 0.46)	Observed significantly < expected
Over 70 EU+UK+Brazil+Australia							

Table 52 **Observed versus expected analysis for CVST without thrombocytopenia (with known normal platelet count) (using SIDIAP_PC HOSP incident rate)**

Concept							
Observed Versus Expected analysis for CVST without TCP cases stratified by age for EU+UK+Brazil+Australia region with Risk Window (21, 30 & 42), including unknown TTO							
18-49 (RW21+Unk TTO) EU+UK+Brazil+Australia	21	0.34	110094983	22	21.52	1.02 (0.64 - 1.55)	Observed > expected
50-59 (RW21+Unk TTO) EU+UK+Brazil+Australia	21	1.57	58336094	14	52.66	0.27 (0.15 - 0.45)	Observed significantly < expected
60-69(RW21+Unk TTO) EU+UK+Brazil+Australia	21	0.68	57960860	8	22.66	0.35 (0.15 - 0.7)	Observed significantly < expected
Over 70(RW21+Unk TTO) EU+UK+Brazil+Australia	21	0.34	32376365	9	6.33	1.42 (0.65 - 2.7)	Observed > expected
18-49 (RW30+Unk TTO) EU+UK+Brazil+Australia	30	0.34	110094983	25	30.75	0.81 (0.53 - 1.2)	Observed < expected
50-59 (RW30+Unk TTO) EU+UK+Brazil+Australia	30	1.57	58336094	20	75.23	0.27 (0.16 - 0.41)	Observed significantly < expected
60-69(RW30+Unk TTO) EU+UK+Brazil+Australia	30	0.68	57960860	12	32.37	0.37 (0.19 - 0.65)	Observed significantly < expected
Over 70 (RW30+Unk TTO) EU+UK+Brazil+Australia	30	0.34	32376365	13	9.04	1.44 (0.77 - 2.46)	Observed > expected
18-49 (RW42+Unk TTO) EU+UK+Brazil+Australia	42	0.34	110094983	29	43.04	0.67 (0.45 - 0.97)	Observed significantly < expected

Table 52 **Observed versus expected analysis for CVST without thrombocytopenia (with known normal platelet count) (using SIDIAP_PC HOSP incident rate)**

Concept							
50-59 (RW42+Unk TTO) EU+UK+Brazil+Australia	42	1.57	58336094	24	105.32	0.23 (0.15 - 0.34)	Observed significantly < expected
60-69 (RW42+Unk TTO) EU+UK+Brazil+Australia	42	0.68	57960860	17	45.32	0.38 (0.22 - 0.6)	Observed significantly < expected
Over 70 (RW42+Unk TTO) EU+UK+Brazil+Australia							
Observed Versus Expected analysis for CVST without TCP cases stratified by age for UK region with Risk Window (21, 30 & 42)							
18-49 UK	21	0.34	14181834	13	2.77	4.69 (2.5 - 8.03)	Observed significantly > expected
50-59 UK	21	1.57	12455887	9	11.24	0.8 (0.37 - 1.52)	Observed < expected
60-69 UK	21	0.68	9718273	3	3.8	0.79 (0.16 - 2.31)	Observed < expected
70-79 UK	21	0.67	6613249	4	2.55	1.57 (0.43 - 4.02)	Observed > expected
Over 80 UK	21	1.49	2655389	1	2.27	0.44 (0.01 - 2.45)	Observed < expected
18-49 UK	30	0.34	14181834	14	3.96	3.54 (1.93 - 5.93)	Observed significantly > expected
50-59 UK	30	1.57	12455887	12	16.06	0.75 (0.39 - 1.31)	Observed < expected

Table 52 Observed versus expected analysis for CVST without thrombocytopenia (with known normal platelet count) (using SIDIAP_PC HOSP incident rate)

Concept							
60-69 UK	30	0.68	9718273	5	5.43	0.92 (0.3 - 2.15)	Observed < expected
70-79 UK	30	0.67	6613249	5	3.64	1.37 (0.45 - 3.21)	Observed > expected
Over 80 UK	30	1.49	2655389	1	3.25	0.31 (0.01 - 1.71)	Observed < expected
18-49 UK	42	0.34	14181834	16	5.54	2.89 (1.65 - 4.69)	Observed significantly > expected
50-59 UK	42	1.57	12455887	14	22.49	0.62 (0.34 - 1.04)	Observed < expected
60-69 UK	42	0.68	9718273	7	7.6	0.92 (0.37 - 1.9)	Observed < expected
70-79 UK	42	0.67	6613249	5	5.1	0.98 (0.32 - 2.29)	Observed < expected
Over 80 UK							
Observed Versus Expected analysis for CVST without TCP cases stratified by age for UK region with Risk Window (21, 30 & 42), including unknown TTO							
18-49 (RW21+Unk TTO) UK	21	0.34	14181834	15	2.77	5.42 (3.03 - 8.93)	Observed significantly > expected
50-59 (RW21+Unk TTO) UK	21	1.57	12455887	11	11.24	0.98 (0.49 - 1.75)	Observed < expected
60-69(RW21+Unk TTO) UK	21	0.68	9718273	5	3.8	1.32 (0.43 - 3.07)	Observed > expected

Table 52 Observed versus expected analysis for CVST without thrombocytopenia (with known normal platelet count) (using SIDIAP_PC HOSP incident rate)

Concept							
70-79(RW21+Unk TTO) UK	21	0.67	6613249	6	2.55	2.35 (0.86 - 5.12)	Observed > expected
Over 80(RW21+Unk TTO) UK	21	1.49	2655389	3	2.27	1.32 (0.27 - 3.86)	Observed > expected
18-49 (RW30+Unk TTO) UK	30	0.34	14181834	17	3.96	4.29 (2.5 - 6.87)	Observed significantly > expected
50-59 (RW30+Unk TTO) UK	30	1.57	12455887	15	16.06	0.93 (0.52 - 1.54)	Observed < expected
60-69(RW30+Unk TTO) UK	30	0.68	9718273	8	5.43	1.47 (0.64 - 2.9)	Observed > expected
70-79(RW30+Unk TTO) UK	30	0.67	6613249	8	3.64	2.2 (0.95 - 4.33)	Observed > expected
Over 80(RW30+Unk TTO) UK	30	1.49	2655389	4	3.25	1.23 (0.34 - 3.15)	Observed > expected
18-49 (RW42+Unk TTO) UK	42	0.34	14181834	21	5.54	3.79 (2.35 - 5.79)	Observed significantly > expected
50-59 (RW42+Unk TTO) UK	42	1.57	12455887	19	22.49	0.84 (0.51 - 1.32)	Observed < expected
60-69 (RW42+Unk TTO) UK	42	0.68	9718273	12	7.6	1.58 (0.82 - 2.76)	Observed > expected
70-79 (RW42+Unk TTO) UK	42	0.67	6613249	10	5.1	1.96 (0.94 - 3.61)	Observed > expected
Over 80 (RW42+Unk TTO) UK	42	1.49	2655389	8	4.55	1.76 (0.76 - 3.46)	Observed > expected

^a Incidence rate Source: Willame et al 2021 (A), from ES_SIDIAP_PCHOSP

^b Exposure is to DLP 28 December 2023.

^c All cases up to DLP 28 December 2023.

Only cases observed within 0-21, 0-30 and 0-42 Days were included; Risk window: 21, 30 and 42 Days.

CI Confidence Interval, CVST Cerebrovascular venous and sinus thrombosis, E Expected; IR Incidence Rate; O Observed; RW Risk Window; SIDIAP Information System for Research in Primary Care TTO Time To Onset; Unk Unknown, UK United Kingdom

As a comparison to the above, the same observed versus expected analyses are carried out using IRs from Truven MarketScan. That approach is aligned with IRs routinely used for TTS O/E monitoring. In particular, the time window for exclusion of patients with TCP (either -7/+7 or -1/+14) was consistent with the one used for TTS. In this analysis, a conservative approach in terms of ICD10 codes for CVST (I63.6 and I67.6) was used. Also, the analysis included only incident (no CVST claims within 12 months prior to index) inpatient claims. Those analyses for CVST are presented with different risk windows (21 Days, 30 Days, and 42 Days) for all global reports in Table 53, stratified by age in the EEA, UK, Australia and Brazil region in Table 53, stratified by age in UK in Table 53 and gender (Female and Male) in the UK (Table 53 All stratifications also included cases with an unknown TTO, as a conservative approach.

The O/E analysis for CVST without thrombocytopenia (with known normal thrombocytes) using IRs from Truven Market Scan showed that the number of observed cases were significantly lower than expected when overall and also cases from EEA, UK, Brazil and Australia were considered. With the stratified O/E analysis by age and gender, there were certain age and gender groups (50-59 years in UK for all risk windows including unknown TTO, 18-49 years in UK for risk window of 21 days, only when unknown TTO is considered) where the observed number was higher than expected. However, when a qualitative review was conducted, many of the cases were missing information such as medical history, concomitant medications, precluding a proper assessment to determine causal relationship.

Table 53 **Observed versus expected analysis for CVST without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates)**

Concept							
Observed Versus Expected analysis for CVST without TCP cases Overall							
Overall RW21	21	1.5	4661156 44	50	402	0.12 (0.09 - 0.16)	Observed significa ntly < expected
Overall (RW21+Unk TTO)	21	1.5	4661156 44	75	402	0.19 (0.15 - 0.23)	Observed significa ntly < expected
Overall RW30	30	1.5	4661156 44	64	574.28	0.11 (0.09 - 0.14)	Observed significa ntly < expected
Overall (RW30+Unk TTO)	30	1.5	4661156 44	89	574.28	0.15 (0.12 - 0.19)	Observed significa ntly < expected
Overall RW42	42	1.5	4661156 44	76	803.99	0.09 (0.07 - 0.12)	Observed significa ntly < expected
Overall (RW42+Unk TTO)							
Observed Versus Expected analysis for CVST without TCP cases stratified by age and gender for UK region with Risk Window (21, 30 & 42)							
Female 18 29 UK	21	2.46	1109488	1	1.57	0.64 (0.02 - 3.55)	Observed < expected
Female 30 39 UK	21	2.23	1892968	3	2.43	1.23 (0.25 - 3.61)	Observed > expected
Female 40 49 UK	21	1.84	4412245	4	4.67	0.86 (0.23 - 2.19)	Observed < expected
Female 50 59 UK	21	0.82	5944683	4	2.8	1.43 (0.39 - 3.66)	Observed > expected

Table 53 Observed versus expected analysis for CVST without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates)

Concept							
Female 60 69 UK	21	1.41	4783416	1	3.88	0.26 (0.01 - 1.44)	Observed < expected
Female 70 79 UK	21	0.71	3475875	2	1.42	1.41 (0.17 - 5.09)	Observed > expected
Female over 80 UK	21	9.32	1630324	0	8.74	0 (0 - 0.42)	Observed significantly < expected
Male 18 29 UK	21	1.1	808938	1	0.51	1.96 (0.05 - 10.92)	Observed > expected
Male 30 39 UK	21	0.69	1415003	1	0.56	1.79 (0.05 - 9.95)	Observed > expected
Male 40 49 UK	21	0.86	4542157	3	2.25	1.33 (0.27 - 3.9)	Observed > expected
Male 50 59 UK	21	0.91	6510960	5	3.41	1.47 (0.48 - 3.42)	Observed > expected
Male 60 69 UK	21	1.92	4934728	2	5.45	0.37 (0.04 - 1.33)	Observed < expected
Male 70 79 UK	21	2.49	3137304	2	4.49	0.45 (0.05 - 1.61)	Observed < expected
Male over 80 UK	21	6.64	1025046	1	3.91	0.26 (0.01 - 1.42)	Observed < expected
Female 18 29 UK	30	2.46	1109488	1	2.24	0.45 (0.01 - 2.49)	Observed < expected
Female 30 39 UK	30	2.23	1892968	3	3.47	0.86 (0.18 - 2.53)	Observed < expected

Table 53 **Observed versus expected analysis for CVST without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates)**

Concept							
Female 40 49 UK	30	1.84	4412245	4	6.67	0.6 (0.16 - 1.54)	Observed < expected
Female 50 59 UK	30	0.82	5944683	5	4	1.25 (0.41 - 2.92)	Observed > expected
Female 60 69 UK	30	1.41	4783416	3	5.54	0.54 (0.11 - 1.58)	Observed < expected
Female 70 79 UK	30	0.71	3475875	3	2.03	1.48 (0.3 - 4.32)	Observed > expected
Female over 80 UK	30	9.32	1630324	0	12.48	0 (0 - 0.3)	Observed significantly < expected
Male 18 29 UK	30	1.1	808938	1	0.73	1.37 (0.03 - 7.63)	Observed > expected
Male 30 39 UK	30	0.69	1415003	1	0.8	1.25 (0.03 - 6.96)	Observed > expected
Male 40 49 UK	30	0.86	4542157	4	3.21	1.25 (0.34 - 3.19)	Observed > expected
Male 50 59 UK	30	0.91	6510960	7	4.87	1.44 (0.58 - 2.96)	Observed > expected
Male 60 69 UK	30	1.92	4934728	2	7.78	0.26 (0.03 - 0.93)	Observed significantly < expected
Male 70 79 UK	30	2.49	3137304	2	6.42	0.31 (0.04 - 1.13)	Observed < expected
Male over 80 UK	30	6.64	1025046	1	5.59	0.18 (0 - 1)	Observed significantly < expected

Table 53 **Observed versus expected analysis for CVST without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates)**

Concept							
Female 18 29 UK	42	2.46	1109488	1	3.14	0.32 (0.01 - 1.77)	Observed < expected
Female 30 39 UK	42	2.23	1892968	3	4.85	0.62 (0.13 - 1.81)	Observed < expected
Female 40 49 UK	42	1.84	4412245	5	9.34	0.54 (0.17 - 1.25)	Observed < expected
Female 50 59 UK	42	0.82	5944683	6	5.61	1.07 (0.39 - 2.33)	Observed > expected
Female 60 69 UK	42	1.41	4783416	4	7.76	0.52 (0.14 - 1.32)	Observed < expected
Female 70 79 UK	42	0.71	3475875	3	2.84	1.06 (0.22 - 3.09)	Observed > expected
Female over 80 UK	42	9.32	1630324	2	17.47	0.11 (0.01 - 0.41)	Observed significantly < expected
Male 18 29 UK	42	1.1	808938	2	1.02	1.96 (0.24 - 7.08)	Observed > expected
Male 30 39 UK	42	0.69	1415003	1	1.12	0.89 (0.02 - 4.97)	Observed < expected
Male 40 49 UK	42	0.86	4542157	4	4.49	0.89 (0.24 - 2.28)	Observed < expected
Male 50 59 UK	42	0.91	6510960	8	6.81	1.17 (0.51 - 2.31)	Observed > expected
Male 60 69 UK	42	1.92	4934728	3	10.9	0.28 (0.06 - 0.8)	Observed significantly < expected

Table 53 **Observed versus expected analysis for CVST without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates)**

Concept							
Male 70 79 UK	42	2.49	3137304	2	8.98	0.22 (0.03 - 0.8)	Observed significantly < expected
Male over 80 UK							
Observed Versus Expected analysis for CVST without TCP cases stratified by age and gender for UK region with Risk Window (21, 30 & 42), including unknown TTO							
Female 18 29 +Unk TTO UK	21	2.46	808938	1	0.73	1.37 (0.03 - 7.63)	Observed > expected
Female 30 39 +Unk TTO UK	21	2.23	1415003	1	0.8	1.25 (0.03 - 6.96)	Observed > expected
Female 40 49 +Unk TTO UK	21	1.84	4542157	4	3.21	1.25 (0.34 - 3.19)	Observed > expected
Female 50 59 +Unk TTO UK	21	0.82	6510960	7	4.87	1.44 (0.58 - 2.96)	Observed > expected
Female 60 69 +Unk TTO UK	21	1.41	4934728	2	7.78	0.26 (0.03 - 0.93)	Observed significantly < expected
Female 70 79 +Unk TTO UK	21	0.71	3137304	2	6.42	0.31 (0.04 - 1.13)	Observed < expected
Female over 80 +Unk TTO UK	21	9.32	1025046	1	5.59	0.18 (0 - 1)	Observed significantly < expected
Male 18 29 +Unk TTO UK	21	1.1	1109488	1	3.14	0.32 (0.01 - 1.77)	Observed < expected
Male 30 39 +Unk TTO UK	21	0.69	1892968	3	4.85	0.62 (0.13 - 1.81)	Observed < expected
Male 40 49 +Unk TTO UK	21	0.86	4412245	5	9.34	0.54 (0.17 - 1.25)	Observed < expected

Table 53 **Observed versus expected analysis for CVST without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates)**

Concept							
Male 50 59 +Unk TTO UK	21	0.91	5944683	6	5.61	1.07 (0.39 - 2.33)	Observed > expected
Male 60 69 +Unk TTO UK	21	1.92	4783416	4	7.76	0.52 (0.14 - 1.32)	Observed < expected
Male 70 79 +Unk TTO UK	21	2.49	3475875	3	2.84	1.06 (0.22 - 3.09)	Observed > expected
Male over 80 +Unk TTO UK	21	6.64	1630324	2	17.47	0.11 (0.01 - 0.41)	Observed significantly < expected
Female 18 29 +Unk TTO UK	30	2.46	808938	2	1.02	1.96 (0.24 - 7.08)	Observed > expected
Female 30 39 +Unk TTO UK	30	2.23	1415003	1	1.12	0.89 (0.02 - 4.97)	Observed < expected
Female 40 49 +Unk TTO UK	30	1.84	4542157	4	4.49	0.89 (0.24 - 2.28)	Observed < expected
Female 50 59 +Unk TTO UK	30	0.82	6510960	8	6.81	1.17 (0.51 - 2.31)	Observed > expected
Female 60 69 +Unk TTO UK	30	1.41	4934728	3	10.9	0.28 (0.06 - 0.8)	Observed significantly < expected
Female 70 79 +Unk TTO UK	30	0.71	3137304	2	8.98	0.22 (0.03 - 0.8)	Observed significantly < expected
Female over 80 +Unk TTO UK	30	9.32	1025046	1	7.83	0.13 (0 - 0.71)	Observed significantly < expected

Table 53 **Observed versus expected analysis for CVST without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates)**

Concept							
Male 18 29 +Unk TTO UK	30	1.1	808938	4	0.73	5.48 (1.49 - 14.03)	Observed significantly > expected
Male 30 39 +Unk TTO UK	30	0.69	1415003	4	0.8	5 (1.36 - 12.8)	Observed significantly > expected
Male 40 49 +Unk TTO UK	30	0.86	4542157	7	3.21	2.18 (0.88 - 4.49)	Observed > expected
Male 50 59 +Unk TTO UK	30	0.91	6510960	10	4.87	2.05 (0.98 - 3.78)	Observed > expected
Male 60 69 +Unk TTO UK	30	1.92	4934728	5	7.78	0.64 (0.21 - 1.5)	Observed < expected
Male 70 79 +Unk TTO UK	30	2.49	3137304	5	6.42	0.78 (0.25 - 1.82)	Observed < expected
Male over 80 +Unk TTO UK	30	6.64	1025046	4	5.59	0.72 (0.19 - 1.83)	Observed < expected
Female 18 29 +Unk TTO UK	42	2.46	1109488	1	3.14	0.32 (0.01 - 1.77)	Observed < expected
Female 30 39 +Unk TTO UK	42	2.23	1892968	3	4.85	0.62 (0.13 - 1.81)	Observed < expected
Female 40 49 +Unk TTO UK	42	1.84	4412245	5	9.34	0.54 (0.17 - 1.25)	Observed < expected
Female 50 59 +Unk TTO UK	42	0.82	5944683	6	5.61	1.07 (0.39 - 2.33)	Observed > expected
Female 60 69 +Unk TTO UK	42	1.41	4783416	4	7.76	0.52 (0.14 - 1.32)	Observed < expected

Table 53 Observed versus expected analysis for CVST without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates)

Concept							
Female 70 79 +Unk TTO UK	42	0.71	3475875	3	2.84	1.06 (0.22 - 3.09)	Observed > expected
Female over 80 +Unk TTO UK	42	9.32	1630324	2	17.47	0.11 (0.01 - 0.41)	Observed significantly < expected
Male 18 29 +Unk TTO UK	42	1.1	808938	7	1.02	6.86 (2.76 - 14.14)	Observed significantly > expected
Male 30 39 +Unk TTO UK	42	0.69	1415003	6	1.12	5.36 (1.97 - 11.66)	Observed significantly > expected
Male 40 49 +Unk TTO UK	42	0.86	4542157	9	4.49	2 (0.92 - 3.81)	Observed > expected
Male 50 59 +Unk TTO UK	42	0.91	6510960	13	6.81	1.91 (1.02 - 3.26)	Observed significantly > expected
Male 60 69 +Unk TTO UK	42	1.92	4934728	8	10.9	0.73 (0.32 - 1.45)	Observed < expected
Male 70 79 +Unk TTO UK	42	2.49	3137304	7	8.98	0.78 (0.31 - 1.61)	Observed < expected
Male over 80 +Unk TTO UK	42	6.64	1025046	6	7.83	0.77 (0.28 - 1.67)	Observed < expected

^a Incidence Rate (per/100,000 PY) from Truven Market Scan database (2019)

^b Exposure is to DLP 28 December 2022.

^c All cases to DLP 28 December 2022.

Truven 14: CVST (I63.6 or I67.6) inpatient without TCP within -1/14 days (incident)

Only cases observed within 0-21, 0-30 and 0-42 Days were included; Risk window: 21, 30 and 42 Days.

CI Confidence Interval; CVST Cerebral Venous Sinus Thrombosis; E Expected; IR Incidence Rate; O Observed
RW Risk Window; TCP Thrombocytopenia; TTO Time To Onset; UK United Kingdom; Unk Unknown.

Literature

A periodic literature search of the databases in Embase, Insight Meme and PubMed was conducted for relevant articles on CVST without TCP in association with VAXZEVRIA.

The search yielded 63 articles, however there was no new information about the topic (as they discussed CVST in the context of Vaccine-Induced Thrombotic Thrombocytopenia (VITT), TTS, or CVST with thrombocytopenia; contained information on unspecified COVID-19 vaccines; or did not provide new safety information to make a meaningful assessment).

Summary

AstraZeneca continued to review the safety information for CVST without thrombocytopenia from sources including clinical trials, post-marketing reports, and the published literature for the reporting period.

There were no case reports indicating recurrence (after the first and second dose of the vaccine). There are 620 and 32 cases for the cumulative and reporting period respectively. Out of the 620 cases, 99 % of the reported cases were serious, 49 (8%) had a seriousness criterion of Fatal, and 138 (22) Life-threatening. Median age was 50 years. There was a preponderance for female gender (60%) versus males (35%), and 69.21% cases were in age group 18-64 years. Cumulatively, 29 (59.18%) out of all 49 fatal cases were reported in females. There was no significant difference noted between the cumulative and reporting period in terms of the safety patterns and distribution of cases. Of the total number of case reports cumulatively, 367 (59.19%) were MC. Cumulatively, one (1) case met WHO-UMC causality criteria for Probable/Likely and 1 case for Conditional/Unclassified. 385 were considered as Possible, out of 385, 147 (38%) were identified with relevant risk/confounding factors.

A review of the published literature did not identify any new safety information on this topic in association with VAXZEVRIA.

The results of observed versus expected analysis showed observed cases were more than expected in the general population globally. The age stratifications suggest that the O/E ratio is higher in younger age groups than in the older age groups and that the O/E ratio is higher in females than in males. However, it is important to note that O/E analyses are complementary to routine signal detection methods and are not designed to determine a causal relationship; confounding factors were not considered in O/E (such as possible COVID-19 infections or other possible causes for CVST without thrombocytopenia).

CVST without thrombocytopenia is an important potential risk in the VAXZEVRIA Core RMP and the topic will continue to be kept under close surveillance by AstraZeneca.

Conclusion

From the data identified during the reporting period and also taking into account the cumulative experience, AstraZeneca considers that there is currently insufficient evidence of a reasonable possibility of causal relationship between VAXZEVRIA and CVST without thrombocytopenia. CVST without thrombocytopenia is included in section 4.4 (section 4.4 Warnings and Precautions) of the CDS to inform prescribers that these events may require different treatment approaches than TTS. Healthcare professionals should consult applicable guidance. No changes to the CDS or product leaflets are warranted at this time.

AstraZeneca will continue to monitor safety information for CVST without thrombocytopenia as an important potential risk and take further actions as deemed appropriate.

16.3.1.2 Immune-mediated neurological conditions

All important potential risks included in Section 16.1 are kept under close surveillance by AstraZeneca.

Immune-mediated neurological condition is considered as an important potential risk for VAXZEVRIA as per the AstraZeneca Core RMP.

Reviews of specific topics relating to Immune-mediated neurological conditions with VAXZEVRIA, including Acute disseminated encephalomyelitis (ADEM), Encephalitis, and Transverse myelitis (TM), as requested by PRAC for inclusion in the previous PBRER (DLP 28 June 2022), and GBS are continued in this PBRER.

During the period covered by this report (29 December 2022 – 28 December 2023), a total of 682 cases from literature, interventional studies, non-interventional studies and spontaneous sources were reported within the concept of immune-mediated neurological disorders. Out of the 682 cases, 322 (47.2%) were MC [serious 287 (89.1%), non-serious 35 (10.9%)] and 360 (52.8%) were consumer reports [serious 288 (80.0%), non-serious 72 (20.0%)]. The 682 cases had 840 PTs. The most commonly reported PTs were Neuralgia (143), Guillain-Barre syndrome (140), Sensory disturbance (78), Neuropathy peripheral (63), Myelitis transverse (46), Demyelination (30), Polyneuropathy (29), Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) (28), Multiple sclerosis (MS) (27), Sensory loss (25), Small fibre neuropathy (25), Optic neuritis (23), ADEM (22), Encephalitis (20), Myelitis (16), CIDP (14), Neuromyelitis optica spectrum disorder (NMOSD) (14), Multiple sclerosis relapse (9), Myelopathy (9), Peripheral sensory neuropathy (9), Demyelinating polyneuropathy (7), Encephalitis autoimmune (7), Encephalomyelitis (6), Neuritis (4), Noninfective encephalitis (4), Relapsing-remitting multiple sclerosis (4), Acute motor axonal neuropathy (3), Autoimmune neuropathy (3), Encephalopathy (3), Peripheral sensorimotor neuropathy (3), Axonal and demyelinating polyneuropathy (2), Axonal neuropathy (2), Decreased vibratory sense (2), Hypoxic-ischaemic encephalopathy (2), Loss of proprioception (2), Miller Fisher syndrome (2), Neuropathic muscular atrophy (2), Peripheral motor neuropathy (2), Sensorimotor disorder (2), Subacute inflammatory demyelinating polyneuropathy (2), Acute

motor sensory axonal neuropathy (1), Ascending flaccid paralysis (1), Autoimmune encephalopathy (1), Bickerstaff's encephalitis (1), Hashimoto's encephalopathy (1), Hyper gamma globulinaemia benign monoclonal (1), Immune-mediated neurological disorder (1), Immuno-mediated neuropathy (1), Leukoencephalopathy (1), Lumbosacral radiculoplexus neuropathy (1), Multifocal motor neuropathy (1), Nerve conduction studies abnormal (1), Noninfective encephalomyelitis (1) and Posterior reversible encephalopathy syndrome (1).

Cumulatively till 31 December 2023, a total of 8964 cases from literature, clinical studies, noninterventional studies and spontaneous sources were reported within the concept of immune-mediated neurological disorders. Out of the 8964 cases, 2644 (29.5%) were MC [2166 (81.9%) serious, 478 (18.1%) non-serious] and 6319 (70.5%) were consumer reports [4189 (66.3%) serious, 2131 (33.7%) non-serious].

Relevant Literature in the reporting period

Francis et al 2023 described the features of patients presenting with new acute Central Nervous System (CNS) demyelination resembling NMOSDs or Melin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) within 8 weeks of SARS-CoV-2 vaccination in UK. The duration of assessment was from the introduction of SARS-CoV-2 vaccination to May 2022.

Patients with CNS inflammation (including at least one of optic neuritis [ON] or TM) within 8 weeks of receiving a vaccination against SARS-CoV-2, who were referred to highly specialized NMOSD services in the UK (Oxford and Liverpool), were included. In-house live cell-based assays were used to quantify immunofluorescence detection of antibodies to Aquaporin 4 (AQP4) and Myelin Oligodendrocyte glycoprotein (MOG) protein for all patients. Patients with pre-existing CNS diseases were excluded from the analysis.

The authors also determined the seasonality of MOGAD-Onset Attacks since 1980. Any deviation from a uniform distribution was analysed in the periods before the SARS-CoV-2 pandemic started (until 29 February 2020) and in the 2 years after (between 01 March 2020, and 28 February 2021, and between 01 March 2021, and 28 February 2022).

Results: Twenty-five patients were included (median age 38 years, 14 female), with 12 (48%) having MOG antibodies (MOGIgG+), 2 (8%) having aquaporin 4 antibodies (AQP4IgG+), and 11 (44%) had neither. All patients presented within 6 weeks of vaccination. Of the 25 patients included, 18 received the ChAdOx1S / VAXZEVRIA vaccine (median age 42.5 years, range 28–65) and 7 received the BNT162b2 vaccine (median age 27 years, range 18–36). Twelve of 14 (86%) antibody-positive patients received the ChAdOx1S / VAXZEVRIA vaccine. The majority (15/25; 67%) received vaccinations between February and April 2021.

Twelve MOGIgG+ patients, developed symptoms at a median time from ChAdOx1S / VAXZEVRIA vaccine of 15 Days (range 6–41 Days). The gender and age distributions were 50% male and median age of 40.5 years (range 22–65). MOGIgG+ patients presented most commonly with TM (10/12, 83%), frequently in combination with ADEM-like brain/brainstem lesions (6/12, 50%). Transverse myelitis was longitudinally extensive in 7 of the 10 patients. Six out of 10 patients with TM had brain involvement, however symptomatic brain lesions were seen in two patients. The remaining 4 patients did not have brain involvement. Two patients experienced isolated Optic neuritis (ON), 1 of whom received BNT162b2 vaccination.

Both AQP4IgG+ patients presented with brain lesions and TM. Four of 6 (67%) seronegative ChAdOx1S / VAXZEVRIA recipients experienced longitudinally extensive TM (LETM). Compared with 1 of 5 (20%) of the BNT162b2 group, and facial nerve inflammation was reported only in ChAdOx1S / VAXZEVRIA recipients (2/5, 40%). Guillain-Barre syndrome was confirmed in 1 seronegative ChAdOx1S / VAXZEVRIA recipient and suspected in another.

The median FU was 322.5 days (range 162–498). Three (25%) had good outcomes, including 2 patients with isolated ON and 1 with LETM and brain lesions. Nine (75%) had moderate outcomes due to bladder and/or erectile dysfunction. Those with moderate outcomes had a longer median FU time (335 days) than those with good outcomes (257 days), so a longer observation does not explain better prognosis. However, 1 of 12 (8%) MOGIgG+ patients relapsed at 5 months, which may raise some concern.

In the seasonality analysis of MOGAD-onset attacks, 286 patients were included. No significant seasonal pattern was identified before the SARS-CoV-2 pandemic ($n = 233$, the Friedman test $v(N) = 0.054$, $p > 0.1$) or in the first year of the pandemic (before vaccine rollout; $n = 24$, the Friedman test $v(N) = 0.106$, $p > 0.1$). In the period from March 2021 to February 2022, a seasonal peak was identified from March to May ($n = 29$, the Friedman test $v(N) = 0.256$, $p < 0.05$, the Ratchet circular scan test, $p < 0.025$). When postvaccine MOGIgG+ patients were excluded, the seasonal peak disappeared ($n = 18$, the Friedman test $v(N) = 0.166$, $p > 0.1$).

Conclusions: The authors concluded that ChAdOx1S / VAXZEVRIA vaccine was associated with antibody-mediated CNS inflammation and mainly with MOGAD. Adult patients who developed MOGAD after vaccination presented atypically with brain lesions and LETM, more reminiscent of MOGIgG+ ADEM seen in children, supporting a causative role. This suggests vaccination may influence the phenotypic presentation of MOGAD, and some adult onset ADEM-like MOGAD cases might be triggered by environmental factors. Further study is required to determine the sequence of immunologic events that link vaccination and autoimmune CNS disease. The authors stressed that SARS-CoV-2 infection is associated with

high morbidity and mortality, and neurologic sequelae are more frequent after infection than vaccination. Consequently, physicians should continue to promote vaccination against SARSCoV-2. The authors have encouraged our postvaccine group to pursue further vaccination with an alternative formulation to that which preceded their illness.

AstraZeneca comment:

This study was prospective case series of de novo CNS demyelination patients from two specialized neurology tertiary care centres in UK. There was limited data on individual case characteristics for a comprehensive causal assessment. The study was limited by absence of a comparison group (non-vaccinated population).

As per the authors, 29 cases of MOGAD-Onset Attacks were identified in the year following vaccination (March 2021 to February 2022) compared to 24 cases the year prior (first year of the pandemic before vaccine rollout). During the same period of March 2021 to February 2022, the actual vaccine exposure in UK was 39,119,781 doses (overall) or 149,67,636 dose 1. The reporting rate of MOGAD-Onset Attack cases per million vaccine exposure in UK were 1.9 and 0.7 respectively. This is similar to the BG IRs of 1.6 to 3.4 per million in an COVID-19 unvaccinated population based on an epidemiological study in Oxford, UK (median age 38 years) (O'Connell et al 2020 cited in Banwell et al 2023).

The authors reported a seasonal peak from March to May 2021 of MOGAD-Onset Attacks cases compared to similar periods of pre-COVID-19 pandemic and first year of COVID-19 pandemic. Although in majority of the months post May 2021 (June, August, October, November, December of 2021 and January 2022), the MOGAD-Onset Attacks case trends were either similar to expected rates or lower than the expected rates. As reported, 92% of MOG+ve cases presented after the first dose of vaccine (all within 6 weeks). The peak in dose 1 VAXZEVRIA exposure in UK was in the month of March (10,899,540 first doses) while the peak in dose 2 VAXZEVRIA exposure in UK was in the month of May 2021 (10,201,732 second doses). The seasonal peak of MOGAD-Onset Attacks cases coincided with the dose 1 VAXZEVRIA exposure peak in UK, however, no consistent trend was seen with the dose 2 VAXZEVRIA exposure peak in UK. Lack of consistency with subsequent VAXZEVRIA doses or in subsequent months may possibly argue against theories of molecular mimicry, or direct vaccine plausibility. A possible role of external factors (such as effect of relaxation of lockdowns from March 2021 in UK, Institute of Government Analysis 2021 or comparison between vaccine types) could not be assessed due to study limitations (such as unmatched baseline characteristics).

For MOG IgG+ve cases, no abnormality in gender distribution was seen. The clinical phenotype of MOG+ve cases were TM alone (33%), ON alone (7%), TM with brain involvement (33%), ON and TM with brain involvement (17%). Although the authors consider the above-mentioned clinical phenotypic trend as unusual as ON is the commonest

presentation in MOGAD, there was limited information provided whether the BG trends were based on de novo or relapsing MOGAD cases. Based on a recent study in non-COVID-19 vaccinated population from UK Jurynczyk et al 2017, the incident clinical phenotype was ON (45%), TM (21%), ADEM or ADEM-like (25%), ON with TM (9%). It may be possible that the included cases were actually referred cases to specialized NMOSD tertiary centres, it could be possible that the ON MOGAD cases were unaccounted for. As per the exploratory data search for all MOG positive cases in the Global Safety Database till DLP of this PBRER, the most common core clinical demyelinating events were ON alone (30%), ADEM (22%), TM alone (16%), CNS inflammation (16%) which were similar to the distribution observed by Jurynczyk et al 2017 in non-COVID-19 vaccinated population from UK. Cumulatively, till the DLP of the PBRER, 116 cases in VAXZEVRIA Global Safety Database had reported an MOG investigation finding following any neurological AE. Out of the 116 cases, 57% were MOG negative (n=66) and 43% were MOG positive (n=50). On review, no consistency for the MOG positivity were seen with the demyelinating neurological AEs [myelitis cases only (30% positive, 70% negative); optic neuritis only (56% positive, 44% negative); ADEM (53% positive, 47% negative); other demyelination AEs (8% positive, 92% negative); Encephalitis (75% positive; 25% negative); NMOSD (50% positive, 50% negative); MS (100% negative); GBS (100% negative)].

Samim et al 2023 presented a retrospective chart review of admitted patients in a specialized tertiary neuropsychiatry centre in India, from 01 February 2021 to 30 June 2022. The authors also presented series of 51 cases with various vaccine associated neurological disorders (VAN), temporally associated with vaccination against SARS-CoV2. Cases with any neurological illness, with a history of a recent vaccination against SARS-CoV2 (ie, within 6 weeks of onset of the first symptom of neurological disorder), not otherwise explained by any alternate aetiology were eligible for recruitment. Inclusion criteria were patients with no history of any proven or radiologically suspected COVID-19 infection irrespective of severity, in the past 3 months.

Exclusion criteria were patients with history of receipt of any other (non-SARSCoV2) vaccination in the past 6 weeks, presence of an alternate diagnosis, pre-existing active neurological disease, and relapse of a pre-existing neurological syndrome. The details of investigations including lumbar puncture for CSF (Lumbar Puncture [LP]-CSF) analysis, serum with or without CSF anti-Aquaporin 4 antibody ie, neuromyelitis optica (NMO) antibodies, MOG antibodies (testing done with IgG1), creatinine phosphokinase (CPK), CRP, ESR, magnetic resonance imaging (MRI) of the brain and/or spine, muscle MRI, nerve conduction studies, electromyography, evoked potentials including brainstem auditory evoked response (BAER), visual evoked potentials (VEP), somatosensory evoked potential (SSEP), serum and CSF autoimmune antibody profile N-methyl-D-Aspartate (NMDA), voltage-gated potassium channel (VGKC), Leucine-rich glioma inactivated 1 (LGI-1), CASPR, Gamma-aminobutyric acid (GABA-A/B), serum antinuclear antibodies (ANA) profile, antineutrophil

cytoplasmic antibodies (ANCA), serum myositis panel, and serum paraneoplastic antibody profile were considered.

The causality of all cases fulfilling the inclusion and exclusion criteria were done by independent authors using causality criteria proposed by Butler et al 2021. The cases were categorized to probable, possible and unlikely to be casually related to post-vaccination neurological complication. Only probable and possible cases were included for further analysis, whereas cases with “unlikely” causality association were excluded. As reported India’s vaccination drive against COVID-19 is mostly based on two types of vaccines, ie, ChAdOx-1 (VAXZEVRIA), and COVAXIN (BBV152). As per the government of India database (Co-WIN), till 28 February 2022, a total of 1,482,649,754 doses of AstraZeneca, Covishield (ChAdOx-1), and 28 8,080,355 doses of COVAXIN (BBV152) was administered.

A total of 4672 medical records were reviewed of which 51 cases were identified to have neurological illness temporally associated with COVID-19 vaccination. Out of 51 cases, 48 had probable association with COVID-19 vaccination while three had possible association. Neurological spectrum included CNS demyelination (n = 39, 76.5 %), GBS (n = 3, 5.9 %), stroke (n = 6, 11.8 %), encephalitis (n = 2, 3.9 %) and myositis (n = 1, 2.0 %). Female gender had a greater predisposition (F:M, 1.13:1). Neurological events were more commonly encountered after the first dose (n = 37, 72.5%). The mean latency to onset of symptoms was 13.2 ± 10.7 days after the last dose of vaccination. Covishield (VAXZEVRIA /ChAdOx1) was the most commonly administered vaccine (n = 43, 84.3 %). Majority of the cases with demyelination were seronegative (n = 23, 59.0 %) which was followed by anti- MOGAD (n = 11, 28.2 %) and NMOSD (n = 5, 12.8 %). Out of 6 Stroke cases, 2 cases (33.3 %) had thrombocytopenia and coagulopathy. At discharge, 25/51 (49.0 %) of the cases had favourable outcome (mRS 0 to 1). Among six patients of stroke, only one of them had favourable outcome.

AstraZeneca comment:

This study was based on retrospective chart review from a tertiary care centre in India. There was no information on the BG frequency of neurological events in the tertiary hospital in India to assess the trend of observed cases.

The most frequently administered vaccine in temporal association to onset of neurological events was reported to be VAXZEVRIA (n=43) as compared to Covaxin (n=8), however, the reported patient exposure to VAXZEVRIA was 5 times more than Covaxin. Majority of the cases with demyelination were seronegative. On review of the 11 cases reporting the PT of MOGAD, in 10 out the 11 cases, a FU information was received in the reporting period of the PBRER which comprised a reclassification of diagnosis such as MOG associated optic neuritis to MOGAD (n=4), MOG associated ADEM to MOGAD (n=3), MOG associated LETM to MOGAD (n=2), MOG associated Optico myelopathy to MOGAD (n=1). The major

FU information as reported by the authors were on AE outcome (improved in 6 cases, mild improvement in 4 cases, minimally improved in one case), however, there was limited information on rationale for reclassification of diagnosis. There was insufficient information on the onset dates of the events in the specialized neuropsychiatry centre in India. These 10 cases were also reported in a previous publication by Netravathi et al 2022 and reviewed in a previous PBRER (DLP 28 December 2022). As discussed above, an explorative cumulative review of all cases reporting an MOG investigation finding following any neurological AE, did not identify any abnormal trend for MOG positivity with the demyelinating neurological AEs or any unusual distribution trends in core clinical demyelinating event (refer to AstraZeneca comments for (Francis et al 2023)).

The reported causality of 43 (out of total 48 cases with probable causality) was reported as probable to VAXZEVRIA vaccination in the article as per suggested causality criteria by Butler et al 2021. However, in 22 out of 43 cases possible risk factors/alternate explanation could also be found such as a concurrent positive autoimmune or paraneoplastic markers in 11 cases (Anti-Jo1 positive, anti-Ro-521/Ro-52, anti-SS-A, anti-Ribonucleoprotein (RNP), anti-sm-RNP, U1RNP along with elevated serum Rheumatoid factor, anti-recoverin, anti-GAD65, anti-Tr); oligoclonal band positivity in the backdrop of clinic-investigational incongruity (heterogenous enhancement of MRI lesions, negative evoked potential) in 5 cases; concurrent type 2 diabetes at relatively younger age-groups, hypertension, Proliferating Cell Nuclear Antigen (PCNA) positive in backdrop of hypothyroidism, focal cervical syrinx, Epstein-Barr Virus (EBV)-IGG positive, unspecified infection and advanced age (80 years) in 5 cases; and TTO of 1 day to dose 1 of vaccination in 1 case. The remaining cases had insufficient information on infectious (causal or triggering) etiological work-up. On consideration of Butler et al 2021 suggested criteria for labelling causality in neurological adverse event following immunization (AEFI) which had included typical time frame AND no indication of an alternative aetiology AND no risk factors, most cases could therefore be also assigned a possible or unlikely causality. Due to limited information in the article on the applied criteria as per Butler et al 2021 in the individual cases and/or limited case details in the retrospective chart review, the assessment could not be duplicated.

Moreover, there was no information on distribution of neurological events, its clinical course, cause or triggers, and causality assessment on the remaining 4621 out of 4672 records. No comparison with the BG rates in the specialized tertiary neuropsychiatry centre in India was provided.

To summarize, the review of cases presented by Samim et al 2023 and Francis et al 2023 could be confounded by referral bias to the respective specialized neurology centres in India and UK. Overall, there was limited data on individual case characteristics for a comprehensive causal assessment or possible risk factors/alternate explanation were identified. Quantitative trends of MOGAD cases were similar to BG frequency with lack of consistency of frequency

trends with subsequent VAXZEVRIA doses or in subsequent months. No significant concerns for MOG positivity frequencies or underlying core clinical demyelinating event distribution were observed. As per the Section 4.4 (Special warnings and special precautions for use) of the current CDS regarding neurological events, demyelinating disorders are very rare events reported following vaccination with VAXZEVRIA. A causal relationship has not been established.

Overall Conclusion for Immune Mediated Neurological Conditions:

It is AstraZeneca's opinion that no further changes to the VAXZEVRIA CDS or RMP, are warranted based on the review of currently available information. Immune-mediated neurological conditions will continue to be closely monitored as part of AstraZeneca's ongoing surveillance efforts for the important potential risk of immune-mediated neurological conditions.

16.3.1.2.1 Encephalitis, including Fatal

Review of Cases (Interval period 29 December 2022 to 28 December 2023)

A search of the AstraZeneca global safety database was conducted for the reporting period (29 December 2022 to 28 December 2023) for AE reports of encephalitis using the narrow MedDRA SMQ: Noninfective Encephalitis (excluding PT of ADEM) and HLT: Encephalopathy with VAXZEVRIA.

The above search identified 70 case reports (24 were initial case reports and 46 were FU reports), in vaccinees who received VAXZEVRIA. Cumulatively, till 28 December 2023, there are 442 cases of encephalitis received, out of which 22 cases were reported with fatal outcome. The below summary will present the data received during the reporting interval.

Out of the 70 reports, 13 (18.6%) were from Germany, 11 (15.7 %) cases were reported from the UK, 6 (8.6%) cases from Brazil and 22 cases from India (31.4%), 3 cases from Belgium and Taiwan (4.3%), 2 cases from Italy (2.9 %), 1 (1.4 %) case each from Canada, Australia, Chile, France, Austria, Norway, Philippines, Spain, US and Vietnam.

The overview of these 70 cases reporting 76 events of topics were presented in the below Table 54.

Table 54 Overview of Encephalitis events/cases for the interval period of PBRER

Parameter	Break-down	Values (%)
Case Count	Medically confirmed	50 (71.4 %)
Case Report Source	Interventional Clinical Study	2 (2.90 %)

Table 54 Overview of Encephalitis events/cases for the interval period of PBRER

Parameter	Break-down	Values (%)
	Non-interventional study	00 (0.00 %)
	Spontaneous ^a	38 (54.3 %)
	Literature	30 (42.90 %)
Sex	Female N (%)	44 (62.90 %)
	Male N (%)	25 (35.70 %)
	Unknown/not reported N (%)	1 (1.4 %)
Age Group	18-65 years	58 (82.90 %)
	>65 years	2 (2.90 %)
	Unknown	10 (12.50 %)
	Median age (range)	43 years (20 to 75)
Event occurrence with dose ^b	Dose 1 (%)	35 (50.00 %)
	Dose 2 (%)	10 (14.28 %)
	Dose 3 (%)	01 (1.42%)
	Dose 4 (%)	00 (0.00%)
	Multiple Doses	00 (0.00%)
	Unknown dose (34.28%)	
Case level -TTO (days)	0-1	02 (2.85 %)
	2-42	36 (51.42%)
	>42 days	09 (12.85%)
	Unknown	23 (32.85%)
	Median TTO (range)	14 (0 to 608)
AE-Outcome	Recovered	10 (13.15 %)
	Recovering	21 (27.63 %)
	Recovered with sequelae	03 (3.9%)
	Not recovered	15 (19.73 %)
	Fatal ^c	02 (2.63 %) c
	Unknown	25 (32.89 %)
Duration of recovered/recovered with sequelae events	Range (days) ^d	00 to 608
	Mean (days)	25
	Unknown duration (number of events)	02

^a Spontaneous case counts also includes regulatory source counts.

^b Known dose information used to calculate the percentage for the case reports.

^c Event recovery duration information is present only in 9 cases.

AE Adverse Event; PBRER Periodic Benefit-Risk Evaluation Report; TTO Time To Onset

Out of 70 cases reporting 76 AEs pertaining to encephalitis, 20 cases reported the singular event of Encephalitis during the reporting period. The distribution of the PTs pertaining to the search term for 'Encephalitis' is shown in the Table 55 below:

Table 55 **Distribution of MedDRA PTs (n =13) pertaining to Encephalitis with VAXZEVRIA Cumulatively through 28 December 2023**

MedDRA PT	Serious	Grand Total
Myelin oligodendrocyte glycoprotein antibody-associated disease	28	28
Encephalitis	20	20
Encephalitis autoimmune	7	7
Encephalomyelitis	6	6
Noninfective encephalitis	4	4
Encephalopathy	3	3
Hypoxic-ischemic encephalopathy	2	2
Autoimmune encephalopathy	1	1
Cytotoxic lesions of corpus callosum	1	1
Hashimoto's encephalopathy	1	1
Leukoencephalopathy	1	1
Noninfective encephalomyelitis	1	1
Posterior reversible encephalopathy syndrome	1	1

MedDRA Medical Dictionary for Regulatory Activities; PBRER Periodic Benefit-Risk Evaluation Report; PT Preferred Term

The most common PTs pertaining to the search term for 'Encephalitis' were MOGAD, Encephalitis, Encephalomyelitis and Encephalitis autoimmune. On review of the 28 cases reporting the PT of MOGAD, majority were received from a single specialized neuro-psychiatry centre via a literature source (Samim et al 2023). In 10 out the 11 cases, a FU information was received in the reporting period of the PBRER which comprised a reclassification of diagnosis such as MOG associated optic neuritis to MOGAD (MOG associated ADEM to MOGAD, MOG associated LETM to MOGAD, MOG associated Opticomyelopathy to MOGAD. The major FU information as reported by the authors were on AE outcome (improved in 6 cases, mild improvement in 4 cases, minimally improved in one case), however, there was limited information on rationale for reclassification of diagnosis, as well as insufficient information on the onset dates of the events in the specialized neuro-psychiatry centre in India. These 10 cases were also reported in a previous publication by

Netravathi et al 2022 and reviewed in a previous PBRER (DLP 28 June 2022). An explorative cumulative review of all cases reporting an MOG investigation finding following any neurological AE, did not identify any abnormal trend for MOG positivity with the demyelinating neurological AEs or any unusual distribution trends in core clinical demyelinating event (please refer to AstraZeneca comments for Francis et al 2023, for details).

Events with fatal outcome

Of the 76 total events reported, 2 (2.63 %) events were reported with a fatal outcome, MC. Summary of these case reports with details are presented below.

██████████ This case was received from the health professional via regulatory authority in Philippines. It was reported that a 56-year-old female patient (unknown medical history) experienced the event of Encephalitis autoimmune about 14 months after VAXZEVRIA vaccination and died from the event on the same day. The presenting symptoms included changes in behaviour with increased sleeping time, abdominal pain, cramping which progressed to lethargy. No other relevant information was provided.

AZ comments: Based on limited information on diagnostic workup, a comprehensive diagnostic certainty assessment was not possible (assessed as BCC4). Additionally, there was insufficient information on medical history and etiological workup. The TTO of 14 months is considered temporarily implausible to vaccination.

██████████ This case was received from a HCP concerning a 69-years old female vaccinee from Brazil, who had a fatal event of encephalitis. The vaccinee experienced onset of encephalitis 6 Days following VAXZEVRIA (unspecified dose) and after an unspecified duration and clinical course experienced a fatal outcome. The medical history was not reported, however the vaccinee was on multiple medications usually prescribed for diabetes (insulin and oral anti-diabetic drugs), hypertension (enalapril, amlodipine, hydrochlorothiazide), dyslipidaemia (valsartan), cardiovascular pathology (propranolol, warfarin). The vaccinee was also on ██████████ (as reported). Limited etiological work-up was done (complete blood counts, liver function tests (LFT), renal function tests, serum electrolytes, inflammation markers, MRI, angiography, virology markers (Anti-HCV), syphilis, rheumatoid factor and ANCA) without any information on biopsy or autopsy. The significant positive findings were T2/ Fluid-Attenuated Inversion Recovery (FLAIR) hypersignal foci in the bilateral periventricular white matter without diffusion restriction ('probably related to 'microangiopathy', aneurysms in carotid vessels and anaemia).

AZ comment: The diagnostic certainty can be conservatively considered as BCC3 based on suggestive radiological findings and encephalopathy. The TTO of encephalitis onset is reasonable. Elderly age, despite medical history was not reported, concomitant medication

suggested possible chronic co-morbid conditions of diabetes, hypertension, dyslipidaemia, cardiovascular disease (CVD), which in addition with the suggested radiological finding of angiopathy in backdrop of carotid aneurysms can be considered as possible confounders for morbidity and mortality. However, insufficient information is noted on autopsy details, [REDACTED] details and exact clinical course of encephalitis, hence WHO-UMC causality is assessed as Possible with limited information.

Review of cases using BCC and causality assessment using WHO-UMC Criteria

Brighton Collaboration Criteria

All the cases during the interval period have been reviewed and analysed using Brighton Collaboration (BCC) classification, summarized along with cumulative data in below sections.

The Brighton collaboration criteria for diagnostic certainty (Law B 2021) was used for the review of the data available in the case reports during the interval period (29 December 2022 – 28 December 2023).

The BCC and WHO-UMC causality assessment performed for these cases is provided in the following Table 56.

Table 56 Overview of BCC and WHO-UMC Causality Assessments / for case reports of (Encephalitis) with VAXZEVRIA reported during the reporting period of PBRER

WHO-UMC/BCC Level	Level 1	Level 2	Level 3	Level 4	Level 5	Grand Total
Certain	0	0	0	0	0	0
Probable/Likely	0	0	0	0	0	0
Possible with risk factors/confounders	0	3	1	3	1	8
Possible with limited information	0	7	2	8	17	34
Unassessable/Unclassifiable with limited information	0	0	2	7	2	11
Unassessable/Unclassifiable with risk factors/confounders	0	1	0	10	2	13
Unlikely	0	1	2	6	1	10
Conditional /Unclassified	0	0	0	0	0	0
Total	0	12	7	34	23	76

BCC Brighton Collaboration Criteria; PBRER Periodic Benefit Risk Evaluation Report; UMC Uppsala Monitoring Centre; WHO World Health Organization

Twelve cases fulfilled BCC Level 2 criteria, seven cases Level 3 criteria, 34 cases were considered in level 4 and 23 cases did not fulfil BCC criteria for certainty (Level 5 criteria). There are no certain or probable cases based on WHO-UMC causality assessment criteria.

Brighton Collaboration Level 2

Summary of cases fulfilling Brighton collaboration level 2 for encephalitis reported during the interval period (29 December 2022 – 28 December 2023).

Twelve out of the 76 events fulfilled Brighton collaboration level 2. Ten (10) case reports concerned females, and other 8 were reported in male vaccinees. The age range was 20-64 years.

In these 9 cases, the TTO range was between 2 to 10 Days. The median TTO was 08 Days. In 7 cases there was limited information about medical history, family history, concomitant medications to make a comprehensive causality assessment. In 4 cases there were confounders noted like monoclonal gammopathy, autoimmune milieu, underlying metabolic disorder, and mitochondrial cytopathy with primary hyper homocysteinemia. In the remaining one case, the WHO-UMC causality was considered as Unassessable / Unclassifiable due to unknown TTO.

Brighton Collaboration Level 3

Summary of Cases fulfilling Brighton collaboration level 3 for encephalitis reported during the interval period (29 December 2022 – 28 December 2023).

Seven (7) out of 70 cases fulfilled Brighton collaboration level 3. Four (4) case reports concerned females, and 3 were reported in male vaccinees. The age range was 36-58 years.

In these 07 cases, the TTO range was between 0 to 60 Days. The median TTO was 10 Days. In 02 cases there was limited information medical history, family history, concomitant medications to make a comprehensive causality assessment, 02 cases were noted with confounders, 01 case report was Unassessable/ Unclassifiable as the TTO was unknown and remaining 02 cases were unlikely as the TTO was 0 and 60 Days.

Brighton Collaboration Level 4

Based on the review, 34 out of 70 cases were classified as Brighton collaboration level 4. These cases did not fulfil criteria for a level 3, 2, or 1 certainty as there was insufficient information to confirm the diagnosis or medical assessment of the cases.

Brighton Collaboration Level 5

Based on the review, 23 out of 70 cases were classified as Brighton collaboration level 5 (ie, Encephalitis was excluded due to an alternative diagnosis). In this case, auto-immune thyroiditis was reported, and there was no event of encephalitis.

Observed vs. Expected Analysis

The observed versus expected analysis for all cases of encephalitis reported cumulatively till DLP 28 December 2023 is presented with three risk windows (14 Days, 30 Days, and 42 Days) in Table 57. This includes all reported cases irrespective of the Brighton collaboration criteria level. The risk window of 2-42 Days was included from the Brighton case definition (Law B 2021). The background IRs used are from a meta-analysis of ACCESS rates (Meningoencephalitis, 2010-2013 and 2017-2019) The outcome of observed versus expected analysis of all cases for encephalitis suggested that observed cases were significantly less than expected. The observed versus expected analysis of cases for encephalitis showed that observed cases occurred significantly less frequently than expected for all age stratifications in EEA/UK, Brazil, and Australia. Most cases in all age groups from EEA/UK, Brazil and Australia showed insufficient information to make any causality assessment and only few cases met the Brighton Collaboration Criteria Level 1, 2 or 3.

O/E analysis showed that observed cases occurred significantly less than expected with all stratifications.

Table 57 **Observed Versus Expected Analysis for all cases reporting encephalitis (Global reports) reported cumulatively till DLP 28 December 2023**

Adverse Events	Risk window	IR	Exposure ^a	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Overall Incidence Rate Encephalitis	14	9.1	466115644	205	1625.85	0.09 (0.08 - 0.11)	Observed significantly < expected
Overall Incidence Rate Encephalitis	30	9.1	466115644	43	3483.97	0.05 (0.04 - 0.06)	Observed significantly < expected
Overall Incidence Rate Encephalitis	42	9.1	466115644	14	4877.56	0.04 (0.04 - 0.05)	Observed significantly < expected
Overall Incidence Rate Encephalitis cases including unknown TTO	>42	9.1	466115644	181	4877.56	0.07 (0.06 - 0.08)	Observed significantly < expected

^a Exposure until 28 December 2023; Incidence rate (IR) source: Meta-analysis of ACCESS rates (Meningoencephalitis, 2010-2013 and 2017-2019)

CI Confidence Interval, DLP Data Lock Point E Expected, IR Incidence rate, O Observed; TTO Time To Onset

An observed versus expected analysis of cases stratified by age range and regions (EU/UK, Brazil and Australia) with different Risk windows are presented in Table 58.

Table 58 Observed Versus Expected Analysis for encephalitis cases stratified by age for EEA/UK, Brazil & Australia reported cumulatively till DLP 28 December 2023

Adverse Events	Risk window	IR ^a	Exposure ^b	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
EEA UK, Brazil & Australia Encephalitis Age 18-49	14	7.48	110094983	71	315.66	0.18 (0.13 - 0.23)	Observed significantly < expected
EEA UK, Brazil & Australia Encephalitis Age 18-49	30	7.48	110094983	82	676.41	0.1 (0.08 - 0.12)	Observed significantly < expected
EEA UK, Brazil & Australia Encephalitis Age 18-49	42	7.48	110094983	85	946.97	0.08 (0.06 - 0.1)	Observed significantly < expected
EEA UK, Brazil & Australia Encephalitis Age 50-59	14	8.66	58336094	24	193.64	0.1 (0.06 - 0.15)	Observed significantly < expected
EEA UK, Brazil & Australia Encephalitis Age 50-59	30	8.66	58336094	32	414.95	0.07 (0.04 - 0.09)	Observed significantly < expected
EEA UK, Brazil & Australia Encephalitis Age 50-59	42	8.66	58336094	36	580.93	0.06 (0.04 - 0.08)	Observed significantly < expected
EEA UK, Brazil & Australia Encephalitis Age 60-69	14	9.87	57960860	46	219.28	0.15 (0.1 - 0.21)	Observed significantly < expected

Table 58 **Observed Versus Expected Analysis for encephalitis cases stratified by age for EEA/UK, Brazil & Australia reported cumulatively till DLP 28 December 2023**

Adverse Events	Risk window	IR ^a	Exposure ^b	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
EEA UK, Brazil & Australia Encephalitis Age 60-69	30	9.87	57960860	58	469.89	0.09 (0.07 - 0.13)	Observed significantly < expected
EEA UK, Brazil & Australia Encephalitis Age 60-69	42	9.87	57960860	59	657.84	0.08 (0.06 - 0.1)	Observed significantly < expected
EEA UK, Brazil & Australia Encephalitis Age 70+	14	10.71	32376365	24	132.91	0.15 (0.09 - 0.23)	Observed significantly < expected
EEA UK, Brazil & Australia Encephalitis Age 70+	30	10.71	32376365	25	284.81	0.07 (0.05 - 0.11)	Observed significantly < expected
EEA UK, Brazil & Australia Encephalitis Age 70+	42	10.71	32376365	26	398.74	0.06 (0.04 - 0.09)	Observed significantly < expected

^a Source: Incidence rate (IR) source: Meta-analysis of ACCESS rates Meningoencephalitis, 2010-2013 and 2017-2019)

^b Exposure until 28 December 2023 for EEA/UK, Brazil, and Australia.

CI Confidence Interval; CPRD Clinical Practice Research Database; DLP Data Lock Point; E Expected; EEA European Economic Area; IR: Incidence rate; O Observed; TTO Time to onset; UK United Kingdom; CI Confidence Interval; CPRD Clinical Practice Research Database

An O/E analysis of cases meeting case definition according to Brighton Criteria (BC) for Level 1, 2 or 3, based on clinical course, examination such as brain histopathology, clinical features, and evaluations (Law B 2021) are presented in Table 59.

Table 59 Observed Versus Expected Analysis for encephalitis cases meeting the Brighton Criteria Level 1, 2 or 3 and stratified by age for EEA/UK Brazil & Australia regions reported cumulatively till DLP 28 December 2023.

Adverse Events	Risk window	IR ^a	Exposure ^b	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
EEA UK, Brazil & Australia; BCC 1-3; Age 18 -49	14	7.48	110094983	27	315.66	0.03 (0.02 - 0.06)	Observed significantly < expected
EEA UK, Brazil & Australia; BCC 1-3; Age 18 -49	30	7.48	110094983	36	676.41	0.02 (0.01 - 0.04)	Observed significantly < expected
EEA UK, Brazil & Australia; BCC 1-3; Age 18 -49	42	7.48	110094983	37	946.97	0.02 (0.01 - 0.03)	Observed significantly < expected
EEA UK, Brazil & Australia; BCC 1-3; Age 50-59	14	8.66	58336094	3	193.64	0.01 (0 - 0.03)	Observed significantly < expected
EEA UK, Brazil & Australia; BCC 1-3; Age 50-59	30	8.66	58336094	3	414.95	0 (0 - 0.01)	Observed significantly < expected
EEA UK, Brazil & Australia; BCC 1-3; Age 50-59	42	8.66	58336094	3	580.93	0.01 (0 - 0.02)	Observed significantly < expected
EEA UK, Brazil & Australia; BCC 1-3; Age 60-69	14	9.87	57960860	6	219.28	0.02 (0.01 - 0.05)	Observed significantly < expected
EEA UK, Brazil & Australia; BCC 1-3; Age 60-69	30	9.87	57960860	8	469.89	0.01 (0.01 - 0.03)	Observed significantly < expected
EEA UK, Brazil & Australia; BCC 1-3; Age 60-69	42	9.87	57960860	8	657.84	0.01 (0 - 0.02)	Observed significantly < expected
EEA UK, Brazil & Australia; BCC 1-3; Age 70+	14	10.71	32376365	2	132.91	0.04 (0.01 - 0.09)	Observed significantly < expected
EEA UK, Brazil & Australia; BCC 1-3; Age 70+	30	10.71	32376365	2	284.81	0.02 (0.01 - 0.04)	Observed significantly < expected
EEA UK, Brazil & Australia; BCC 1-3; Age 70+	42	10.71	32376365	2	398.74	0.01 (0 - 0.03)	Observed significantly < expected

^a Incidence rate (IR) source: Meta-analysis of ACCESS rates (Meningoencephalitis, 2010-2013 and 2017-2019)

^b Exposure until 28 December 2023 for EEA/UK, Brazil, and Australia.

CI Confidence Interval, E Expected, EEA European Economic Area; IR Incidence rate, O Observed PY Patient Years; TTO Time to onset; UK United Kingdom.

Literature review during the reporting period

During the reporting period, Six (6) relevant articles were identified. These included 5 literature case reports of encephalitis/encephalopathy with VAXZEVRIA which are included in the AstraZeneca safety database review above (REDACTED). These cases are reviewed and discussed as part of safety database review. The review of articles Francis et al 2023 and Samim et al 2023 have been presented in section Immune-mediated neurological conditions

There were no other relevant articles identified in the reporting period concerning Encephalitis and VAXZEVRIA.

Summary

Encephalitis is known to occur naturally at an overall annual incidence up to 10 cases per 100,000 persons. (Willame et al 2021 (A))

Incidence is highly variable dependent upon age, demographics, season, causative agent, and presence of epidemic illness. The natural aetiology is multifactorial but includes infectious, toxic, neoplastic, autoimmune, and metabolic causes (Wang et al 2022 [A]).

Of the 70 cases received during the reporting period, 58 (82.8%) of vaccinees were from the age group of 18-<65 (adult) and median age was found to be 43 years. In 35 (50.00 %) cases, the events were reported to have occurred after the first dose, 10 (14.28 %) case reports after the second dose of vaccine, and dose was not reported in 24 (34.28%) case reports. There was no report of recurrence of events.

Review of all cases during the interval period revealed no clear pattern in clinical presentation or medical history. There is a wide range in time to onset (TTO) of cases from vaccination (0-608 days). The median TTO for all the cases was 14 days. Thirty-Six (36) (51.42%) out of 70 cases were within the risk window of 2-42 days. 69 cases were serious. Case fatality rate is variable and dependent on causative factor (Wang et al 2022 [A]). The review of 2 case reports with fatal outcome did not identify any substantial evidence of a causal association between encephalitis and VAXZEVRIA. No changes were identified for interval data considering both safety patterns and volumes.

Based on Brighton Collaboration criteria approach, out of the 76 events, 12 fulfilled level 2 criteria, 07 fulfilled level 3 criteria, 34 fulfilled level 4 criteria, and 23 fulfilled level 5 criteria.

5 (7.14%) cases were evaluated with alternative causal factors noted and the remaining cases were evaluated with limited information to make any comprehensive causality assessment. The review of post authorization case reports did not find any evidence of a causal association between encephalitis and VAXZEVRIA.

The observed versus expected analysis of cumulative cases for encephalitis showed that observed cases occurred significantly less frequently than expected for all cases (442) and cases with BCC 1-3 (83), all age stratifications in EEA/UK, Brazil, and Australia, and risk windows. The contribution of under-reporting cannot be estimated, but observed cases are significantly below expected and do not indicate any disproportionality.

Overall, the clinical pattern of case presentation and numbers of reports are broadly consistent with what might be expected from the natural epidemiology of encephalitis, and there was no specific biological mechanism for development of encephalitis post vaccination with VAXZEVRIA.

Conclusion

From the data identified during the reporting period and taking into account the cumulative experience, there is currently insufficient evidence of a causal association between encephalitis and VAXZEVRIA.

VAXZEVRIA CDS Section 4.4 (Special warnings and special precautions for use) includes warnings on Neurological events: "Very rare events of demyelinating disorders, including GBS, have been reported following vaccination with VAXZEVRIA. A causal relationship has not been established. As with other vaccines, the benefits and potential risks of vaccinating individuals with VAXZEVRIA should be considered". In addition, encephalitis (immune mediated neurological condition/ nervous system disorders, including immune mediated neurological conditions.) is considered as an Important potential risk in the Core and EU RMPs for VAXZEVRIA. No further updates to the VAXZEVRIA CDS or RMP are warranted at this time. As such, the topic will continue to be closely monitored as part of AstraZeneca's ongoing surveillance for the important potential risk of immune-mediated neurological conditions.

16.3.1.2.2 Transverse Myelitis

Review of Cases (29 December 2022 to 28 December 2023)

A search of the AstraZeneca global safety database was conducted for the reporting period (29 December 2022 to 28 December 2023) for AE reports of TM with VAXZEVRIA was performed using MedDRA version 26.1. The search strategy included: PTs: Myelitis transverse, Myelitis, and Acute necrotizing myelitis, and Lowest Level Terms (LLT): MOG-TM.

The above search retrieved a total of 64 events (2 events of MOGAD, 16 events of myelitis and 46 events of Myelitis transverse) in 62 case reports reported during the reporting period predominantly from the following countries: UK (27.4%), Brazil (25.8%) and India (14.5%). Thirty-one were initial and 33 were FU reports. There was no predominance in the events reported by gender (male 50.8% and female 49.2%). Age of the vaccinees were reported in 48 cases and most of the cases (79.1%) were reported in young adult population. Around 45.8% reported in vaccinees aged between 25-44 years and 33.3% aged between 45-64 years. The median age was 46 years. The time to onset of the event was available in 37 cases and it ranged between 1-126 days (median TTO: 14 days). During the reporting interval 4 cases were reported with fatal outcome and in 3 cases the cause of death was reported as TM and 1 case vaccinee died due to ADEM. A summary of these fatal case is included below.

Cumulatively, till 28 December 2023, there are 419 cases of TM received, out of which 7 cases were reported with fatal outcome. The below summary includes the data received during the reporting interval.

Cases with fatal outcome

Of the 62 cases received during the interval period, 4 (6.5%) cases were reported with fatal outcome. In three cases, the cause of the death was related to TM and are summarized below. One case reporting ADEM as cause of death is described under Section 16.3.1.2.3

Report received as an abstract from a conference concerning a 59-year-old male patient who presented with progressive, symmetrical and ascending loss of strength in the lower limbs (with 3 Days of evolution), on the fifth day post VAXZEVRIA vaccination. Any medical history of diabetes, systemic arterial hypertension, alcohol consumption or smoking was denied. On clinical examination, the patient was observed to have grade 0 in the lower limbs, areflexia in the lower limbs and decrease of superficial and deep sensitivity in the lower limbs. Initially, the patient was admitted to the Intensive Care Unit (ICU), staying for 11 Days for investigation for Guillain-Barre Syndrome (GBS) and for pulse therapy with methylprednisolone 1000 mg IV for 5 Days, but without improvement of symptoms. At a different tertiary centre, persistence of the previous findings, in addition to the presence of horizontal choreic movements of the head, intention tremor in the upper limbs (UL), significant dysmetria, worse on the left, nystagmus and without alteration of cranial nerves was identified. During hospitalization, two biochemical evaluations of CSF were performed, but with unspecific results.

As reported, the patient evolved with complications of cutaneous, urinary and pulmonary infections and died of sepsis after 110 Days of hospitalization. It was also reported that the patient experienced TM, ADEM, and cerebellar syndrome. The authors further comment on presenting a case of a possible and rare correlation between the AstraZeneca vaccine for COVID-19 and ADEM.

AstraZeneca comment: The short time to onset of neurological symptoms on the second day post VAXZEVRIA is considered improbable for an immune-mediated pathogenesis for TM. Due to absent information on investigations, a comprehensive diagnostic certainty of TM was not possible. Moreover, there was insufficient information on vaccination dose number, neurological medical history, concomitant medications, details of investigations and etiological work-up such neoplasm, trauma, infection or vascular disorder.

Report from a health professional in UK concerning fatality of a 76-year-old male patient. The patient had received two doses of VAXZEVRIA vaccination on 30 January 2021 and on 21 April 2021. The patient had medical history of longstanding steroid dependent adrenal insufficiency, prostatic carcinoma, osteopenia, hypertension, suspected Parkinson's disease, deteriorating mobility since mid-2020 and suspected normal pressure hydrocephalus. The patient experienced a sudden loss of mobility leading to fall about 33 Days following dose 1 of vaccination and a subsequent similar episode of acute neurological deterioration about 32 Days following dose 2 of vaccination. Neuroradiological investigations two Days later showed definite increase in signal from T9 to conus medullaris with diffuse enhancement and swelling. The features were thought to be in keeping with myelitis with a differential diagnosis of a vascular insult. A repeat MRI after 23 Days showed some enhancement at T9/10 with residual signal abnormality from T7-12. Aquaporin 4, MOG anti-neuronal antibodies were negative. It was reported that after 15 Days, the patient was admitted to a rehabilitation facility due to progressive weakness of lower limbs and needed to have mobility assistance. Thirty-five Days later, the patient had gasping and had stopped responding and eventually died.

A post-mortem was done. Relevant post-mortem findings were severe atherosclerosis of all 3 coronary arteries, mild to marked dilatation of Left and right ventricles, mild to moderate atherosclerosis of aorta and other arteries, no acute infarcts, congested lungs, pleural plaque in right apex of lung. multinodular prostate (histology – patchy residual tumour in the form of small acini with an infiltrative growth pattern, in keeping with the ante-mortem clinical diagnosis of prostatic adenocarcinoma). In the Spinal cord, the histology showed extensive and severe active inflammatory process with bilateral involvement of entire cord extending from cervical spinal cord segments into thoracic, lumbosacral also involving the cauda equina and spinal roots at most levels. The fasciculus gracilis and cuneatus appeared degenerate with neutrophil vacuolation. There was also irregular neutrophil vacuolation in the posterior and to a lesser extent, anterior horns of the grey matter. Axonal bulbs were evident in places. Patchy degeneration of other ascending and descending white matter tracts. Mild perivascular and parenchymal inflammation was evident in the spinal cord focally. Spinal nerve roots were extensively affected with perivascular lymphocytic inflammation with occasional multinucleate giant cells. Some spinal nerve roots appeared hyalinised with complete loss of myelinated nerve fibres. Many endoneurial blood vessels showed hyaline thickening with an occasional endoneurial vessel showing tiny vascular channels within the hyalinised mural

vasculature suggestive of recanalization. Severe multifocal lymphocytic inflammation is also seen in the cauda equina. There are numerous dilated thin-walled blood vessels within or associated with the cauda and spinal nerve roots. The brain did not show any evidence of neuro-inflammatory disease and no evidence of neoplasia. Pituitary gland showed apparent reduction in proportion of adrenocorticotrophic hormone (ACTH) producing neuro-endocrine cells. The adrenal glands showed no significant histopathological changes.

Neuropathological impression: severe inflammatory disease affecting the entire spinal cord with involvement of spinal nerve roots and cauda equina.

AstraZeneca comment:

The diagnostic certainty is considered BCC1 based on autopsy findings of inflammation in spinal cord.

As reported, the patient had pre-existing deteriorating mobility (since 2020, prior to vaccination) which could be suggestive of possible pre-existing neurological pathology. As reported, a possibility of Parkinson's disease was also suspected prior to vaccination. The post-vaccination clinical presentation of episodic and hyperacute loss of mobility may be more consistent to a vascular insult over a BG TM pathogenesis, which has an acute or subacute presentation with progression to a peak in days to weeks. There was no increase in frequency or shorter time to onset of acute neurological deterioration episode following second vaccination dose. It may be suggestive of possible vascular etiopathogenesis in the backdrop of autopsy findings of endoneural recanalization, atherosclerotic cardiovascular disease (CVD) (severe atherosclerosis of all 3 coronary arteries, mild to marked dilatation of Left and right ventricles, mild to moderate atherosclerosis of aorta and other arteries), and medical history of adrenal insufficiency with hyponatremia, hypertension, prostatic carcinoma chronic steroid use.

Repeat MRI showed reduction in TM lesions (possibly explained by methylprednisolone therapy), however there was a clinical progression in progressive limb weakness. There were no complaints suggestive of bowel and bladder involvement. This could also point to possible pre-existing neurological pathology. A medical history of longstanding steroid dependent adrenal insufficiency was reported; however, it is unknown whether any action was taken with the steroids prior to vaccination doses. This case also had limited information on any investigation or treatment following dose 1 event episode, onset date of atrial flutter (reported as medical history). Based on information on any investigation or treatment following dose 1 event and presence of pre-existing progressive mobility issues and suspected Parkinson's disease, it cannot be comprehensively confirmed that the second episode following dose 2 of vaccination is a recurrence.

Pre-existing longstanding steroid dependent adrenal insufficiency, prostatic carcinoma, hypertension, suspected Parkinson's disease, and concomitant use of medications which has potential to cause arrhythmias or dyselectrolytemia (such as Bicalutamide – QT prolongation, Amlodipine – arrhythmias, Alendronate – hypocalcemia) in the backdrop of advanced age are possible confounders for the sudden death.

The WHO-UMC causality as assessed as Possible based on TTO, however multiple confounders were identified.

██████████ refers to elderly male patient (77 years) with a medical history of inflammatory myelitis, prostate cancer, hypertension, adrenal insufficiency (steroid dependent) and atrial flutter. He received two doses of Vaxzervria. Vaccinee experienced a sudden onset of neurological deficits with severe inflammation of the spinal nerve roots and entire spinal cord after Dose 2 of VAXZEVRIA. On Day 77, patient died due to TM and cardiac arrest. It was unknown autopsy was performed.

AstraZeneca comment: This elderly patient with a medical history of inflammatory myelitis died of TM post dose 2 of VAXZEVRIA on Day 77. In this case, the clinical course of the event post Dose 1 is not reported. Moreover, the event occurred after 77 days (beyond the risk window) and hence, the event is considered as unlikely with VAXZEVRIA.

The WHO-UMC causality as assessed as Unlikely as the TTO of the event is beyond the risk window of 42 Days.

Recurrence case reports

There were no cases indicating a recurrence in the reporting period.

WHO -UMC and Brighton Collaboration Classification (BCC) Assessment

The BCC for diagnostic certainty Law B 2021 [C] was used for review of information available in all case reports. Cases were categorised as Brighton Collaboration Level 1- 5 for acute myelitis based on clinical history, examination, and laboratory investigation results. Causality assessment of all cases was performed using WHO- UMC causality assessment criteria with a risk window of 42 days.

The BCC and WHO-UMC assessment performed for these cases is provided in the following Table 60.

Table 60 Overview of BCC and WHO-UMC Causality Assessments / for case reports of Transverse myelitis with VAXZEVRIA reported during the reporting period

WHO-UMC/BCC Level	Level 1	Level 2	Level 3	Level 4	Level 5	Grand Total
Certain	0	0	0	0	0	0
Probable/Likely	0	0	0	0	0	0
Possible with risk factors/confounders	1	4	2	6	1	15
Possible with limited information	0	6	6	13	0	23
Unassessable/Unclassifiable	0	0	2	11	1	14
Unlikely	0	2	0	5	0	7
Conditional /Unclassified	0	0	0	0	0	0
Total	1	12	10	37	2	62

Cases were considered to have “risk factors/confounders” where the event could also be explained by the vaccinee’s diseases, or where relevant risk factors were present, or concomitant medications that could potentially contribute to the development of the event were reported.

BCC Brighton Collaboration Criteria; UMC Uppsala Monitoring Centre; WHO World Health Organization.

There were no cases assessed as certain or probable in the reporting period.

Review of cases as per BCC classification in the reporting period of the PBRER

The BCC (Law B 2021 [C]) was used for the review of the data available in the case reports. Based on this approach, out of the 47 cases: one of the cases fulfilled BCC Level 1 criteria; 9 cases fulfilled BCC Level 2 criteria; 7 cases fulfilled BCC Level 3 criteria; 28 cases fulfilled BCC Level 4 criteria and 2 cases fulfilled BCC Level 5 criteria.

In addition to the BCC, the published Brighton Case Definition for Acute Myelitis (Law B 2021 [C]) was also referenced during the review of the cases for the assessment of evidence related to associated risk factors (eg, comorbidities, infections, vaccines and malignancies).

The cases fulfil BCC levels 1-5 based on the available information on clinical course, clinical examination, and diagnostic investigations.

BCC Level 1 for Transverse myelitis:

A single case fulfilled the BCC level 1 criteria (REDACTED). The case was reported in a 76-year-old male and has been discussed above. The case was assessed as Possible (with confounders) as per WHO-UMC Causality assessment criteria.

BCC Level 2 for Transverse myelitis

Twelve out of the 47 case reports fulfilled BCC level 2 criteria. The cases fulfil this classification by clinical course, examination, and radiological features. Seven were female vaccinees and 5 were male vaccinees and their age ranges between 24-68 years (median 36 years). Time to onset was available in 8 cases and all were within the risk window of 42 Days (median=14, range 3-42 Days).

Out of these 9 cases, 8 cases reported to have occurred after receiving the first dose, 1 case after dose 2 and the dose was unknown in remaining cases.

Out of the 12 cases fulfilling BCC Level 2, 4 ([REDACTED]) were assessed as Possible (with limited information), four ([REDACTED]) as Possible (with confounders/alternative cause) and two Unlikely ([REDACTED]) as per WHO-UMC Causality assessment criteria.

Predominantly (6 out of 9 cases) presented with bowel/bladder dysfunction in addition to sensory and motor involvement of extremities. This also roughly correlated with involvement of multiple vertebral segments.

The CSF cell count differentials were reported in 4 cases with 2 cases having polymorphic picture, 1 monocytic, one lymphocytic predominance. Information on oligoclonal bands (OCB) in TM cases was reported in 3 cases (2 negative and 1 positive). Information on serum or CSF levels on anti-neuronal antibodies (eg: MOG-Ab, NMO-Ab, AQP4-Ab) was reported in all 12 cases with MOG positivity in 1 case and AQP4 positivity in 1 case. The anti-neuronal antibodies were normal in the remaining cases. To summarize, either there was limited information or CSF picture including neuronal antibodies had a varied presentation to identify any possible singular immune etiopathogenetic role of VAXZEVRIA vaccine.

BCC Level 3 for Transverse myelitis

Ten out of the 62 case reports fulfilled BCC level 3 criteria. The cases fulfil this classification by clinical course, examination features, and investigations. Four cases were reported in female vaccinees and 5 were male vaccinees and one case gender was not reported. Age of the vaccinees was reported in 7 cases and it range between 27-53 years (median 44 years). Time to onset was available in 5 cases and all were within the risk window of 42 Days (median 16 Days, range 1-28 Days).

Out of these 10 cases, 3 cases reported to have occurred after receiving the first dose, 1 case after dose 2 and the dose was unknown in remaining cases.

Of the 10 cases fulfilling BCC Level 3, 6 were assessed as Possible (with limited information) as per WHO Causality assessment criteria. The limited information was a lack of

comprehensive etiological work-up (especially for infectious aetiologies), medical history and concomitant medications. Two were assessed as Possible (with confounders/alternative cause), one with a concomitant paraneoplastic condition and one with a possible pre-existing condition based on examination features. The remaining two cases were assessed as Unassessable/Unclassifiable.

The CSF results presented a varied picture with respect to extent of pleocytosis (no pleiocytosis in 4 out of 5 cases and monocytic picture in 1 out of 5 cases). There was insufficient information on CSF counts in the remaining 5 cases. Information on serum or CSF levels on anti-neuronal antibodies (eg: MOG-Ab, NMO-Ab, AQP4-Ab) and OCB was reported in 7 out of 10 cases and was normal in 3 cases, MOG-Ab positive in 2, OCB positive in 1 case and AQP4 positive in 1 case. To summarize, either there was limited information or CSF picture including neuronal antibodies had a varied presentation to identify any singular etiopathogenetic possible role of VAXZEVRIA.

BCC Level 4 for Transverse Myelitis

A total of 37 cases fulfilled BCC Level 4 criteria, limited information to make any causality assessment was noted in 11 of the cases, 15 cases were assessed as “Possible” (with limited information), 6 cases were assessed as “Possible” (with confounders) and the remaining 5 cases were assessed as “Unlikely” as per WHO Causality assessment criteria.

BCC Level 5 for Transverse Myelitis

A total of 2 case reports fulfilled BCC level 5 criteria. Limited information to make any causality assessment was noted in one of the cases and the remaining case was assessed as “Possible” (with confounders) as per WHO Causality assessment criteria.

Observed Versus Expected (O/E) Analyses

An O/E analysis of TM was conducted cumulatively.

Willame et al 2021 (B) have as part of ADVANCE EUROPE given IRs for TM, stratified by age. The rates are slightly lower than other rates found corresponding to a more conservative estimate for BG rates. An appendix to the same article by Willame et al 2021 (B) has given IRs stratified by age and gender.

Global overall rates based on the rates from ADVANCED Europe are presented in Table 61. The observed numbers are presented both including and excluding cases with an unknown time to onset and stratified by cases fulfilling Brighton collaboration criteria levels 1-3 (BCC 1-3).

The risk window for myelitis as a product related reaction for inactivated or subunit vaccines is likely similar to ADEM, where the recommended risk window for individuals is 2-42 Days. A risk window of 42 Days was used for this analysis, ie, cases that have the time to onset of 42 Days or less from receiving the vaccine until the event occurred are counted in the observed numbers.

Conservatively, the exposure of global reports (466115644) is based on the doses administered in markets as explained in Appendix 8.

Table 61 Observed versus Expected Analysis for Transverse Myelitis Overall and for Brighton Collaboration cases

Age group/ Gender	Risk window (days)	Back- ground rates	Exposure a	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusio n
Overall	42	0.97	466115644	218	519.92	0.42 (0.37 - 0.48)	Observed significantl y < expected
Overall +Unk TTO	42	0.97	466115644	339	519.92	0.65 (0.58 - 0.73)	Observed significantl y < expected
Overall BCC 1-3	42	0.97	466115644	55	519.92	0.11 (0.08 - 0.14)	Observed significantl y < expected
Overall +Unk TTO BCC 1-3	42	0.97	466115644	64	519.92	0.12 (0.09 - 0.16)	Observed significantl y < expected
Overall	42	0.97	466115644	218	519.92	0.42 (0.37 - 0.48)	Observed significantl y < expected

^a Exposure until 28 December 2022. All global reports are included in observed numbers. Exposure numbers are from United Kingdom, EEA, Australia, Canada, Philippines and Brazil. Exposure numbers from India are not included.

BCC, Brighton collaboration criteria; CI, Confidence Interval; TTO: Time to onset; Unk, Unknown.

Observed versus expected analyses stratified by age in the UK, using rates from ADVANCED Europe Willame et al 2021 (B) are presented in Table 62. The observed numbers are presented both including and excluding cases with an unknown time to onset and stratified by cases fulfilling Brighton collaboration criteria levels 1-3 (BCC 1-3).

Table 62 **Observed versus expected analysis, stratified by age, BCC and with and without cases with an unknown TTO in the UK**

Age Group	Risk Window	BG rates	Exposure ^a	Observed number of cases	Expected number of cases	O over E ratio	Conclusion
18-24 years	42	0.64	871474	3	0.64	4.69 (0.97 - 13.7)	Observed > expected
25-44 years	42	1.36	8438999	26	13.2	1.97 (1.29 - 2.89)	Observed significantly > expected
45-64 years	42	1.23	22877522	35	32.36	1.08 (0.75 - 1.5)	Observed > expected
65 years +	42	0.76	13443624	34	11.75	2.89 (2 - 4.04)	Observed significantly > expected
18-24 years including cases with an unknown TTO	42	0.64	871474	4	0.64	6.25 (1.7 - 16)	Observed significantly > expected
25-44 years Including cases with an Unknown TTO	42	1.36	8438999	37	13.2	2.8 (1.97 - 3.86)	Observed significantly > expected
45-64 Years Including cases with an Unknown TTO	42	1.23	22877522	58	32.36	1.79 (1.36 - 2.32)	Observed significantly > expected

Table 62 **Observed versus expected analysis, stratified by age, BCC and with and without cases with an unknown TTO in the UK**

Age Group	Risk Window	BG rates	Exposure ^a	Observed number of cases	Expected number of cases	O over E ratio	Conclusion
65 Years + Including cases with an Unknown TTO	42	0.76	13443624	55	11.75	4.68 (3.53 - 6.09)	Observed significantly > expected
18-24 years BCC 1-3	42	0.64	871474	0	0.64	0 (0 - 5.76)	Observed < expected
25-44 Years BCC 1-3	42	1.36	8438999	7	13.2	0.53 (0.21 - 1.09)	Observed significantly < expected
45-64 Years BCC 1-3	42	1.23	22877522	10	32.36	0.31 (0.15 - 0.57)	Observed significantly < expected
65 Years + BCC 1-3	42	0.76	13443624	2	11.75	0.17 (0.15 - 0.57)	Observed significantly < expected
18-24 years BCC 1-3 including cases with an unknown TTO	42	0.64	871474	0	0.64	0 (0 - 5.76)	Observed < expected
25-44 years BCC 1-3 including cases with an unknown TTO	42	1.36	8438999	9	13.2	0.68 (0.31 - 1.29)	Observed < expected

Table 62 Observed versus expected analysis, stratified by age, BCC and with and without cases with an unknown TTO in the UK

Age Group	Risk Window	BG rates	Exposure ^a	Observed number of cases	Expected number of cases	O over E ratio	Conclusion
45-64 years BCC 1-3 including cases with an unknown TTO	42	1.23	22877522	12	32.36	0.37 (0.19 - 0.65)	Observed significantly < expected
65 years + BCC 1-3 including cases with an unknown TTO	42	0.76	13443624	5	11.75	0.43 (0.14 - 0.99)	Observed significantly < expected

^a Exposure until 28 December 2023.

BCC, Brighton Criteria; CI, Confidence Interval; TTO: Time to onset; Unk, Unknown.

Observed versus expected analyses stratified by age and gender in the UK, using UK IRs from Willame et al 2021 (B), ie, UK The Health Improvement Network (UK_THIN), are presented in Table 63. The observed numbers are presented both including and excluding cases with an unknown time to onset.

Table 63 Observed versus expected analysis, stratified by age and gender in the UK in the context of the UK THIN BG rates

Age group/Gender	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio	Risk window
Female 18-24 years UK THIN	42	1.2	501919	1	0.69	1.45 (0.04 - 8.07)	Observed > expected
Female 25-44 years UK THIN	42	2.6	4545840	19	13.59	1.4 (0.84 - 2.18)	Observed > expected
Female 45-64 years UK THIN	42	1.9	10997650	17	24.03	0.71 (0.41 - 1.13)	Observed < expected

Table 63 **Observed versus expected analysis, stratified by age and gender in the UK in the context of the UK THIN BG rates**

Age group/Gender	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio	Risk window
Female 65 years+ UK THIN	42	0.8	7206922	19	6.63	2.87 (1.73 - 4.48)	Observed significantly > expected
Female Overall UK THIN	42	1.6	23252503	56	42.78	1.31 (0.99 - 1.7)	Observed > expected
Female 18- 24 years UKTHIN + Unk TTO	42	1.2	501919	2	0.69	2.9 (0.35 - 10.47)	Observed > expected
Female 25- 44 years UKTHIN + Unk TTO	42	2.6	4545840	28	13.59	2.06 (1.37 - 2.98)	Observed significantly > expected
Female 45- 64 years UKTHIN + Unk TTO	42	1.9	10997650	27	24.03	1.12 (0.74 - 1.63)	Observed > expected
Female 65 years+ UKTHIN + Unk TTO	42	0.8	7206922	27	6.63	4.07 (2.68 - 5.93)	Observed significantly > expected
Female Overall UKTHIN + Unk TTO	42	1.6	23252503	84	42.78	1.96 (1.57 - 2.43)	Observed significantly > expected
Male 18- 24 years UK THIN	42	0.7	369342	2	0.3	6.67 (0.81 - 24.08)	Observed > expected

Table 63 **Observed versus expected analysis, stratified by age and gender in the UK in the context of the UK THIN BG rates**

Age group/Gender	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio	Risk window
Male 25-44 years UK THIN	42	1.5	3892485	7	6.71	1.04 (0.42 - 2.15)	Observed > expected
Male 45-64 years UK THIN	42	1.4	11879400	18	19.12	0.94 (0.56 - 1.49)	Observed < expected
Male 65 years + UK THIN	42	0.9	6236564	14	6.45	2.17 (1.19 - 3.64)	Observed significantly > expected
Male Overall UK THIN	42	1.1	22377923	41	28.31	1.45 (1.04 - 1.96)	Observed significantly > expected
Male 18-24 years UKTHIN +Unk TTO	42	0.7	369342	2	0.3	6.67 (0.81 - 24.08)	Observed > expected
Male 25-44 years UKTHIN +Unk TTO	42	1.5	3892485	8	6.71	1.19 (0.51 - 2.35)	Observed > expected
Male 45-64 years UKTHIN +Unk TTO	42	1.4	11879400	31	19.12	1.62 (1.1 - 2.3)	Observed significantly > expected
Male 65 years + UKTHIN +Unk TTO	42	0.9	6236564	25	6.45	3.88 (2.51 - 5.72)	Observed significantly > expected
Male Overall UKTHIN +Unk TTO	42	1.1	22377923	66	28.31	2.33 (1.8 - 2.97)	Observed significantly > expected

CI, Confidence Interval; E, Expected; O, Observed TTO: Time to onset; Unk, Unknown; UK, United Kingdom

An observed versus expected analysis, including cases fulfilling Brighton collaboration levels 1-3, stratified by age and gender in the UK are provided below, using BG rates from UK THIN are presented in Table 64.

Table 64 Observed versus expected analysis, stratified by age and gender, BCC levels 1-3 in the UK in the context of the UK THIN BG rates

Age group/Gender	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female 18-24 years UK THIN BCC 1-3	42	1.2	501919	0	0.69	0 (0 - 5.35)	Observed < expected
Female 25-44 years UK THIN BCC 1-3	42	2.6	4545840	7	13.59	0.52 (0.21 - 1.06)	Observed < expected
Female 45-64 years UK THIN BCC 1-3	42	1.9	10997650	3	24.03	0.12 (0.03 - 0.36)	Observed significantly < expected
Female 65 years+ UK THIN BCC 1-3	42	0.8	7206922	0	6.63	0 (0 - 0.56)	Observed significantly < expected
Female Overall UK THIN BCC 1-3	42	1.6	23252503	10	42.78	0.23 (0.11 - 0.43)	Observed significantly < expected
Female 18-24 years UK THIN +Unk TTO BCC 1-3	42	1.2	501919	0	0.69	0 (0 - 5.35)	Observed < expected

Table 64 **Observed versus expected analysis, stratified by age and gender, BCC levels 1-3 in the UK in the context of the UK THIN BG rates**

Age group/Gender	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female 25-44 years UKTHIN +Unk TTO BCC 1-3	42	2.6	4545840	9	13.59	0.66 (0.3 - 1.26)	Observed < expected
Female 45-64 years UKTHIN +Unk TTO BCC 1-3	42	1.9	10997650	4	24.03	0.17 (0.05 - 0.43)	Observed significantly < expected
Female 65 years + UKTHIN +Unk TTO BCC 1-3	42	0.8	7206922	1	6.63	0.15 (0 - 0.84)	Observed significantly < expected
Female Overall UKTHIN +Unk TTO BCC 1-3	42	1.6	23252503	14	42.78	0.33 (0.18 - 0.55)	Observed significantly < expected
Male 18-24 years UK THIN BCC 1-3	42	0.7	369342	0	0.3	0 (0 - 12.3)	Observed < expected
Male 25-44 years UK THIN BCC 1-3	42	1.5	3892485	0	6.71	0 (0 - 0.55)	Observed significantly < expected
Male 45-64 years UK THIN BCC 1-3	42	1.4	11879400	7	19.12	0.37 (0.15 - 0.75)	Observed significantly < expected

Table 64 Observed versus expected analysis, stratified by age and gender, BCC levels 1-3 in the UK in the context of the UK THIN BG rates

Age group/Gender	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Male 65 years + UK THIN BCC 1-3	42	0.9	6236564	2	6.45	0.31 (0.04 - 1.12)	Observed < expected
Male Overall UK THIN BCC 1-3	42	1.1	22377923	9	28.31	0.32 (0.15 - 0.6)	Observed significantly < expected
Male 18- 24 years UKTHIN +Unk TTO BCC 1-3	42	0.7	369342	0	0.3	0 (0 - 12.3)	Observed < expected
Male 25- 44 years UKTHIN +Unk TTO BCC 1-3	42	1.5	3892485	0	6.71	0 (0 - 0.55)	Observed significantly < expected
Male 45- 64 years UKTHIN +Unk TTO BCC 1-3	42	1.4	11879400	8	19.12	0.42 (0.18 - 0.82)	Observed significantly < expected
Male 65 years + UKTHIN +Unk TTO BCC 1-3	42	0.9	6236564	3	6.45	0.47 (0.1 - 1.36)	Observed < expected
Male Overall UKTHIN +Unk TTO BCC 1-3	42	1.1	22377923	11	28.31	0.39 (0.19 - 0.7)	Observed significantly < expected

BCC Brighton collaboration criteria; CI Confidence Interval; E Expected; O Observed; TTO Time to Onset; UK United Kingdom; UKTHIN United Kingdom The Health Improvement Network; Unk Unknown;

Observed versus expected analyses stratified by Dose number, age and gender, BCC in the UK, using UK IRs from Willame et al 2021 (B), ie UK The Health Improvement Network (UK_THIN), are presented in Table 65.

Table 65 Observed versus expected analyses stratified by Dose number, age and gender, BCC in UK

Gender /Age group / Dose #	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	Observed over Expected ratio (95% CI)	Conclusion
Male/ 18-24 years/ Dose 1	42	0.7	188628	0	0.15	6.67 (0.17 - 37.14)	Observed > expected
Male/ 25-44 years/ Dose 1	42	1.5	1980408	6	3.42	2.05 (0.82 - 4.22)	Observed > expected
Male/ 45-64 years/ Dose 1	42	1.4	5990807	12	9.64	1.97 (1.19 - 3.08)	Observed significantly > expected
Male/ 65 years +/- Dose 1	42	0.9	3126893	8	3.24	4.94 (2.82 - 8.02)	Observed significantly > expected
Male/ Overall/ Dose 1	42	1.1	11286808	26	14.28	3.01 (2.18 - 4.06)	Observed significantly > expected
Male/ 18-24 years/ Dose 1/ BCC 1-3	42	0.7	188508	0	0.15	0 (0 - 24.59)	Observed < expected
Male/ 25-44 years/ Dose 1/ BCC 1-3	42	1.5	1980408	0	3.42	0 (0 - 1.08)	Observed < expected
Male/ 45-64 years/ Dose 1/ BCC 1-3	42	1.4	5990807	5	9.64	0.52 (0.17 - 1.21)	Observed < expected
Male/ 65 years +/- Dose 1/ BCC 1-3	42	0.9	3126893	0	3.24	0 (0 - 1.14)	Observed < expected

Table 65 Observed versus expected analyses stratified by Dose number, age and gender, BCC in UK

Gender /Age group / Dose #	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Male/ Overall/ Dose 1/ BCC-1-3	42	1.1	11286808	5	14.28	0.35 (0.11 - 0.82)	Observed significantly < expected
Male/ 18-24 years/ Dose 2	42	0.7	188628	0	0.15	0 (0 - 24.59)	Observed < expected
Male/ 25-44 years/ Dose 2	42	1.5	1980408	0	3.42	0 (0 - 1.08)	Observed < expected
Male/ 45-64 years/ Dose 2	42	1.4	5990807	5	9.64	0.62 (0.23 - 1.35)	Observed < expected
Male/ 65 years +/- Dose 2	42	0.9	3126893	3	3.24	0 (0 - 1.14)	Observed < expected
Male/ Overall/ Dose 2	42	1.1	11286808	8	14.28	0.42 (0.15 - 0.91)	Observed significantly < expected
Male/ 18-24 years/ Dose 2/ BCC 1-3	42	0.7	188628	0	0.15	0 (0 - 24.59)	Observed < expected
Male/ 25-44 years/ Dose 2/ BCC 1-3	42	1.5	1980408	0	3.42	0 (0 - 1.08)	Observed < expected
Male/ 45-64 years/ Dose 2/ BCC 1-3	42	1.4	5990807	1	9.64	0.1 (0 - 0.58)	Observed significantly < expected
Male/ 65 years +/- Dose 2/ BCC 1-3	42	0.9	3126893	1	3.24	0.31 (0.01 - 1.72)	Observed < expected
Male/ Overall/ Dose 2/ BCC 1-3	42	1.1	11286808	2	14.28	0.14 (0.02 - 0.51)	Observed significantly < expected

Table 65 **Observed versus expected analyses stratified by Dose number, age and gender, BCC in UK**

Gender /Age group / Dose #	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female/ 18-24 years/ Dose 1	42	1.2	255840	1	0.35	2.86 (0.07 - 15.92)	Observed > expected
Female/ 25-44 years/ Dose 1	42	2.6	2310305	12	6.91	2.6 (1.54 - 4.12)	Observed significantly > expected
Female/ 45-64 years/ Dose 1	42	1.9	5537396	10	12.1	1.24 (0.69 - 2.04)	Observed > expected
Female/ 65 years +/ Dose 1	42	0.8	3610734	10	3.32	3.31 (1.65 - 5.93)	Observed significantly > expected
Female/ Overall/ Dose 1	42	1.6	11714377	33	21.55	2.09 (1.52 - 2.79)	Observed significantly > expected
Female/ 18-24 years/ Dose 1/ BCC 1-3	42	1.2	255840	0	0.35	0 (0 - 10.54)	Observed < expected
Female/ 25-44 years/ Dose 1/ BCC 1-3	42	2.6	2310305	3	6.91	0.72 (0.23 - 1.69)	Observed < expected
Female/ 45-64 years/ Dose 1/ BCC 1-3	42	1.9	5537396	1	12.1	0.08 (0 - 0.46)	Observed significantly < expected
Female/ 65 years +/ Dose 1/ BCC 1-3	42	0.8	3610734	0	3.32	0 (0 - 1.11)	Observed < expected
Female/ Overall/ Dose 1/ BCC 1-3	42	1.6	11714377	4	21.55	0.28 (0.1 - 0.61)	Observed significantly < expected
Female/ 18-24 years/ Dose 2	42	1.2	245605	0	0.34	0 (0 - 10.85)	Observed < expected

Table 65 Observed versus expected analyses stratified by Dose number, age and gender, BCC in UK

Gender /Age group / Dose #	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female/ 25-44 years/ Dose 2	42	2.6	2230888	3	6.67	0.45 (0.09 - 1.31)	Observed < expected
Female/ 45-64 years/ Dose 2	42	1.9	5446094	3	11.9	0.34 (0.09 - 0.86)	Observed significantly < expected
Female/ 65 years +/ Dose 2	42	0.8	3577761	1	3.29	1.22 (0.33 - 3.11)	Observed > expected
Female/ Overall/ Dose 2	42	1.6	11500418	7	21.16	0.52 (0.26 - 0.93)	Observed significantly < expected
Female/ 18-24 years/ Dose 2/ BCC 1-3	42	1.2	245554	0	0.34	0 (0 - 10.85)	Observed < expected
Female/ 25-44 years/ Dose 2 / BCC 1-3	42	2.6	255840	1	0.35	0 (0 - 10.54)	Observed < expected
Female/ 45-64 years/ Dose 2 / BCC 1-3	42	1.9	2310305	0	6.91	0.14 (0 - 0.81)	Observed significantly < expected
Female/ 65 years +/ Dose 2 / BCC 1-3	42	0.8	5537396	0	12.1	0 (0 - 0.3)	Observed significantly < expected
Female/ Overall/ Dose 2 / BCC 1-3	42	1.6	3610734	1	3.32	0 (0 - 1.11)	Observed < expected

BCC, Brighton collaboration criteria; CI, Confidence Interval; E Expected; O Observed TTO: Time to onset; UK United Kingdom; Unk, Unknown.

Observed versus expected analyses stratified by Dose number, age and gender, BCC in the UK, using UK IRs from Willame et al 2021 (B), ie, ADVANCED Europe, are presented in Table 66. The observed numbers are presented both including and excluding cases with an

unknown time to onset and stratified by cases fulfilling Brighton collaboration criteria levels 1-3 (BCC 1-3).

Table 66 Observed versus expected analysis, stratified by Dose, age, BCC in the UK

Age Group/Dose	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
18-24 years/ Dose 1	42	0.64	444578	1	0.33	6.06 (0.73 - 21.89)	Observed > expected
25-44 years/ Dose 1	42	1.36	4291068	18	6.71	3.87 (2.53 - 5.68)	Observed significantly > expected
45-64 years/ Dose 1	42	1.23	11528448	22	16.31	2.08 (1.44 - 2.91)	Observed significantly > expected
65 Years + Dose 1	42	0.76	6737698	19	5.89	4.92 (3.3 - 7.07)	Observed significantly > expected
Overall/ Dose 1	42	0.97	24725401	60	27.58	3.3 (2.66 - 4.05)	Observed significantly > expected
18-24 years/ Dose 1/ BCC 1-3	42	0.64	444578	0	0.33	0 (0 - 11.18)	Observed < expected
25-44 years/ Dose 1/ BCC1-3	42	1.36	4291068	3	6.71	0.75 (0.24 - 1.74)	Observed < expected
45-64 years/ Dose 1/ BCC 1-3	42	1.23	11528448	6	16.31	0.43 (0.17 - 0.88)	Observed significantly < expected
65 years +/ Dose 1/ BCC 1-3	42	0.76	6737698	0	5.89	0 (0 - 0.63)	Observed significantly < expected

Table 66 Observed versus expected analysis, stratified by Dose, age, BCC in the UK

Age Group/Dose	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Overall/ Dose 1/ BCC-1-3	42	0.97	24725401	9	27.58	0.44 (0.22 - 0.76)	Observed significantly < expected
18- 24 years/ Dose 2	42	0.64	426111	0	0.31	0 (0 - 11.9)	Observed < expected
25- 44 years/ Dose 2	42	1.36	4140925	3	6.48	0.46 (0.1 - 1.35)	Observed < expected
45- 64 years/ Dose 2	42	1.23	11328542	8	16.02	0.62 (0.3 - 1.15)	Observed < expected
65 years +/ Dose 2	42	0.76	6679268	4	5.84	1.2 (0.48 - 2.47)	Observed > expected
Overall/ Dose 2	42	0.97	24141350	15	26.93	0.74 (0.45 - 1.15)	Observed < expected
18- 24 years/ Dose 2/ BCC 1-3	42	0.64	426111	0	0.31	0 (0 - 11.9)	Observed < expected
25- 44 years/ Dose 2/ BCC 1-3	42	1.36	4140925	1	6.48	0.15 (0 - 0.86)	Observed significantly < expected
45- 64 years/ Dose 2/ BCC 1-3	42	1.23	11328542	1	16.02	0.06 (0 - 0.35)	Observed significantly < expected
65 years +/ Dose 2/ BCC 1-3	42	0.76	6679268	1	5.84	0.17 (0 - 0.95)	Observed significantly < expected
Overall/ Dose 2/ BCC 1-3	42	0.97	24141350	3	26.93	0.11 (0.02 - 0.33)	Observed significantly < expected

BCC, Brighton collaboration classification criteria; CI, Confidence Interval; E Expected; EEA, European Economic Area O Observed TTO: Time to onset; Unk, Unknown; UK United Kingdom.

Observed vs expected analysis summary:

When the observed versus expected analysis is carried out overall for global reports for all ages and genders, the number of observed cases is significantly less than expected for all stratifications provided.

When stratified by age only in the UK using the ADVANCE EUROPE rates, observed cases are significantly more than expected for age groups 25-44 years regardless of whether cases with an unknown time to onset are included or not. For the age group 18-24 years, observed cases are more than expected, however the disproportionality was significant when cases with unknown TTO are included. For the age group 45-64 years observed cases are less than expected when cases with an unknown TTO are not included. For the older age group (65+) observed cases are significantly more than expected when cases with an unknown TTO are not included as well as when cases with an unknown TTO are included. When the cases without an unknown TTO are included for all age groups, observed cases are more than expected with a significant disproportionality.

When only cases of TM fulfilling BCC levels 1-3 are included, observed cases are significantly less than/less than expected for all stratifications.

The observed cases for females in the UK using the rate from UKTHIN are more than expected. When stratified by age and gender, observed cases for females were greater than expected in all the age groups except for 45-64 years, without the result being significant. In the 65+ years group, observed cases were significantly more than expected. Observed cases were significantly more than expected for females overall when rate from UKTHIN and when cases with unknown TTO were included. Observed cases were more than expected, with a significant disproportionality in the 25-44 and 65+ year groups when cases with unknown TTO are included and were more than expected, without a significant disproportionality in the 18-24 and the 45-64 year groups.

When only cases fulfilling BCC levels 1-3 are included, observed cases are either less or significantly less than expected for all age stratifications (result is not significant for the youngest age group, 18-24 years, however, there are no observed cases with BCC 1-3 in that age group).

When stratified by age and gender, the observed cases for males are significantly more than expected for males overall when cases with and without an unknown TTO are included. When the UKTHIN rates are used, the 18-24 years group and the 25-44 years group have observed cases more than expected. Observed cases were significantly more than expected in the older

(65+) age group. When cases with unknown TTO were included, however, all age groups had observed higher than expected with or without a significant disproportionality.

When males are stratified by BCC levels 1-3, observed cases were less/significantly less than expected in all age groups, regardless of whether unknown TTO was included.

Cases were also stratified by dose. For Dose 1 Overall, the observed cases were significantly less than expected. When Dose 1 cases in males were stratified using UK THIN BG rates, the cases were either more or less than expected in all age stratifications, with the exception of the older (65+) age group in which there was a significant disproportionality. Overall, the observed number of cases was significantly more than expected (26 cases to 14.28). Cases fulfilling BCC 1-3 criteria showed observed cases were significantly less than expected in males overall. For the other age groups observed cases were less than expected.

Cases in female patients after dose 1 stratified using the same UK THIN BG rates had a significant disproportionality in the older age group (65+) and was significantly more than expected overall. When the cases were stratified by BCC 1-3, the observed cases were significantly less than expected (overall in females and in the 45-64 years age group).

When stratified by age only in UK using the ADVANCE EUROPE rates, the observed cases were more than expected or significantly greater expected in all age groups with Dose 1. However, when stratified by cases fulfilling BCC 1-3, observed cases were significantly less than/less than expected.

For Dose 2, overall, the observed cases were significantly less than expected with and without unknown TTO cases and the same when stratified by BCC 1-3. With the UK THIN BG rates, observed cases were overall significantly less than expected in males and females after dose 2. This was also significantly less than observed for cases stratified by dose, age and BCC in the UK using ADVANCE EUROPE rates.

Relevant Literature in the reporting period

During the reporting period of the PBRER, two relevant articles have been identified and reviewed further. The review of articles Francis et al 2023 and Samim et al 2023 have been presented in section 16.3.1.2.

Summary

The pathogenesis TM is thought to be immune-mediated from infection, para-infectious processes, autoimmune disease, or paraneoplastic processes. The exact mechanism of TM following immunization is unknown.

There were 23 cases of TM (fulfilling at least BCC 1-3 criteria) received during the reporting period, of these, 19 were assessed to be classified as “Possible” according to WHO-UMC causality criteria (as either “Possible” with limited information/ “Possible” with confounders). Twelve of the 15 cases were classified as “Possible” with Limited Information based solely on the TTO parameter (reasonable TTO considered) as there was insufficient case information (such as vaccinees’ medical history, comorbidities, concomitant medications, etiological work-up etc). For the remaining 7 cases the event could also be explained by the vaccinees’ diseases or other medications.

In addition, an observed versus expected analysis of cumulative cases meeting Brighton collaboration criteria levels 1-3 showed that the observed number of TM cases fulfilling case definition are either less than or significantly less than the number of expected cases in all risk windows.

Conclusion

The information from this periodic review found insufficient evidence for a new or emerging signal regarding TM and VAXZEVRIA. No changes to the CDS or RMP are recommended for TM at this time. As such, the topic will continue to be closely monitored as part of AstraZeneca’s ongoing surveillance efforts for the important potential risk of immune mediated neurological conditions.

16.3.1.2.3 Acute disseminated encephalomyelitis (ADEM)

A search of the AstraZeneca global safety database was conducted for AE reports of ADEM using the PT ‘ADEM’ as per MedDRA Version 26.1, in association with the use of VAXZEVRIA.

Based on the search 22 reports were received during the reporting interval (11 Initial and 11 FU). Most of the cases were from following countries (≥ 1): India (11), UK (5) and Brazil and Germany (2, each). Further analysis in this report is focused on the interval report.

Cumulatively, till 28 December 2023, a total of 98 events of ‘ADE’ in 98 case reports was received. On review 07 case reports ([REDACTED]

[REDACTED]) were identified to be potential duplicates and have been excluded from further analysis. In total 91 unique ADEM cases were reported cumulatively.

All the 22 ADEM case reports received in the reporting period of the PBRER were reported as serious and they were MC. Most of the case reports (86.4%) were from literature source. Thirteen cases were reported in female vaccinees, 8 in male vaccines and in one case gender was not reported. Age was reported in 21 cases, and it ranges between 23-61 years (median

49 years). Time to onset was reported in 14 cases (64%) and in all these cases the event was reported within the risk window of 2-42 days (median 13 days; range 5-35 days). Most of the cases (91%; 20/22) were reported after Dose 1 of vaccination and 2 cases (9%) after Dose 2.

The most commonly co-reported PTs in ADEM cases were (≥ 1): Headache (3), Neurological decompensation, Arthralgia, Myelitis transverse, Back pain, Vith nerve paralysis, Encephalitis and Musculoskeletal stiffness (2, each) and the and the remaining AEs were singularly reported.

Events with fatal outcome

During the reporting period of the PBRER, 4 out of 22 cases (18%) cases were reported with a fatal outcome (2 initial, 2 follow-up, no information updated on fatal event). All the events were MC. The assessment of the fatal case reports identified in reporting period is presented below.

[REDACTED]: Report received as an abstract from a conference concerning a 59 year-old male patient who presented with progressive, symmetrical, and ascending loss of strength in the lower limbs (with 3 days of evolution), on the fifth day post VAXZEVRIA vaccination (unspecified dose number). Any medical history of diabetes, systemic arterial hypertension, alcohol consumption or smoking was denied. On clinical examination, the patient was observed to have grade 0 in the lower limbs, areflexia in the lower limbs and decrease of superficial and deep sensitivity in the lower limbs. Initially, the patient was admitted to the ICU, staying for 11 days for investigation for Guillain-Barre Syndrome and for pulse therapy with methylprednisolone 1000 mg intravenous (IV) for 5 days, but without improvement of symptoms. At a different tertiary centre, persistence of the previous findings, in addition to the presence of horizontal choreic movements of the head, intention tremor in the UL, significant dysmetria, worse on the left, nystagmus and without alteration of cranial nerves, was identified. During hospitalization, two biochemical evaluations of CSF were performed, but with unspecific results.

As reported, the patient evolved with complications of cutaneous, urinary and pulmonary infections and died of sepsis after 110 days of hospitalization. It was also reported that the patient experienced TM, ADEM, and cerebellar syndrome. The authors further comment on presenting a case of a possible and rare correlation between the AstraZeneca vaccine for COVID-19 and ADEM.

AstraZeneca comment: The case has been conservatively assessed as ADEM BCC3 based on clinical features, however GBS is differential diagnosis. No information on nerve conduction abnormalities, or treatment with immunoglobulins. Due to absent information on investigations, a comprehensive diagnostic certainty was not possible. The short time to onset of neurological symptoms on the second day post VAXZEVRIA is considered improbable.

Moreover, there was insufficient information on vaccination dose number, neurological medical history, concomitant medications, details of investigations and etiological work-up such as neoplasm, trauma, infection or vascular disorder. Development of Sepsis post treatment can possibly be attributed to methylprednisolone therapy, and this could be a possible confounder for the fatality.

Report from a literature source in Germany concerning a 61-year-old male with a history of hypothyroidism, polymyalgia rheumatica and suspected Monoclonal Gammopathy of Undetermined Significance (MGUS) who developed fever, headache and apathy 2 days after the first shot of the ChAdOx1 nCoV-19 vaccine. Two days later, he was discovered by [REDACTED] unconscious in [REDACTED]. Upon arrival of the emergency doctor, he exhibited a generalized seizure, was subsequently comatose and underwent endotracheal intubation. A head computed tomography (CT) scan including CT-angiography revealed diffuse hypodense areas in the right subcortical frontotemporal and the right thalamic region. There were no signs of vessel occlusions, especially no sinus vein thrombosis. Magnetic resonance imaging in revealed bilateral confluent cortical and subcortical FLAIR hyperintense lesions with hemorrhagic involvement of the basal ganglia. A repeat MRI about two months post clinical onset showed Diffuse hemorrhagic leukoencephalopathy on both sides, similar in distribution to a previous diagnosis. CSF examination revealed normal cell counts and moderate disturbance of the blood-brain-barrier [CSF/serum quotient for albumin of 22.8 units, age-adjusted upper reference limit 10.2 units]. No CSF-specific OCB or intrathecal IgG/-A/-M-synthesis were detected, while flow cytometry analysis revealed normal CSF cell subsets (64% CD4+ T cells, 19% CD8+ T cells, 7% CD14+ monocytes, 0.7% CD19+ B cells, and 4% CD56+ Natural killer (NK) cells as portions of CD45+ cells in the CSF). Laboratory testing for bacterial and viral infectious agents of CNS via serology (in serum) and PCR (CSF and/or serum) remained negative, including testing for Human immunodeficiency virus (HIV), *Borrelia burgdorferi*, *Treponema pallidum*, HSV, John Cunningham virus, tick-borne encephalitis virus, Epstein-Barr virus, measles, mumps, rubella West Nile/ lymphocytic choriomeningitis- / varicella-zoster virus and SARS-CoV-2 repeatedly via RT-PCR from nasopharyngeal swabs. Screening for ANA, ANCA, antiphospholipid antibodies, neuronal and paraneoplastic antibodies, aquaporin-4 (AQP4) or MOG in cell-based assays (CBA) were negative. Considering an autoimmune acute longitudinal extensive transverse and hemorrhagic myelitis (spinal variant of acute hemorrhagic encephalomyelitis [AHEM]), the patient was administered high dose steroid treatment (1 g methylprednisolone intravenously per day) over 5 days, followed by seven plasma exchange sessions with concomitant methylprednisolone administration (250 mg per day via nasogastric tube on days of plasma exchange, 100 mg per day via nasogastric tube on days between plasma exchanges, followed by tapering beginning with 100 mg orally per day and subtraction of 20 mg every 2 days), upon which there was slight improvement of alertness and reduction in size of the brain lesions in FU MRI already after 5 days. On clinical FU after 14 weeks of rehabilitation, the patient presented with a vegetative state.

The clinical course worsened over the period of one year with the patient experiencing infections (Haemophilus influenza, Klebsiella pneumoniae, Staphylococcus epidermidis, COVID-19) and septic shock with the symptoms of aspiration pneumonia, septic acute renal insufficiency, sudden stiffness in the body, in which all muscles became extremely tense, discrete increase in inflammatory values, increase in triglycerides (169 mg/dl) with Low-Density Lipoprotein (LDL) elevation (123 mg/dl) and High-Density Lipoprotein (HDL) reduction (35 mg/dl). The patient died from the event of acute haemorrhagic encephalomyelitis and protracted coma after about 14 months.

AstraZeneca comment: The short time to onset of neurological symptoms post VAXZEVRIA dose 1 is considered less likely, considering known ADEM etiopathogenesis. Infectious work-up was reasonable and negative. Screening for ANA, ANCA, antiphospholipid antibodies, neuronal and paraneoplastic antibodies were negative. AQP4 or MOG antibodies were negative. However, the clinico-radiological features of symmetrical lesions, chronic course over a year without evidence of monophasic course and insufficient response to immunosuppression could also point to alternate causes for encephalopathy, especially in the backdrop of polymyalgia rheumatica, hypothyroidism, suspected MGUS which could confound the onset and clinical course. No information on autopsy was provided. The WHO-UMC causality for ADEM occurrence was assessed as Possible with confounder. The fatality was confounded by infections during protracted comatose state.

[REDACTED]: The literature case was received as part of prospective case series of de novo CNS demyelination occurring within 6 weeks post COVID-19 vaccination, from two specialized neurology tertiary care centres in UK.

A patient (unspecified gender and age) with cerebral palsy presented with rapidly progressive paraparesis and brainstem signs and died on day 25 after receiving IV methylprednisolone and plasma exchange. MRI showed LETM and widespread ADEM-like lesions. Both AQP4 and MOG antibodies were negative on in-house live cell-based assays. Post-mortem studies confirmed multifocal areas of demyelination associated with foamy macrophages, consistent with ADEM.

AstraZeneca comment: Based on post-mortem confirmation, the diagnostic certainty of ADEM is considered BCC1. The time to onset is suggested within 6 weeks though exact time to onset is unknown. There was insufficient information on patient demographics, cause for underlying cerebral palsy, etiological work-up (infectious, autoimmune, paraneoplastic). Autopsy details were only limited to diagnostic confirmation with no information on exploration for etiological causes or other pathologic findings. The WHO-UMC causality is considered Possible based on temporal relationship only, with limited information (as described above) precluding a comprehensive causal assessment.

[REDACTED]: This literature case was received as part of retrospective analysis of medical records of all patients from a tertiary care hospital in India. This case refers to a 54-year-old female patient reporting presented with a progressive quadriparesis followed by altered sensorium. Examination finding revealed drowsiness, bilateral UL flexion posturing, quadriparesis with 2/5 power in UL and 0/5 power in lower limbs (LL). Investigations of cerebrospinal fluid (CSF) showed 8 cells lymphocytic predominant, protein (P) was 77 mg/dl, glucose (G) was 98 mg/dl, ANA, ANCA and C -reactive protein (CRP) were negative, Serum NMO MOG were negative and MRI brain showed T2/ FLAIR (T2 weighted/ Fluid- attenuated inversion recovery) hyperintensities in the corpus callosum, bilateral periventricular and subcortical white matter, infratentorial region with patchy contrast enhancement. Patient was diagnosed with ADEM (preferred term: Acute disseminated encephalomyelitis) with tumefactive demyelinating lesions remained critically ill, requiring invasive ventilation and died after a prolonged ICU stay and superimposed infection. Patient was treated with methylprednisolone, intravenous immunoglobulin (Iv Ig) and prednisolone tablet. Due to superinfection, she was could not be treated with rituximab or other immunosuppressants. Inadequate improvement with immunomodulation and the superimposed infection might have contributed to the severe illness and fatality in this patient.

AstraZeneca comment:

Tumefactive demyelination in the backdrop of concomitant infection and sepsis which might explain the clinical picture and subsequent death the case does not fit diagnostic criteria for ADEM per the Brighton Criteria. Insufficient information on neurological medical history, infectious workup both prior and after the onset of the event. The WHO-UMC causality is considered Possible based on temporal relationship only, with limited information (as described above) precluding a comprehensive causal assessment.

Recurrence case reports

There were no cases identified for ADEM after Dose 1, with a recurrence or worsening of ADEM with the Dose 2/Dose 3 of vaccination indicating potential recurrence/positive rechallenge.

WHO -UMC causality and BCC Assessment

The BCC (Law B 2021 [B]) was used for the case level of certainty (LOC) assessment based on the data available in the cases. The strongest level of certainty was 1, with levels of certainty 2 and 3 being less strong. Level of certainty 4 was reached for cases where the diagnosis was named but not supported with history, clinical findings, clinical course or diagnostic tests. Level of certainty 5 was the designation for cases where another diagnosis was noted. Based on this approach, of the 22 cases, 4 cases fulfilled level 1 criteria, 7 cases fulfilled level 2 criteria, 2 cases fulfilled level 3 criteria, 1 case fulfilled level 4 criteria, and 7

cases fulfilled level 5 criteria. In addition to the BCC, the published Brighton Case Definition for ADEM (Law B 2021 [A]) was also referenced during the review of the cases for the assessment of evidence related to associated risk factors (eg, malignancy, infections, use of vaccines, or surgery).

The recommended risk window (RW) for ADEM as a vaccine -related reaction (Rowhani-Rahbara et al 2012) as cited in Law B 2021 [B] for inactivated or subunit vaccines is 2 to 42 days. Causality assessment of all cases (or cases fulfilling BCC 1 to 5 - based on the topic and approach) was performed using WHO- UMC causality assessment criteria with a risk window of 2 to 42 days.

The BCC and WHO-UMC causality assessment performed for these cases is provided in the following Table 67.

Table 67 Overview of BCC and WHO-UMC Causality Assessments / for case reports of ADEM with VAXZEVRIA in the reporting interval

WHO-UMC/BCC Level	Level 1	Level 2	Level 3	Level 4	Level 5	Grand Total
Certain	0	0	0	0	0	0
Probable/Likely	0	0	0	0	0	0
Possible with risk factors/confounders*	0	1	0	0	1	2
Possible with limited information	4	7	2	1	5	19
Unassessable/Unclassifiable with limited information	0	0	0	0	0	0
Unassessable/Unclassifiable with risk factors/confounders*	0	0	0	0	1	1
Unassessable/ Unclassifiable with confounders	0	0	0	0	0	0
Unlikely	0	0	0	0	0	0
Conditional /Unclassified	0	0	0	0	0	0
Grand Total	4	8	2	1	7	22

ADEM Acute Disseminated Encephalomyelitis; BCC Brighton Collaboration Criteria; WHO-UMC World Health Organization-Uppsala Monitoring Centre

Cases were considered to have “risk factors/confounders” where the event could also be explained by the vaccinee’s diseases, or where relevant risk factors were present, or concomitant medications that could potentially contribute to the development of the event were reported.

Brighton Collaboration Criteria Level 1

Out of the 22 cases, 4 cases (3 initial version, 1 FU version) fulfilled BCC level 1 according to classification by clinical course, examination features, and/or level of certainty. Of the 4 cases, 1 case were reported in a male vaccinee, 2 in female vaccinees and in other case the gender was unknown. The age of the vaccinees was reported in 3 cases and it ranged between 27-

45 years (median 49 years). In all four cases, the event occurred after Days 1 of vaccine and the TTO of event was reported in three cases (range 11-15 days; median-13 days). The outcome in one case [REDACTED] was fatal, in this case has limited information on medical history, concomitant medication, detailed diagnostic, and etiologic workup prior fatal outcome (complete blood panel, lumbar puncture) and further risk factors. The remaining 3 cases were also assessed as “Possible” with limited information as per the WHO UMC causality assessment criteria (regarding medical history, or patient demographics, cause for underlying cerebral palsy, etiological work-up (infectious, autoimmune, paraneoplastic).

Brighton Collaboration Criteria Level 2

Eight of the 22 cases fulfilled BCC level 2. The cases fulfilled this classification by clinical course, examination features, and confirmatory tests. Six cases were reported in female vaccinees and 2 were reported in male vaccinees. The age range was 25 to 60 years (median 44 years). In 7 cases event occurred after Dose 1 of vaccine and in one case post Dose 2 of vaccination. The TTO of event was available in 5 cases (range 5 -35 Days; median 12 Days). The outcome was unknown in 2 cases, not recovered in 1 case and recovering in 5 cases. Out of the 8 cases fulfilling BCC level 2, 7 cases were assessed as ‘Possible with limited information’ (regarding medical history or comorbidities, or investigations) and 1 case was confounded by medical history of progressive paraparesis.

Brighton Collaboration Criteria Level 3

Two of the 22 cases fulfilled BCC level 3. The cases fulfilled this classification by clinical course, examination features, and confirmatory tests. One case was reported in female vaccinees and 01 were reported in male vaccinees. The age range was 23 to 59 years with mean and median of 41 years and 41 years, respectively. The TTO ranged between the 05 day to 24 Days and the median TTO was 14.6 Days. One case [REDACTED] had a fatal outcome. The outcome was unknown in 01 case. These cases occurred after the 1st dose, and they occurred within the risk window of 2 to 42 Days. These 02 cases were assessed as “Possible with limited information” per the WHO-UMC causality assessment criteria.

Brighton Collaboration Criteria Level 4

One of the 22 cases fulfilled BCC level 4. This case did not fulfil criteria for a level 3, 2 or 1 certainty as there was insufficient information (pertaining to exclusion of alternate diagnosis for illnesses such as neoplasm, vascular disorder, infection, and toxic/ metabolic encephalopathy) to confirm the diagnosis or medical assessment of the case as ADEM. This case was assessed as possible with limited information as per the WHO-UMC causality assessment criteria.

Brighton Collaboration Criteria Level 5

Seven of the 22 cases fulfilled BCC level 5. Five cases were assessed as possible with limited information, 1 were assessed as possible with risk factors/confounders, 1 were assessed as unassessable/unclassifiable with confounders as per the WHO-UMC causality assessment criteria. On review of the global safety database, no specific trend with respect to MOG antibody positive status ADEM in individuals vaccinated with VAXZEVRIA was seen.

Observed Versus Expected (O/E) Analyses

An O/E analysis of 'ADEM' was conducted cumulatively to 28 December 2023. The results were stratified by 3 risk windows (14, 30 and 42 days) for all global reports, stratified by age in the European Union (EU) UK, Brazil, and Australia, and by age and gender. The risk window of 2 to 42 days was included from the Brighton case definition (Law B 2021 [B]). In order to provide an accurate IR for this rare event, a meta-analysis using random-effect model was performed based on data from years 2017 to 2019 from databases (ES_BIFAP_PC, ES_BIFAP_PCHOSP, ES_FISABIO, ES_SIDIAP_PC (Spain Information System for the Development of Research in Primary Care), ES_SIDIAP_PCHOSP, and IT_ARS, UK_CPRD) presented in the revised ACCESS protocol Willame et al 2021 (A).

The O/E analysis for the cumulative cases of 'Acute disseminated encephalomyelitis' with risk windows 14, 30, and 42 Days is presented with results in Table 68. Conservatively, the exposure for global reports (470543084) is based on doses administered in 13 markets.

Table 68 Observed Versus Expected Analysis for all Reports of ADEM (Global Reports)

Adverse Events	Risk Window (Days)	BG Rates/ 100,000 PY	Exposure	Observed Number of Cases	Expected Number of Cases	O Over E Ratio (95% CI)	Conclusion
Overall (global) ACCESS IR ADEM	14	0.15	470543084	46	27.05	1.7 (1.25 - 2.27)	Observed significantly > expected
	30	0.15	470543084	56	57.97	0.97 (0.73 - 1.25)	Observed < expected
	42	0.15	470543084	58	81.16	0.71 (0.54 - 0.92)	Observed significantly < expected
Overall (global) ACCESS IR including cases with an unknown time to onset	14	0.15	470543084	69	27.05	2.55 (1.98 - 3.23)	Observed significantly > expected
	30	0.15	470543084	79	57.97	1.36 (1.08 - 1.7)	Observed significantly > expected
	42	0.15	470543084	81	81.16	1 (0.79 - 1.24)	Observed < expected

IR = 0.15/100,000 person years.

ADEM-acute disseminated encephalomyelitis; CI-confidence interval; E-expected; IR-incidence rate; O-Observed; PY-patient years.

Source:

Willame et al 2021 (A) (Meta-analysis IR from 2017-2019 ADEM-Narrow).

Table 69 Observed Versus Expected Analysis for Cases for ADEM Meeting BCC Level 1, 2 or 3 (Global Reports)

Adverse Events	Risk Window (Days)	BG Rates/ 100,000 PY	Exposure	Observed Number of Cases	Expected Number of Cases	O Over E Ratio (95% CI)	Conclusion
Overall (global) ACCESS IR ADEM BCC levels 1 to 3	14	0.15	470543084	22	27.05	0.81 (0.51 - 1.23)	Observed < expected

Adverse Events	Risk Window (Days)	BG Rates/100,000 PY	Exposure	Observed Number of Cases	Expected Number of Cases	O Over E Ratio (95% CI)	Conclusion
	30	0.15	470543084	29	57.97	0.5 (0.34 - 0.72)	Observed significantly < expected
	42	0.15	470543084	30	81.16	0.37 (0.25 - 0.53)	Observed significantly < expected
Overall (global) ACCESS IR ADEM BCC levels 1 to 3 including cases with an unknown TTO	14	0.15	470543084	28	27.05	1.04 (0.69 - 1.5)	Observed > expected
	30	0.15	470543084	35	57.97	0.6 (0.42 - 0.84)	Observed significantly < expected
	42	0.15	470543084	36	81.16	0.44 (0.31 - 0.61)	Observed significantly < expected

ADEM Acute Disseminated Encephalomyelitis; BCC Brighton Collaboration Criteria; CI Confidence Interval; E Expected PY Patient Years; O Observed; TTO Time To Onset

Table 70 Observed Versus Expected Analysis for ADEM Cases Stratified by Age for EU, UK, Brazil, and Australia Regions

Age group	Risk Window (Days)	IR ^a / 100,000 PY	Exposure ^b	Observed Number of Cases	Expected Number of Cases	O Over E Ratio (95% CI)	Conclusion
Age 18 to 49	14	0.15	110783127	17	6.37	2.67 (1.55 - 4.27)	Observed significantly > expected
	30	0.15	110783127	19	13.65	1.39 (0.84 - 2.17)	Observed > expected
	42	0.15	110783127	19	19.11	0.99 (0.6 - 1.55)	Observed < expected
Age 50 to 59	14	0.07	57255811	9	1.54	5.84 (2.67 - 11.09)	Observed significantly > expected
	30	0.07	57255811	10	3.29	3.04 (1.46 - 5.59)	Observed significantly > expected
	42	0.07	57255811	10	4.61	2.17 (1.04 - 3.99)	Observed significantly > expected
Age 60 to 69	14	0.16	56132187	6	3.44	1.74 (0.64 - 3.8)	Observed > expected
	30	0.16	56132187	7	7.38	0.95 (0.38 - 1.95)	Observed < expected
	42	0.16	56132187	7	10.33	0.68 (0.27 - 1.4)	Observed < expected
Age over 70	14	0.08	35352819	3	1.08	2.78 (0.57 - 8.12)	Observed > expected
	30	0.08	35352819	4	2.32	1.72 (0.47 - 4.41)	Observed > expected
	42	0.08	35352819	5	3.25	1.54 (0.5 - 3.59)	Observed > expected

^a Source Willame et al 2021 (A) (Meta-analysis estimates of ACCESS from 2017-2019 ADEM-Narrow)

^b Exposure till 28 December 2022.

ADEM Acute disseminated encephalomyelitis; AE Adverse Event; CI Confidence Interval; E Expected; EEA European Economic Area IR Incidence Rate; O Observed; PY Patient Years, TTO Time to Onset; UK United Kingdom

Table 71 **Observed Versus Expected Analysis for ADEM Cases Meeting BCC Level 1, 2 or 3 and Stratified by Age for EU, UK, Brazil, and Australia Regions**

Age group BCC Level	Risk Window (Days)	IR ^a / 100,000 PY	Exposure ^b	Observed Number of Cases	Expected Number of Cases	O Over E Ratio (95% CI)	Conclusion
Age 18 to 49 ADEM BCC levels 1 to 3	14	0.15	110783127	7	6.37	1.1 (0.44 - 2.26)	Observed > expected
	30	0.15	110783127	8	13.65	0.59 (0.25 - 1.15)	Observed < expected
	42	0.15	110783127	8	19.11	0.42 (0.18 - 0.82)	Observed significantly < expected
Age 50 to 59 ADEM BCC levels 1 to 3	14	0.07	57255811	5	1.54	3.25 (1.05 - 7.58)	Observed significantly > expected
	30	0.07	57255811	5	3.29	1.52 (0.49 - 3.55)	Observed > expected
	42	0.07	57255811	5	4.61	1.08 (0.35 - 2.53)	Observed > expected
Age 60 to 69 ADEM BCC levels 1 to 3	14	0.16	56132187	2	3.44	0.58 (0.07 - 2.1)	Observed < expected
	30	0.16	56132187	3	7.38	0.41 (0.08 - 1.19)	Observed < expected
	42	0.16	56132187	3	10.33	0.29 (0.06 - 0.85)	Observed significantly < expected
Age over 70 ADEM BCC levels 1 to 3	14	0.08	35352819	0	1.08	0 (0 - 3.42)	Observed < expected
	30	0.08	35352819	0	2.32	0 (0 - 1.59)	Observed < expected
	42	0.08	35352819	0	3.25	0 (0 - 1.14)	Observed < expected

^a Willame et al 2021 (A) (Meta-analysis estimates of ACCESS from 2017-2019 ADEM-Narrow).

^b Exposure till 28 December 2022.

ADEM- Acute disseminated encephalomyelitis; AE-Adverse Events; CI Confidence Interval; E Expected; EEA-European Economic Area IR Incidence Rate; O-Observed; PY-Patient Years, TTO-Time to Onset; UK-United Kingdom

Table 72 An O/E analysis of cases meeting case definition according to BCC Level 1, 2 or 3 stratified by age and gender for UK is presented.

Age group BCC Level Sex	Risk Window (Days)	IR ^a / 100,000 PY	Exposure ^b	Observed Number of Cases	Expected Number of Cases ^a	O Over E Ratio (95% CI)	Conclusion
Age 18 to 49 (BCC 1 to 3) Female	14	0.07	7414701	2	0.2	10 (1.21 - 36.12)	Observed significantly > expected
	30	0.07	7414701	2	0.43	4.65 (0.56 - 16.8)	Observed > expected
	42	0.07	7414701	2	0.6	3.33 (0.4 - 12.04)	Observed > expected
Age 50 to 59 (BCC 1 to 3) Female	14	0.05	5944683	0	0.11	0 (0 - 33.54)	Observed < expected
	30	0.05	5944683	0	0.24	0 (0 - 15.37)	Observed < expected
	42	0.05	5944683	0	0.34	0 (0 - 10.85)	Observed < expected
Age 60 to 69 (BCC 1 to 3) Female	14	0.12	4783416	0	0.22	0 (0 - 16.77)	Observed < expected
	30	0.12	4783416	0	0.47	0 (0 - 7.85)	Observed < expected
	42	0.12	4783416	0	0.66	0 (0 - 5.59)	Observed < expected
Age 70 to 79 (BCC 1 to 3) Female	14	0.09	3475875	0	0.12	0 (0 - 30.74)	Observed < expected
	30	0.09	3475875	0	0.26	0 (0 - 14.19)	Observed < expected
	42	0.09	3475875	0	0.36	0 (0 - 10.25)	Observed < expected
Age over 80 (BCC 1 to 3) Female	14	0.02	1630324	0	0.01	0 (0 - 368.89)	Observed < expected
	30	0.02	1630324	0	0.03	0 (0 - 122.96)	Observed < expected
	42	0.02	1630324	0	0.04	0 (0 - 92.22)	Observed < expected
Age 18 to 49 (BCC 1 to 3) Male	14	0.21	6766098	0	0.54	0 (0 - 6.83)	Observed < expected
	30	0.21	6766098	0	1.17	0 (0 - 3.15)	Observed < expected
	42	0.21	6766098	0	1.63	0 (0 - 2.26)	Observed < expected
Age 50 to 59 (BCC 1 to 3) Male	14	0.07	6510960	2	0.17	11.76 (1.42 - 42.5)	Observed significantly > expected

Table 72 An O/E analysis of cases meeting case definition according to BCC Level 1, 2 or 3 stratified by age and gender for UK is presented.

Age group BCC Level Sex	Risk Window (Days)	IR ^a / 100,000 PY	Exposure ^b	Observed Number of Cases	Expected Number of Cases ^a	O Over E Ratio (95% CI)	Conclusion
	30	0.07	6510960	2	0.37	5.41 (0.65 - 19.53)	Observed > expected
	42	0.07	6510960	2	0.52	3.85 (0.47 - 13.89)	Observed > expected
Age 60 to 69 (BCC 1 to 3) Male	14	0.12	4934728	0	0.23	0 (0 - 16.04)	Observed < expected
	30	0.12	4934728	0	0.49	0 (0 - 7.53)	Observed < expected
	42	0.12	4934728	0	0.68	0 (0 - 5.42)	Observed < expected
Age 70 to 79 (BCC 1 to 3) Male	14	0.09	3137304	0	0.11	0 (0 - 33.54)	Observed < expected
	30	0.09	3137304	0	0.23	0 (0 - 16.04)	Observed < expected
	42	0.09	3137304	0	0.32	0 (0 - 11.53)	Observed < expected

^a Willame et al 2021 (A) (meta-analysis estimates of ACCESS from 2017-2019 ADEM-Narrow)

^b Exposure until 28 December 2022.

ADEM Acute disseminated encephalomyelitis; BCC-Brighton collaboration criteria; CI Confidence Interval; E Expected; IR Incidence Rate; O-Observed; PY-Patient Years, UK United Kingdom.

The O/E analysis of all cases of ADEM suggested that the observed cases of ADEM cases were less than the number of expected cases in the 30-day risk and the 42-day risk windows, while for the 14-day risk window the analysis suggested that the observed cases of ADEM were significantly more than the number of expected cases. As a conservative approach all cases with time to onset within 0 to 42 Days and all cases with unknown time to onset were included in the O/E analysis. The vaccine exposure by doses administered for O/E analysis were only considered from few countries where the data were available. Eighteen cases were reported with the ADEM onset within 0 to 5 Days of VAXZEVRIA vaccination. A latency of ADEM within 0 to 5 Days of immunization is considered too short and cases less than 5 Days from vaccination would be questionable in any causative association and may be possibly indicative of pre-existing infection or underlying condition. While immunization with the Semple rabies vaccine, which has a proven association with ADEM.

Sejvar et al 2007, Hemachudha et al 1987 [A] has been shown to be associated with a peak interval of 1 to 2 weeks between immunization and onset of ADEM's neurologic symptoms among some vaccine recipients (Hemachudha et al 1987 [B], Leake et al 2004) in an epidemiologic study of 64 ADEM cases also reported 93% of ADEM patients had one or more of the following symptoms or signs of infection within the preceding 21 Days: fever, cough, rhinorrhea; vomiting; or diarrhoea.

Of the 46 cases within 14 Days TTO, there were 18 reports of ADEM reported within the risk window of 0-5 Days; if the 18 reports are excluded the observed cases are less than expected. Also, there is a possibility of reporting bias for increased reporting of cases with a shorter risk window for the passive event reporting of rare diseases.

When cases with unknown TTO were added to the observed numbers, observed cases were significantly more than expected for the 14-day and 30-day risk windows and observed cases were less than expected for the 42-day risk window. However, an O/E analysis of cases meeting BCC levels 1 to 3 showed that the observed number ADEM cases fulfilling case definition were generally less and/or significantly less than number of expected in all risk windows except the 14-day risk window including cases with unknown TTO. Also, there is too much variability in these data to make an assessment.

When O/E analyses are stratified by age in EU, UK, Australia, and Brazil, and different risk windows (14, 30, and 42 Days), numbers of cases become very small resulting in observed as greater than expected for all age groups. The O/E analysis for cases meeting the BCC level 1, 2 or 3 and stratified by age group with different risk windows (14, 30, and 42 Days) suggested that observed cases were less than expected for most age groups. Also, there is too much variability in these data to make an assessment.

When O/E analysis are stratified by age and gender in the UK for cases meeting BCC level 1, 2, or, 3 the observed numbers were significantly greater or greater than expected in females aged 18 to 49 and males aged 50 to 59 in all risk windows. The observed numbers were less than expected in other age and sex stratifications.

Further review of cases in these groups where observed were above expected showed that most cases had insufficient information to make a causality assessment. Of the 86 cases reported cumulatively, only 36 (42%) cases met BCC level 1 to 3.

The O/E analyses provided is based on the most recent and available data, but there is a level of assumption made and any change in the data would impact the results. The following are some of the limitations/assumptions of the data used:

- Doses administered for determination of exposure: Currently only exposure data from certain countries are available, but these countries generate the majority of cases reported to AstraZeneca.
- The BG IR used for the calculation is the same as the population vaccinated: The identification of IRs can vary depending on the source of the data.
- Most of the observed events are spontaneously reported: Spontaneously reported events may only represent a fraction of the events that have actually occurred. Both under-reporting for certain events, and conversely, over-reporting for certain events could have played a role.
- The risk period reflects the period of time an event would occur post-vaccination: Overestimating the risk window would increase the “Person-Years at Risk” period and include events that are outside the actual period of time a true event would occur. Under estimating the risk window will result in reduced sensitivity making it difficult to reach statistical significance.

The O/E analyses does not account for confounding/risk factors which might be present in the cases, such as seasonal effects on the occurrence of certain events, or for example the effect of COVID which may also contribute. Also, when stratified by age/gender, there are small numbers of cases in each stratification, which should be considered when interpreting the significance of the results.

Literature

During the reporting period of the PBRER, three relevant articles have been identified and reviewed further. The review of articles Francis et al 2023 and Samim et al 2023 have been presented in section 16.3.1.2. The remaining article Nabizadeh et al 2023 has been summarized below.

Nabizadeh et al 2023 conducted a comprehensive systematic search using three databases including PubMed, Scopus, and Web of Science. Studies that reported ADEM after COVID-19 vaccination were eligible to include in the study. Observational studies, case reports, and case series which reported cases of ADEM with sufficient detail to confirm clinical diagnosis following COVID-19 vaccination were eligible to be included. Also, studies reported patients with prior history of any demyelinating disease were excluded.

Twenty studies were included in the systematic review after the abstract and full-text screening with a total of 54 cases. Thirty-five of these cases were reported following COVID-19 AstraZeneca, 11 for Pfizer and 2 for Moderna respectively. Among included patients, 45 (85.1 %) developed ADEM after the first dose of the COVID-19 vaccine, and seven (12.9 %)

cases experienced ADEM after the second dose. The median time interval between vaccination and neurological symptoms was 14 days (range - 12 hours to 63 days). Twelve (22.2 %) patients experienced symptoms of muscle weakness, ten (18.5 %) presented unconsciousness, nine (16.6 %) patients had urinary complaints, nine (16.6 %) had visual impairments, and five (9.2 %) experienced a seizure. After treatments, four (13.8 %) patients died. Forty-six patients had clinical improvement (85.1 %), also improvement in brain MRI was observed among 44 (81.4 %) patients.

As per the authors, the AEs of ADEM and ADEM mortality rate (25% vs 13.8%) following SARS-COV-2 infection was higher than that that occurred post-vaccination (Etemadifar et al 2022).

Conclusion

The authors' concluded that it is not clear that ADEM could be a potential complication of COVID-19 vaccination based on the current evidence and further studies are needed. However, this rare condition should not trigger stopping the mass vaccination programs and vaccine hesitancy since the only way to eradicate the current pandemic of COVID-19 is to extend the number of immunized people. Considering the causal and temporal association between SARS-CoV-2 vaccination and the occurrence of ADEM, neurologists must be aware of the serious neurological consequences that may arise after COVID-19 immunization in particular for the ChAdOx1 vaccine and take immediate measures to avoid severe outcomes. Moreover, providing an integrated registry system for gathering detailed information on ADEM cases is highly recommended in order to report the cases in a standardized manner from all over the world.

AstraZeneca comment: This is a systematic review of case reports and may be prone to reporting and publication bias. ADEM being a diagnosis of exclusion, incomplete follow-up durations in most cases may be a limited information for excluding initial onset of common demyelinating disorders with a multiphasic course. Out of the 54 cases, 35 of these cases were reported following COVID-19 AstraZeneca, 11 for Pfizer and 2 for Moderna respectively. However, as there was an unequal distribution of vaccine types in various countries, including introduction of vaccine at different times and to varying BG population, a direct comparison may not be appropriate. For instance, 10 out of 35 cases were received from India where VAXZEVRIA was the most common vaccine, and no mRNA-based vaccine was available (such as more than 75% of the vaccination doses in India comprised COVISHIELD/VAXZEVRIA (<https://dashboard.cowin.gov.in/>). Also, there was no information on reporting rates of the events with respect to respective vaccine exposure precluding direct comparison of AE frequency between the vaccines. In the case series from UK (Francis et al 2023), MOGAD cases were similar to BG frequency with lack of consistency of frequency trends with subsequent VAXZEVRIA doses or in subsequent months (please refer to AstraZeneca comments for 3 in section 16.3.1.2. Immune-mediated neurological conditions). The differential COVID-19 vaccine availability was similarly seen in other countries such as US, China. Also, the VAXZEVRIA ADEM cases were majorly reported from specialized neurology centres in India and UK with insufficient information on

BG rates and can be confounded by referral bias. Exclusion of non-English studies could also possibly influence the reporting bias for vaccine types.

The authors' concluded that it is not clear that ADEM could be a potential complication of COVID-19 vaccination based on the current evidence and further studies are needed. As per Section 4.4 (Special warnings and special precautions for use) of the current CDS regarding neurological events, demyelinating disorders are very rare events reported following vaccination with VAXZEVRIA. A causal relationship has not been established.

Summary

Of the 22 cases of ADEM reported in the period of this report, most of the cases occurred in the age group between 23 and 61 years with no significant difference between the genders. All the cases were MC and serious, 4 cases had a fatal outcome. Most of the cases event occurred with Dose 1 of vaccination (20/22) and in two cases after Dose 2. Fourteen cases that met the Brighton Collaboration level 1-3 were assessed as per WHO-UMC causality assessment criteria. These cases were considered as "Possible" based on the temporal relationship only, with limited information precluding a comprehensive causal assessment.

The O/E analysis of all ADEM cases suggested that overall, the observed numbers were significantly less than the expected numbers in the 42-day risk windows. The observed numbers were greater than expected in a few subgroup stratifications and may be explained by reporting bias for increased reporting of cases with a shorter risk window for the passive event reporting of rare diseases. Review of cases in these subgroups where observed numbers were above expected showed that most cases had insufficient information to make any causality assessment. AstraZeneca does not consider the trend analysis to be suggestive of increased risk due to VAXZEVRIA.

On review of the literatures received in the reporting period of the PBRER, there is insufficient evidence of a causal association or any conclusive mechanism leading to the development of ADEM.

Conclusion

The information from this updated review found insufficient evidence for a new or emerging signal regarding ADEM and VAXZEVRIA. No changes to the CDS or RMP are recommended. The topic 'ADEM' will continue to be closely monitored as part of AstraZeneca's ongoing surveillance activities for the important potential risk of immune-mediated neurological conditions.

16.3.1.2.4 Guillain-Barré Syndrome

The detailed description of the topic is included in Section 15.2.6.

16.3.2 New information on important identified risks

No new information relevant to the previously recognised important identified risks has been identified during the reporting period. Characterisation of the important identified risks is provided in Section 16.4.1.

16.3.2.1 Thrombosis in combination with thrombocytopenia / Thrombosis with thrombocytopenia syndrome

A cumulative search till 28 December 2023 of the AstraZeneca Global Safety Database for Thrombosis in combination with thrombocytopenia with VAXZEVRIA was performed using MedDRA version 26.1.

The search strategy included: A cumulative search of the AstraZeneca safety database for AE reports under the HLT: Thrombocytopenia and SMQ: Hematopoietic Thrombocytopenia Narrow co-reported with events identified from the SMQ: Embolic and thrombotic events with VAXZEVRIA. This search criteria were also applied to retrieve case reports of Thrombosis with thrombocytopenia syndrome (TTS) following both primary dose series and booster doses. Also, cases with a reported PT of TTS or Vaccine-Induced Prothrombotic Immune Thrombocytopenia (VIPIT) or VITT were included, as there is now corresponding PTs in MedDRA version 26.1. Also, cases of CVST from Section (16.3.2.1) with platelet count less than $150 \times 10^9/L$ were included. This covered the period up to 28 December 2023.

The search resulted in a total of 2811 individual cases (cumulative up to 28 December 2023). Of the 2811 cases, 2799 (99.5%) were serious and 12 were non serious, 2016 case reports were MC and 795 were consumer reports, 1795 case reports were from regulatory, 511 from literature sources, 503 from spontaneous, 1 from post-marketing/non-interventional study and 1 from clinical trial.

There were 307 cases reported with thrombosis in combination with thrombocytopenia after Dose 2 (either of VAXZEVRIA or an mRNA vaccine): 305 after an VAXZEVRIA and 2 after an mRNA. These 2 cases are not further discussed here as they do not concern the use of VAXZEVRIA. There were 21 cases occurred after administration of a Dose 3/booster (either of VAXZEVRIA or an mRNA vaccine): 15 after an VAXZEVRIA booster, and 6 after an mRNA booster. The 6 cases after an mRNA booster are not further discussed here as they do not concern the use of VAXZEVRIA as a booster.

During the reporting interval, 317 cases (11.27 % of the total cumulative cases) were reported. Of the 317 case reports, 207 initial reports (183 concerning Dose 1, 21 concerning Dose 2, 1 concerning Dose 2 after an mRNA, 2 concerning Dose 3 after an mRNA). There were 110 FU reports concerning (107 Dose 1, 01 concerning Dose 2 and 02 concerning Dose 3). Further analysis in this report is focused on the cumulative report.

About 32.37 % (910/2811) cases originated from UK and the other cases (≥ 20) were from the following countries: Australia (446), Germany (368), Brazil (186), Italy (146), Canada

(81), France (71), India (69), Spain (63), Netherlands (63), Belgium (43), Austria (29), Poland (25), Taiwan (25), Sweden (24), Norway (22), Finland (20).

Eighteen percent 18.6% (522/2811) of the cases reported fatal outcome and it is similar to previous reporting interval (18%; 482/2644) and October-November, August-September, July, June, May, April, and March SSRs with rates of 17% (332/1987), 17% (310/1809), 18% (267/1503), 18% (245/1375), 19% (210/1095), 22% (150/679) and 27% (49 out of 184), respectively. Fatality/survival rate cumulatively for each month up to 28 December 2023 is presented in Table 81.

Time to onset (TTO) to TTS event was available in 73% (2048/2811) case reports and ranged from 0 day to 649 Days; median time to onset (TTO) was 12 Days. TTO for events within 14, 21 and 42 Days by Dose 1, Dose 2, Dose 3 and fatal reports are presented in Table 73. Overall, there were more fatal reports for TTO within 14 and 21 Days. Seventy-five percent of the fatal report occurred with 14 Days compare to 65% for all cases and 89% of the fatal report occurred with 21 Days compare to 81% for all cases.

Table 73 Time to onset for thrombosis in combination with thrombocytopenia cases

Time to onset available	All cases N (%)	Dose 1 N (%)	Dose 2 N (%)	Dose 3 N (%)	Fatal reports N (%)
	2048(73)	1805(73)	231(76)	10(67)	361(69)
14 days	1336(65)	1200(66)	126(55)	8(80)	272(75)
21 days	1656(81)	1491(83)	154(67)	9(90)	320(89)
42 days	1924(94)	1713(95)	200(87)	9(90)	348(96)

Percentage represents percent of total number of cases each dose and fatal report.

Percentage of fatal reports= number of cases within TTO (in days)/total number of fatal cases (522 cases).

Of the 2811 case reports, the reported venous thrombotic sites included CVST (HLT: Cerebrovascular venous and sinus thrombosis) in 720 (25.61%) cases. Of the 2811 case reports, 128 (5.0%) had the co-reported events from the HLT: Coagulopathies (including 59 cases with DIC) and 959 (34%) case reports had co-reported bleeding event from the narrow SMQ: Haemorrhage terms (excl laboratory terms). The most common (≥ 10) bleeding events included Cerebral haemorrhage (242), Immune thrombocytopenia (ITP) (241), Haemorrhage (77), Haemorrhage intracranial (75), Subarachnoid haemorrhage (70), Contusion (65), Petechiae (63), Disseminated intravascular coagulation (59), Thrombotic thrombocytopenic purpura (TTP) (50), Haematoma (31), Haemorrhagic stroke (28), Haemoptysis (28), Adrenal haemorrhage (23), Cerebral haematoma (22), Epistaxis (17), Subdural haematoma (16), Haemorrhagic transformation stroke (15), Rectal haemorrhage (15), Haemorrhagic infarction (15), Ecchymosis (12), Haematuria (11), Haemorrhagic cerebral infarction (11), Purpura (10), Melaena (10), Gastrointestinal haemorrhage (10).

A total of 403 case reports contained PTs from the SMQ: Embolic and thrombotic events, arterial; 1557 reports contained PTs from the SMQ: Embolic and thrombotic events, vessel

type unspecified and mixed arterial and venous, and 1882 reports contained PTs from the SMQ: Embolic and thrombotic events, venous. One case may contain >1 reported thrombosis event; hence the event count is more than the case count.

There are 633 events in 403 case reports for SMQ: Embolic and thrombotic events, arterial. The most common (≥ 30) arterial Embolic and thrombotic events included Peripheral artery thrombosis (60), Ischaemic stroke (60), TTP (58), Myocardial infarction (44), Acute myocardial infarction (43), Aortic thrombosis (42), Carotid artery thrombosis (42), Arterial thrombosis (36).

There are 2298 events in 1557 case reports for SMQ: Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous. This included most common events (>30) TTS (857), Thrombosis (511), Cerebrovascular accident (110), Hemiparesis (99), Cerebral infarction (82), Embolism (77), Disseminated intravascular coagulation (67), Cerebral thrombosis (66), Heparin-induced thrombocytopenia (HIT) (45), Hemiplegia (36), Haemorrhagic stroke (33).

There are 3166 events in 1882 case reports for SMQ: Embolic and thrombotic events, venous. This included most common events (>30) Pulmonary embolism (901), Cerebral venous sinus thrombosis (577), DVT (542), Portal vein thrombosis (216), Cerebral venous thrombosis (148), Superior sagittal sinus thrombosis (89), Venous thrombosis (70), Mesenteric vein thrombosis (65), Jugular vein thrombosis (57), Splenic vein thrombosis (49), Transverse sinus thrombosis (47), Hepatic vein thrombosis (43), Visceral venous thrombosis (43), Superficial vein thrombosis (35), Pulmonary thrombosis (33), Pelvic venous thrombosis (31)

Reporting Rate

Reporting rate for thrombosis in combination with thrombocytopenia across all age groups stratified by doses (Dose 1 and Dose 2) and based on the data from both UK and EEA by risk window of 21 Days and 42 Days is presented below.

The overall TTS reporting rate from the UK was 11.41/million (558 identified reports with time to onset ≤ 21 days; estimated exposure 48.91 million administered doses) when compared to 5.6 (event rates per 1M PYs per 21 days Truven Market Scan- 2019, aligned with the Observational Health Data Science and Informatics [OHDSI] TTS algorithm) and 10.7 (event rates per 1M PY per 21days Truven Market Scan-2019). The reporting rate for the cases where the MHRA case classification criteria was met (confirmed, probable, and possible) cases was 9.85/million administered doses.

The reporting rate for Dose 1, and Dose 2 was 19.5 and 3.02/million doses administered doses respectively. For all administered doses and Dose 1, the reporting rate in the age group 18 to 39 and 40 to 49 was higher when compared to BG rate however reporting rate in 50 to 64 age group was less compared to the BG rate. Reporting rate for Dose 2 was less when compared to the BG rate for overall and all age stratifications.

The overall TTS reporting rate from the EEA was 13.19 /million (670 identified reports with time to onset $\leq$ 21 Days; estimated exposure 48.15 million administered doses) when compared to 5.6 (event rates per 1M PY per 21 Days Truven Market Scan-2019, aligned with the OHDSI TTS algorithm) and 10.7 (event rates per 1M PY per 21 days Truven Market Scan- 2019). The reporting rate for the cases where the MHRA case classification criteria was met (confirmed, probable and possible) was 7.58/million administered doses.

Reporting rate for Dose 1 and Dose 2 was 25.58 and 1.01 /million doses administered doses. EEA Reporting rate in 18-49 age group and 50-59 years age group with all doses and Dose 1 was higher when compared to BG rate. The reporting rate for Dose 2 was within the BG rate for both overall and also when stratified by age. About 94% of the cases have occurred within 42 Days after vaccination.

Observed versus Expected Analysis

Observed versus expected analyses for TTS (including CVST) and CVST with thrombocytopenia are presented below (Table 74, Table 75 and Table 76). Background rates for TTS were derived from MarketScan (US claims) data, using OHDSI-aligned code lists and definitions for TTS. Algorithm 2 for TTS uses updated OHDSI-aligned code lists and washout periods (previously patients with thrombosis in the 2 years prior to 2019 were excluded).

The BG rate (IR) of TTS is 9.77 /100,000-person year and 11.14/100,000-person year. The observed number of cases, for all risk windows of 14, 21 and 42 days (with unknown time to onset not included) is less than expected post vaccination by VAXZEVRIA.

The observed number of cases are significantly more than expected, for risk windows of 14 days (with unknown time to onset included) post vaccination by VAXZEVRIA with both BG rates.

The observed number of cases for risk windows of 21 days (with unknown time to onset included) post vaccination by VAXZEVRIA of TTS is less than the expected with BG rate 9.77/100,000-person year and 11.14/100,000 person year.

The observed number of cases for risk windows of 42 days (with unknown time to onset included) post vaccination by VAXZEVRIA of TTS is less than expected with both BG rates.

Table 74 Observed Versus Expected analysis for Thrombosis with thrombocytopenia (Overall)

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	Observed ratio (95% CI)	Conclusion
TTS Overall	14	9.77	46611564	1336	1745.56	0.77 (0.72 - 0.81)	Observed significantly < expected

Table 74 Observed Versus Expected analysis for Thrombosis with thrombocytopenia (Overall)

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	Observed ratio (95% CI)	Conclusion
TTS Overall	21	9.77	466115644	1656	2618.34	0.63 (0.6 - 0.66)	Observed significantly < expected
TTS Overall	42	9.77	466115644	1924	5236.68	0.37 (0.35 - 0.38)	Observed significantly < expected
TTS Overall (RW14+Unk TTO)	14	9.77	466115644	2099	1745.56	1.2 (1.15 - 1.26)	Observed significantly > expected
TTS Overall (RW21+Unk TTO)	21	9.77	466115644	2419	2618.34	0.92 (0.89 - 0.96)	Observed significantly < expected
TTS Overall (RW42+Unk TTO)	42	9.77	466115644	2687	5236.68	0.51 (0.49 - 0.53)	Observed significantly < expected
TTS Overall	14	11.14	466115644	1336	1990.33	0.67 (0.64 - 0.71)	Observed significantly < expected
TTS Overall	21	11.14	466115644	1656	2985.5	0.55 (0.53 - 0.58)	Observed significantly < expected
TTS Overall	42	11.14	466115644	1924	5971	0.32 (0.31 - 0.34)	Observed significantly < expected
TTS Overall (RW14+Unk TTO)	14	11.14	466115644	2099	1990.33	1.05 (1.01 - 1.1)	Observed significantly > expected
TTS Overall (RW21+Unk TTO)	21	11.14	466115644	2419	2985.5	0.81 (0.78 - 0.84)	Observed significantly < expected

Table 74 **Observed Versus Expected analysis for Thrombosis with thrombocytopenia (Overall)**

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
TTS Overall (RW42+Unk TTO)	42	11.14	466115644	2687	5971	0.45 (0.43 - 0.47)	Observed significantly < expected

Incidence Rate 9.77/100,000 PY from Truven Market Scan (2019) aligned with the OHDSI TTS algorithm.

CI Confidence Interval; E Expected; O Observed; TTS Thrombosis with Thrombocytopenia Syndrome

Table 75 Observed Versus Expected analysis for Thrombosis with thrombocytopenia by age group (EU+UK+Brazil+Australia)

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Incidence Rate from Truven Market Scan (2019) aligned with the OHDSI TTS algorithm							
TTS - 18-49 EU+UK+Brazil+Australia	14	4.99	110094983	509	191.17	2.66 (2.44 - 2.9)	Observed significantly > expected
TTS - 50-59 EU+UK+Brazil+Australia	14	12.6	58336094	229	232.55	0.98 (0.86 - 1.12)	Observed < expected
TTS - 60-69 EU+UK+Brazil+Australia	14	22.33	57960860	254	426.34	0.6 (0.52 - 0.67)	Observed significantly < expected
Over 70 EU+UK+Brazil+Australia	14	49.5	32376365	193	574.71	0.34 (0.29 - 0.39)	Observed significantly < expected
TTS - 18-49 EU+UK+Brazil+Australia	21	4.99	110094983	592	286.75	2.06 (1.9 - 2.24)	Observed significantly > expected
TTS - 50-59 EU+UK+Brazil+Australia	21	12.6	58336094	301	348.83	0.86 (0.77 - 0.97)	Observed significantly < expected
TTS - 60-69 EU+UK+Brazil+Australia	21	22.33	57960860	328	639.51	0.51 (0.46 - 0.57)	Observed significantly < expected
Over 70 EU+UK+Brazil+Australia	21	49.5	32376365	254	862.07	0.29 (0.26 - 0.33)	Observed significantly < expected

Table 75 Observed Versus Expected analysis for Thrombosis with thrombocytopenia by age group (EU+UK+Brazil+Australia)

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
TTS - 18-49 EU+UK+Brazil+Australia	42	4.99	110094983	651	573.5	1.14 (1.05 - 1.23)	Observed significantly > expected
TTS - 50-59 EU+UK+Brazil+Australia	42	12.6	58336094	348	697.65	0.5 (0.45 - 0.55)	Observed significantly < expected
TTS - 60-69 EU+UK+Brazil+Australia	42	22.33	57960860	393	1279.02	0.31 (0.28 - 0.34)	Observed significantly < expected
Over 70 EU+UK+Brazil+Australia	42	49.5	32376365	327	1724.13	0.19 (0.17 - 0.21)	Observed significantly < expected
Incidence Rate from Truven Market Scan database (2019) aligned with the OHDSI TTS algorithm, updated OHDSI-aligned codelists and washout periods							
TTS - 18-49 EU+UK+Brazil+Australia	14	4.99	110094983	509	210.58	2.42 (2.21 - 2.64)	Observed significantly > expected
TTS - 50-59 EU+UK+Brazil+Australia	14	12.6	58336094	229	281.74	0.81 (0.71 - 0.93)	Observed significantly < expected
TTS - 60-69 EU+UK+Brazil+Australia	14	22.33	57960860	254	496.1	0.51 (0.45 - 0.58)	Observed significantly < expected
Over 70 EU+UK+Brazil+Australia	14	49.5	32376365	193	614.3	0.31 (0.27 - 0.36)	Observed significantly < expected

Table 75 Observed Versus Expected analysis for Thrombosis with thrombocytopenia by age group (EU+UK+Brazil+Australia)

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
TTS - 18-49 EU+UK+Brazil+Australia	21	4.99	110094983	592	315.87	1.87 (1.73 - 2.03)	Observed significantly > expected
TTS - 50-59 EU+UK+Brazil+Australia	21	12.6	58336094	301	422.62	0.71 (0.63 - 0.8)	Observed significantly < expected
TTS - 60-69 EU+UK+Brazil+Australia	21	22.33	57960860	328	744.15	0.44 (0.39 - 0.49)	Observed significantly < expected
Over 70 EU+UK+Brazil+Australia	21	49.5	32376365	254	921.45	0.28 (0.24 - 0.31)	Observed significantly < expected
TTS - 18-49 EU+UK+Brazil+Australia	42	4.99	110094983	651	631.74	1.03 (0.95 - 1.11)	Observed > expected
TTS - 50-59 EU+UK+Brazil+Australia	42	12.6	58336094	348	845.23	0.41 (0.37 - 0.46)	Observed significantly < expected
TTS - 60-69 EU+UK+Brazil+Australia	42	22.33	57960860	393	1488.3	0.26 (0.24 - 0.29)	Observed significantly < expected
Over 70 EU+UK+Brazil+Australia	42	49.5	32376365	327	1842.9	0.18 (0.16 - 0.2)	Observed significantly < expected

Incidence Rate from Truven Market Scan database (2019) aligned with the OHDSI TTS algorithm, updated OHDSI-aligned code lists and washout periods
CI Confidence Interval; E Expected; EU European Union; O Observed; TTS Thrombosis with Thrombocytopenia Syndrome; UK United Kingdom

Table 76 Observed Versus Expected analysis for Thrombosis with thrombocytopenia by age group/sex (UK)

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Incidence Rate from Truven Market Scan (2019) aligned with the OHDSI TTS algorithm							
TTS - Female UK	14	8.2	23252503	224	73.09	3.06 (2.68 - 3.49)	Observed significantly > expected
TTS - Male UK	14	11.49	22377923	203	98.56	2.06 (1.79 - 2.36)	Observed significantly > expected
TTS - Female 18-49 UK	14	4.53	7414701	110	12.87	8.55 (7.02 - 10.3)	Observed significantly > expected
TTS - Female 50-59 UK	14	9.07	5944683	47	20.67	2.27 (1.67 - 3.02)	Observed significantly > expected
TTS - Female 60-69 UK	14	12.88	4783416	30	23.62	1.27 (0.86 - 1.81)	Observed > expected
TTS - Female 70-79 UK	14	31.05	3475875	16	41.37	0.39 (0.22 - 0.63)	Observed significantly < expected
TTS - Female over 80 UK	14	40.77	1630324	8	25.48	0.31 (0.14 - 0.62)	Observed significantly < expected
TTS - Male 18-49 UK	14	4.54	6766098	90	11.77	7.65 (6.15 - 9.4)	Observed significantly > expected
TTS - Male 50-59 UK	14	11.87	6510960	53	29.62	1.79 (1.34 - 2.34)	Observed significantly > expected

Table 76 Observed Versus Expected analysis for Thrombosis with thrombocytopenia by age group/sex (UK)

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	Observed over Expected ratio (95% CI)	Conclusion
TTS - Male 60-69 UK	14	26.19	4934728	22	49.54	0.44 (0.28 - 0.67)	Observed significantly < expected
TTS - Male 70-79 UK	14	48.22	3137304	22	57.99	0.38 (0.24 - 0.57)	Observed significantly < expected
TTS - Male over 80 UK	14	86.28	1025046	7	33.9	0.21 (0.08 - 0.43)	Observed significantly < expected
TTS - Female UK	21	8.2	23252503	292	109.63	2.66 (2.37 - 2.99)	Observed significantly > expected
TTS - Male UK	21	11.49	22377923	261	147.84	1.77 (1.56 - 1.99)	Observed significantly > expected
TTS - Female 18-49 UK	21	4.53	7414701	136	19.31	7.04 (5.91 - 8.33)	Observed significantly > expected
TTS - Female 50-59 UK	21	9.07	5944683	64	31	2.06 (1.59 - 2.64)	Observed significantly > expected
TTS - Female 60-69 UK	21	12.88	4783416	39	35.42	1.1 (0.78 - 1.51)	Observed > expected
TTS - Female 70-79 UK	21	31.05	3475875	27	62.05	0.44 (0.29 - 0.63)	Observed significantly < expected
TTS - Female over 80 UK	21	40.77	1630324	8	38.22	0.21 (0.09 - 0.41)	Observed significantly < expected

Table 76 Observed Versus Expected analysis for Thrombosis with thrombocytopenia by age group/sex (UK)

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	Observed over Expected ratio (95% CI)	Conclusion
TTS - Male 18-49 UK	21	4.54	6766098	108	17.66	6.12 (5.02 - 7.38)	Observed significantly > expected
TTS - Male 50-59 UK	21	11.87	6510960	70	44.44	1.58 (1.23 - 1.99)	Observed significantly > expected
TTS - Male 60-69 UK	21	26.19	4934728	34	74.31	0.46 (0.32 - 0.64)	Observed significantly < expected
TTS - Male 70-79 UK	21	48.22	3137304	27	86.98	0.31 (0.2 - 0.45)	Observed significantly < expected
TTS - Male over 80 UK	21	86.28	1025046	8	50.85	0.16 (0.07 - 0.31)	Observed significantly < expected
TTS - Female UK	42	8.2	23252503	340	219.26	1.55 (1.39 - 1.72)	Observed significantly > expected
TTS - Male UK	42	11.49	22377923	319	295.67	1.08 (0.96 - 1.2)	Observed > expected
TTS - Female 18-49 UK	42	4.53	7414701	156	38.62	4.04 (3.43 - 4.73)	Observed significantly > expected
TTS - Female 50-59 UK	42	9.07	5944683	73	62	1.18 (0.92 - 1.48)	Observed > expected
TTS - Female 60-69 UK	42	12.88	4783416	45	70.85	0.64 (0.46 - 0.85)	Observed significantly < expected

Table 76 Observed Versus Expected analysis for Thrombosis with thrombocytopenia by age group/sex (UK)

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	Observed over Expected ratio (95% CI)	Conclusion
TTS - Female 70-79 UK	42	31.05	3475875	33	124.11	0.27 (0.18 - 0.37)	Observed significantly < expected
TTS - Female over 80 UK	42	40.77	1630324	11	76.43	0.14 (0.07 - 0.26)	Observed significantly < expected
TTS - Male 18-49 UK	42	4.54	6766098	118	35.32	3.34 (2.77 - 4)	Observed significantly > expected
TTS - Male 50-59 UK	42	11.87	6510960	88	88.87	0.99 (0.79 - 1.22)	Observed < expected
TTS - Male 60-69 UK	42	26.19	4934728	47	148.62	0.32 (0.23 - 0.42)	Observed significantly < expected
TTS - Male 70-79 UK	42	48.22	3137304	36	173.96	0.21 (0.14 - 0.29)	Observed significantly < expected
TTS - Male over 80 UK	42	86.28	1025046	11	101.7	0.11 (0.05 - 0.19)	Observed significantly < expected
Incidence Rate from Truven Market Scan database (2019) aligned with the OHDSI TTS algorithm, updated OHDSI-aligned codelists and washout periods							
TTS - Female UK	14	9.22	23252503	224	82.18	2.73 (2.38 - 3.11)	Observed significantly > expected
TTS - Male UK	14	13.24	22377923	203	113.57	1.79 (1.55 - 2.05)	Observed significantly > expected

Table 76 Observed Versus Expected analysis for Thrombosis with thrombocytopenia by age group/sex (UK)

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
TTS - Female 18-49 UK	14	4.64	7414701	110	13.19	8.34 (6.85 - 10.05)	Observed significantly > expected
TTS - Female 50-59 UK	14	10.71	5944683	47	24.4	1.93 (1.42 - 2.56)	Observed significantly > expected
TTS - Female 60-69 UK	14	15.87	4783416	30	29.1	1.03 (0.7 - 1.47)	Observed > expected
TTS - Female 70-79 UK	14	36.7	3475875	16	48.9	0.33 (0.19 - 0.53)	Observed significantly < expected
TTS - Female over 80 UK	14	39.61	1630324	8	24.75	0.32 (0.14 - 0.64)	Observed significantly < expected
TTS - Male 18-49 UK	14	5.36	6766098	90	13.9	6.47 (5.21 - 7.96)	Observed significantly > expected
TTS - Male 50-59 UK	14	14.7	6510960	53	36.69	1.44 (1.08 - 1.89)	Observed significantly > expected
TTS - Male 60-69 UK	14	29.51	4934728	22	55.82	0.39 (0.25 - 0.6)	Observed significantly < expected
TTS - Male 70-79 UK	14	54.04	3137304	22	64.99	0.34 (0.21 - 0.51)	Observed significantly < expected
TTS - Male over 80 UK	14	84.62	1025046	7	33.25	0.21 (0.08 - 0.43)	Observed significantly < expected

Table 76 Observed Versus Expected analysis for Thrombosis with thrombocytopenia by age group/sex (UK)

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	Observed over Expected ratio (95% CI)	Conclusion
TTS - Female UK	21	9.22	23252503	292	123.26	2.37 (2.11 - 2.66)	Observed significantly > expected
TTS - Male UK	21	13.24	22377923	261	170.35	1.53 (1.35 - 1.73)	Observed significantly > expected
TTS - Female 18-49 UK	21	4.64	7414701	136	19.78	6.88 (5.77 - 8.13)	Observed significantly > expected
TTS - Female 50-59 UK	21	10.71	5944683	64	36.61	1.75 (1.35 - 2.23)	Observed significantly > expected
TTS - Female 60-69 UK	21	15.87	4783416	39	43.65	0.89 (0.64 - 1.22)	Observed < expected
TTS - Female 70-79 UK	21	36.7	3475875	27	73.34	0.37 (0.24 - 0.54)	Observed significantly < expected
TTS - Female over 80 UK	21	39.61	1630324	8	37.13	0.22 (0.09 - 0.42)	Observed significantly < expected
TTS - Male 18-49 UK	21	5.36	6766098	108	20.85	5.18 (4.25 - 6.25)	Observed significantly > expected
TTS - Male 50-59 UK	21	14.7	6510960	70	55.03	1.27 (0.99 - 1.61)	Observed > expected
TTS - Male 60-69 UK	21	29.51	4934728	34	83.73	0.41 (0.28 - 0.57)	Observed significantly < expected

Table 76 Observed Versus Expected analysis for Thrombosis with thrombocytopenia by age group/sex (UK)

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
TTS - Male 70-79 UK	21	54.04	3137304	27	97.48	0.28 (0.18 - 0.4)	Observed significantly < expected
TTS - Male over 80 UK	21	84.62	1025046	8	49.87	0.16 (0.07 - 0.32)	Observed significantly < expected
TTS - Female UK	42	9.22	23252503	340	246.53	1.38 (1.24 - 1.53)	Observed significantly > expected
TTS - Male UK	42	13.24	22377923	319	340.7	0.94 (0.84 - 1.04)	Observed < expected
TTS - Female 18-49 UK	42	4.64	7414701	156	39.56	3.94 (3.35 - 4.61)	Observed significantly > expected
TTS - Female 50-59 UK	42	10.71	5944683	73	73.21	1 (0.78 - 1.25)	Observed < expected
TTS - Female 60-69 UK	42	15.87	4783416	45	87.29	0.52 (0.38 - 0.69)	Observed significantly < expected
TTS - Female 70-79 UK	42	36.7	3475875	33	146.69	0.22 (0.15 - 0.32)	Observed significantly < expected
TTS - Female over 80 UK	42	39.61	1630324	11	74.26	0.15 (0.07 - 0.27)	Observed significantly < expected
TTS - Male 18-49 UK	42	5.36	6766098	118	41.7	2.83 (2.34 - 3.39)	Observed significantly > expected

Table 76 Observed Versus Expected analysis for Thrombosis with thrombocytopenia by age group/sex (UK)

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
TTS - Male 50-59 UK	42	14.7	6510960	88	110.06	0.8 (0.64 - 0.99)	Observed significantly < expected
TTS - Male 60-69 UK	42	29.51	4934728	47	167.46	0.28 (0.21 - 0.37)	Observed significantly < expected
TTS - Male 70-79 UK	42	54.04	3137304	36	194.96	0.18 (0.13 - 0.26)	Observed significantly < expected
TTS - Male over 80 UK	42	84.62	1025046	11	99.74	0.11 (0.06 - 0.2)	Observed significantly < expected

Incidence Rate from Truven Market Scan database (2019) aligned with the OHDSI TTS algorithm, updated OHDSI-aligned code lists and washout periods

CI Confidence Interval; E Expected; EU European Union; O Observed; TTS Thrombosis with Thrombocytopenia Syndrome; UK United Kingdom.

MHRA Case Definition

Anti-PF-4, D-Dimer, and platelet levels for Dose 1, Dose 2, Dose 3 and Fatal Reports

All 2811 case reports were reviewed to classify the cases based on the PTs and laboratory data, as per the Medicines and Healthcare products Regulatory Agency (MHRA) case definition for thrombosis in combination with thrombocytopenia Figure 1.

Figure 1 Medicines and Healthcare products Regulatory Agency case definition for thrombosis in combination with thrombocytopenia

Confirmed	Any venous/arterial thrombosis +	Platelet count $<150 \times 10^9/L$ +	D-dimer $>4000\text{ng/mL}$ +	Anti-PF4 Abs
Probable	Any venous/arterial thrombosis +	Platelet count $<150 \times 10^9/L$ +	D-dimer $>4000\text{ng/mL}$	
Possible	Any venous/arterial thrombosis +	Platelet count $<150 \times 10^9/L$ OR wording compatible with platelet count decreased		
Unlikely	Criteria met for any of the above BUT alternative diagnosis more likely to explain the event			
Criteria Not met	One or none of the criteria are met			

Information in case reports was limited, with missing laboratory data on platelet count, D-dimer level, and PF-4 antibodies and also in many case reports there were incomplete entries (units, date of test, and type of test) for platelet levels, D-dimer, and PF-4.

Information on platelet count was available in 1846 (65.67%) of 2811 case reports; platelet count was $<150 \times 10^9/L$ in 1772 of the 1846 reports and in 74 case reports platelet count was $>150 \times 10^9/L$.

Among these 1772 vaccinees with reported platelet count $<150 \times 10^9/L$, 800 (45%) had a platelet count of $<50 \times 10^9/L$; in 469 (26%) had a platelet count was between 50 to $<100 \times 10^9/L$; and 482 (28%) had a platelet count between 100 to $150 \times 10^9/L$; 21 had a platelet count reported as $<150 \times 10^9/L$, however exact value was not provided. In remaining 965 (34%) of the 2786 case reports information on platelet count was not available.

In 26 of the 2811 case reports site of thrombosis unknown. Of the 2811 case reports, PF-4 antibodies were positive in 747 (26.57%) reports, negative in 643 (22.87%) reports, unknown or pending in 1421 (50.55%) case reports.

D-dimer levels were reported in 1085 (38.59%) of the 2811 case reports, however, in many reports the units were not specified. In 241 (9%) D-dimer levels were $<4000 \text{ ng/mL}$, in 844 (30%) case reports D-dimer levels were $>4000 \text{ ng/mL}$ and in 1726 (61%) case reports D-dimer levels were not provided/reported.

Of the 2811 case reports reviewed, based on the above case classification criteria, there were 1765 cases which met the MHRA criteria of TTS (Confirmed, probable or possible). The total number of confirmed cases were 395 (14%), probable cases were 405 (15%), possible cases were 965 (34%), unlikely 1 (0.03%) and criteria not met cases were 1045 (37%). Out of all cases 1765 which met the criteria, the confirmed cases 395 comprised 22% of the total cases.

In cases 1765 where the MHRA case classification criteria were met, 582 (33%) cases had confounding factors. Many of the cases had more than one confounding factor. The confounding factors were reported as follows:

- Autoimmune disease (ITP, autoimmune thyroiditis, psoriasis, antiphospholipid syndrome (APLS), Crohn's disease, myasthenia gravis, inflammatory bowel disease, UC, ankylosing spondylitis, rheumatoid arthritis, guillain-barre syndrome, sarcoidosis, systemic lupus erythematosus (SLE), autoimmune hepatitis (AIH), vasculitis, MS, hemolytic anaemia, polymyalgia rheumatica, thalassemia minor and connective tissue disorder);
- Malignancies (breast cancer, prostate cancer, malignant melanoma, brain cancer, thyroid cancer, non-hodgkin's lymphoma, polycythemia vera, bladder cancer, pituitary tumour, lung cancer, metastatic cancer, tonsil cancer, ovarian cancer, pancreatic cancer, testicular cancer, carcinoma endometrium uterus, vulvar cancer, cervix carcinoma, renal cell carcinoma, chronic lymphocytic leukemia, glioblastoma, gliomas, leukemia, lymphoma, lymphoproliferative disease, metastatic neoplasm, myelodysplastic neoplasm, neoplasm, sarcoma);
- Past history of heparin administration information specially on the dates of heparin administration was not available, obesity, past and current history of contraceptives, past history of thrombosis, HIT, past history of frequent abortion, HIV infection, chronic hepatitis b, liver disease, covid-19 illness, cardiomyopathy resulting from fredrich's ataxia, chronic kidney disease, chronic glomerulonephritis, DRESS syndrome, liver transplant, past history of stroke, polycystic ovary syndrome, protein c deficiency, sickle cell disease, TCP chronic.
- Concomitant medications; venlafaxine, and combination of citalopram and clopidogrel.

Out of 395 confirmed reports, there were 161 (41%) cases with confounding factors. The confounding factor associated were past history of heparin use malignancies (neoplasm, abdominal neoplasm, thyroid cancer, prostate cancer, vulvar cancer, metastatic cancer, skin cancer, pancreatic cancer, carcinoma endometrium uterus, non-Hodgkin's disease, breast cancer, malignant melanoma), obesity, contraceptives, ITP, autoimmune disease (sarcoidosis, Guillain-Barre syndrome, myasthenia gravis, ankylosing spondylitis, autoimmune thyroiditis, antiphospholipid syndrome, UC, rheumatoid arthritis, Crohn's disease), HIT, past history of thrombosis, chronic kidney disease. The dates of heparin administration were not reported in all cases.

Table 77 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed	Probable	Possible	Unlikely	Criteria not met	All Reports
Dose						
Dose 1	376	349	821	1	935	2482
Dose 2	16	53	133		103	305
Dose 3	2	2	5		6	15
Dose 4			1			1

Table 77 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed	Probable	Possible	Unlikely	Criteria not met	All Reports
Median Time to onset in days: AZD1222 Dose 1	11	12.5	12	9	11	12
Median Time to onset in days: AZD1222 Dose 2	9.5	13	14	NA	10	13
Median Time to onset in days: AZD1222 Dose 3	NA	10	8	NA	7.5	9
Median Time to onset in days: AZD1222 Dose 4	NA	NA	Unk TTO	NA	NA	Unk TTO
Embolic and thrombotic sites						
Embolic and thrombotic events, Arterial	76	57	135	1	134	403
Embolic and thrombotic events, Venous	245	190	463	1	658	1557
Embolic and thrombotic events, Mixed	306	324	680		572	1882
Embolic and thrombotic events, Unspecified	328	365	840	1	890	2424
Embolic and thrombotic events, Arterial						
Acute coronary syndrome	1		1		3	5
Acute myocardial infarction	11	8	13		11	43
Amaurosis fugax					8	8
Aortic embolus	1	2	3		2	8
Aortic thrombosis	16	4	13	1	8	42
Arterial occlusive disease			3		1	4
Arterial thrombosis	11	7	9		9	36
Basilar artery thrombosis					1	1
Blindness transient					1	1

Table 77 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed	Probable	Possible	Unlikely	Criteria not met	All Reports
Carotid artery occlusion	2	1	2		3	8
Carotid artery thrombosis	10	9	11		12	42
Cerebral artery embolism			1		1	2
Cerebral artery occlusion	5	1	5		1	12
Cerebral artery thrombosis	6	5	10		2	23
Cerebrovascular insufficiency	1					1
Coronary artery bypass					1	1
Coronary artery occlusion	1					1
Coronary artery reocclusion	1					1
Coronary artery thrombosis	6		6		2	14
Embolism arterial	2	8	1		1	12
Femoral artery embolism		1				1
Hepatic artery occlusion		1				1
Hepatic artery thrombosis		3			2	5
Iliac artery occlusion				1	2	3
Internal capsule infarction			1			1
Ischaemic cerebral infarction	3		3		2	8
Ischaemic stroke	11	7	19		23	60
Lacunar infarction	1	1	1		2	5
Leriche syndrome			1			1
Mesenteric arterial occlusion			2			2
Mesenteric artery stenosis					4	4

Table 77 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed	Probable	Possible	Unlikely	Criteria not met	All Reports
Mesenteric artery thrombosis		2	3		1	6
Myocardial infarction	7	4	12		21	44
Peripheral arterial occlusive disease		1	3		2	6
Peripheral artery occlusion	5		12		1	18
Peripheral artery thrombosis	17	7	18		18	60
Peripheral embolism	1	1	7		3	12
Pulmonary artery occlusion	1		2		1	4
Pulmonary artery thrombosis	4	1	1		3	9
Renal artery occlusion				1		1
Renal artery thrombosis		1	2		2	5
Renal embolism		1				1
Retinal artery occlusion		1			3	4
Retinal artery thrombosis					2	2
Splenic artery thrombosis		2	4		3	9
Stress cardiomyopathy	1					1
Subclavian artery thrombosis	1				1	2
Thromboembolism		1				1
Thrombotic microangiopathy	1	1			8	10
Thrombotic thrombocytopenic purpura	4	7	21		26	58
Transient ischaemic attack	1	1	3		13	18
Truncus coeliacus thrombosis					1	1

Table 77 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed	Probable	Possible	Unlikely	Criteria not met	All Reports
Vertebral artery occlusion			1			1
Vertebral artery thrombosis	2				2	4
Embolic and thrombotic events, Mixed						
Adrenal thrombosis	2	1				3
Antiphospholipid syndrome	2	1	5		1	9
Atrial thrombosis	1	1	2		1	5
Autoimmune heparin-induced thrombocytopenia	1					1
Brain stem infarction			1		3	4
Brain stem stroke					2	2
Cardiac ventricular thrombosis	4	3	2		5	14
Cerebellar infarction	1		2		1	4
Cerebral congestion	1		1		2	4
Cerebral infarction	13	13	26		30	82
Cerebral ischaemia	3	1	2		2	8
Cerebral thrombosis	8	17	22		19	66
Cerebrovascular accident	7	11	31		61	110
Cerebrovascular disorder	1					1
Device occlusion			1			1
Diplegia	1		1		1	3
Disseminated intravascular coagulation	19	14	11		23	67
Embolic cerebral infarction	1		2			3
Embolic stroke			1		1	2
Embolism	7	20	34		16	77
Eye infarction					1	1
Foetal vascular malperfusion	4		1			5

Table 77 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed	Probable	Possible	Unlikely	Criteria not met	All Reports
Haemorrhagic adrenal infarction	4	1	3		1	9
Haemorrhagic cerebral infarction	8	6	3		1	18
Haemorrhagic infarction	2	2	8		4	16
Haemorrhagic stroke	2	5	14		12	33
Haemorrhagic transformation stroke	7	2	4		3	16
Haemorrhoids thrombosed					2	2
Hemiparesis	27	19	33		20	99
Hemiplegia	5	6	9		16	36
Heparin-induced thrombocytopenia	9	4	12		20	45
Hepatic infarction	1	2	2		4	9
Hepatic vascular thrombosis			2		4	6
Infarction	2		4		4	10
Injection site thrombosis					2	2
Intestinal infarction		3	4		2	9
Intracardiac thrombus	2	3	5		1	11
Monoparesis	2	1	6		1	10
Monoplegia			2		2	4
Pancreatic infarction					1	1
Paraparesis		1				1
Paresis		1	1		2	4
Post procedural stroke					1	1
Prosthetic cardiac valve thrombosis	1	1				2
Quadriparesis		2	2		2	6
Quadriplegia	1	1	1			3
Renal infarct	5	7	7	1	8	28
Renal vascular thrombosis	1		1		1	3

Table 77 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed	Probable	Possible	Unlikely	Criteria not met	All Reports
Retinal vascular thrombosis					1	1
Splenic infarction	2	9	11		7	29
Splenic thrombosis	3		2		1	6
Spontaneous heparin-induced thrombocytopenia syndrome			1		3	4
Thalamic infarction			1			1
Thrombectomy					3	3
Thromboangiitis obliterans					1	1
Thrombosis	57	65	144		245	511
Thrombosis in device				1		1
Thrombosis mesenteric vessel	4	1	4		2	11
Thrombosis with thrombocytopenia syndrome	156	79	224		398	857
Thrombotic stroke	2	1	2		4	9
Vascular graft thrombosis			1			1
Vascular stent thrombosis		1	2		4	7
Embolic and thrombotic events, Venous						
Axillary vein thrombosis					2	2
Budd-Chiari syndrome	1		1			2
Cavernous sinus thrombosis	1	4	2		2	9
Cerebral venous sinus thrombosis	144	91	156		186	577
Cerebral venous thrombosis	41	16	60		31	148
Deep vein thrombosis	54	94	228		166	542
Embolism venous	3	2	1		3	9

Table 77 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed	Probable	Possible	Unlikely	Criteria not met	All Reports
Hepatic vein embolism			1			1
Hepatic vein occlusion	1				1	2
Hepatic vein thrombosis	8	10	13		12	43
Iliac vein occlusion		1				1
Jugular vein embolism					1	1
Jugular vein occlusion	2					2
Jugular vein thrombosis	14	10	15		18	57
Mesenteric vein thrombosis	13	14	25		13	65
Mesenteric venous occlusion			1		1	2
Ophthalmic vein thrombosis	1	5	4		1	11
Ovarian vein thrombosis		1	2		1	4
Pelvic venous thrombosis	5	8	10		8	31
Penile vein thrombosis			2			2
Peripheral vein occlusion	1					1
Peripheral vein thrombosis					4	4
Portal vein cavernous transformation			1			1
Portal vein embolism		1	1		1	3
Portal vein occlusion	1		2			3
Portal vein thrombosis	40	39	79		58	216
Portosplenomesenteric venous thrombosis	2	2	2		7	13
Post thrombotic syndrome	1					1

Table 77 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed	Probable	Possible	Unlikely	Criteria not met	All Reports
Pulmonary embolism	124	191	333		253	901
Pulmonary infarction	4	3	9		7	23
Pulmonary thrombosis	6	3	11		13	33
Pulmonary venous thrombosis			2		1	3
Renal vein embolism	1					1
Renal vein thrombosis	3	7	6		3	19
Retinal vein occlusion	1		2		6	9
Retinal vein thrombosis			1		3	4
Sigmoid sinus thrombosis	4		3		3	10
Splenic vein occlusion			2		2	4
Splenic vein thrombosis	12	11	13		13	49
Subclavian vein thrombosis			1		1	2
Superficial vein thrombosis	9	6	10		10	35
Superior sagittal sinus thrombosis	22	15	32		20	89
Superior vena cava syndrome					1	1
Thrombophlebitis	1	3	13		8	25
Transverse sinus thrombosis	20	3	11		13	47
Vena cava filter insertion					1	1
Vena cava thrombosis	1	7	2		1	11
Venoocclusive liver disease			1			1
Venous occlusion	1	1	1		2	5
Venous thrombosis	9	9	31		21	70
Venous thrombosis limb	6	2	6		13	27

Table 77 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed	Probable	Possible	Unlikely	Criteria not met	All Reports
Visceral venous thrombosis	17	7	12		7	43
Platelet Level						
<150 x 10 ⁹ /L	394	404	954	1	19	1772
Reported as < 150 x 10 ⁹ /L, however value not provided	5	4	11		1	21
100-150 x 10 ⁹ /L	34	108	336		4	482
50-100 x 10 ⁹ /L	118	103	242		6	469
<50 x 10 ⁹ /L	237	189	365	1	8	800
>150 x 10 ⁹ /L or 'normal'		1	4		68	73
Unk	1		7		957	965
Co-Reported Events						
Coagulopathy	24	24	27		34	109
Co-reported bleeding event from Haemorrhage terms (excl laboratory terms) (SMQ)- Narrow* (≥10 events)	201	152	290		316	959
Immune thrombocytopenia	65	23	74		103	265
Cerebral haemorrhage	69	41	78		76	264
Haemorrhage	23	15	33		13	84
Haemorrhage intracranial	24	15	26		18	83
Contusion	12	10	32		27	81
Petechiae	11	13	27		22	73
Subarachnoid haemorrhage	21	18	21		12	72
Disseminated intravascular coagulation	19	14	11		23	67
Thrombotic thrombocytopenic purpura	4	7	21		26	58

Table 77 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed	Probable	Possible	Unlikely	Criteria not met	All Reports
Haematoma	4	5	10		20	39
Haemorrhagic stroke	2	5	14		12	33
Adrenal haemorrhage	20	4	4		2	30
Haemoptysis	6	9	10		4	29
Cerebral haematoma	5	7	4		6	22
Melaena			7		12	19
Epistaxis		2	8		8	18
Haemorrhagic cerebral infarction	8	6	3		1	18
Rectal haemorrhage	5	2	7		3	17
Haematuria	6	6	3		2	17
Subdural haematoma	4		5		8	17
Haemorrhagic infarction	2	2	8		4	16
Haemorrhagic transformation stroke	7	2	4		3	16
Ecchymosis	3	2	4		4	13
Purpura	1	2	3		5	11

NA Not Applicable; TTO Time To Onset; Unk Unknown

Table 78 Comparison of platelet levels, thrombosis event, PF-4 antibodies and D-dimer levels in Thrombosis in combination with thrombocytopenia case reports (N=2811)

Venous or arterial thrombosis					PF4 Antibodies				D dimer level			
Platelet count (10 ⁹ /L)	Yes	No	Unk	Grand Total	Yes	No	Pending/Unk	Grand Total	Yes (>4000ng/mL)	Yes (<4000ng/mL)	Unk	Grand Total
<150	1749	11	3	1763	631	414	727	1772	807	215	750	1772
>150	73			73	9	13	51	73	20	20	33	73
Unk	932	15	2	949	107	215	643	965	17	5	943	965

Table 78 Comparison of platelet levels, thrombosis event, PF-4 antibodies and D-dimer levels in Thrombosis in combination with thrombocytopenia case reports (N=2811)

Venous or arterial thrombosis					PF4 Antibodies				D dimer level			
Platelet count (10 ⁹ /L)	Yes	No	Unk	Grand Total	Yes	No	Pending/Unk	Grand Total	Yes (>4000ng/mL)	Yes (<4000ng/mL)	Unk	Grand Total
Grand Total	2754	26	5	2785	747	642	1421	2810	844	240	1726	2810
Dose 1												
<150	1540	11	2	1553	591	337	625	1553	732	179	642	1553
>150	60			60	9	9	42	60	15	15	30	60
Unk	852	14	2	868	102	193	573	868	11	4	853	868
Grand Total	2452	25	4	2481	702	539	1240	2481	758	198	1525	2481
Dose 2												
<150	201		1	202	32	74	96	202	69	33	100	202
>150	12			12		4	8	12	5	5	2	12
Unk	90	1		91	4	20	67	91	5	1	85	91
Grand Total	303	1	1	305	36	98	171	305	79	39	187	305
Dose 3												
<150	9			9	4	1	4	9	4	1	4	9
>150	1			1			1	1			1	1
Unk	5			5	1	1	3	5	1		4	5
Grand Total	15			15	5	2	8	15	5	1	9	15
Fatal reports												
<150	328	2		330	128	50	152	330	173	14	143	330

Table 78 Comparison of platelet levels, thrombosis event, PF-4 antibodies and D-dimer levels in Thrombosis in combination with thrombocytopenia case reports (N=2811)

Venous or arterial thrombosis					PF4 Antibodies				D dimer level			
Platelet count (10 ⁹ /L)	Yes	No	Unk	Grand Total	Yes	No	Pending/Unk	Grand Total	Yes (>4000ng/mL)	Yes (<4000ng/mL)	Unk	Grand Total
>150	8			8		2	6	8	3		5	8
Unk	182	1	1	184	18	52	114	184	2		182	184
Grand Total	518	3	1	522	146	104	272	522	178	14	330	522

PF4 Platelet Factor 4; Unk Unknown.

Table 79 Thrombosis with Thrombocytopenia Syndrome Case Reports by age/gender, Dose, MHRA Case Classification and fatality (N)

All dose																
	Confirmed			Probable			Possible			Unlikely			Criteria not met			Grand Total
	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	
Age - 18-29 Yrs	21 (4)	20 (4)	0 (0)	21 (8)	13 (4)	1 (1)	46 (10)	37 (6)	0 (0)	0 (0)	0 (0)	0 (0)	50 (11)	29 (7)	1 (0)	239 (55)
Age - 30-39 Yrs	35 (12)	26 (7)	0 (0)	19 (7)	13 (4)	0 (0)	76 (22)	39 (10)	0 (0)	0 (0)	0 (0)	0 (0)	58 (12)	37 (8)	0 (0)	303 (82)
Age - 40-49 Yrs	66 (15)	44 (6)	1 (0)	50 (11)	26 (2)	0 (0)	55 (14)	62 (6)	0 (0)	0 (0)	0 (0)	0 (0)	83 (18)	48 (10)	1 (0)	436 (82)
Age - 50-59 Yrs	51 (9)	38 (8)	0 (0)	47 (15)	41 (5)	2 (0)	97 (11)	74 (11)	2 (1)	0 (0)	0 (0)	0 (0)	64 (15)	52 (12)	0 (0)	468 (87)
Age - 60-69 Yrs	24 (4)	25 (5)	0 (0)	37 (5)	45 (7)	1 (0)	120 (24)	99 (10)	0 (0)	0 (0)	1 (1)	0 (0)	92 (12)	102 (15)	1 (1)	547 (84)
Age - 70-79 Yrs	14 (4)	7 (3)	0 (0)	22 (2)	23 (3)	0 (0)	56 (11)	84 (4)	1 (0)	0 (0)	0 (0)	0 (0)	50 (5)	67 (8)	1 (0)	325 (40)
Age - 80+ Yrs	4 (1)	2 (1)	0 (0)	8 (3)	11 (2)	0 (0)	27 (3)	31 (2)	0 (0)	0 (0)	0 (0)	0 (0)	23 (3)	23 (5)	0 (0)	129 (20)

Table 79 Thrombosis with Thrombocytopenia Syndrome Case Reports by age/gender, Dose, MHRA Case Classification and fatality (N)

All dose																
Age Unknown																
Grand Total	231 (53)	163 (34)	1 (0)	218 (54)	181 (28)	6 (1)	497 (102)	452 (52)	16 (5)	0 (0)	1 (1)	0 (0)	502 (96)	419 (75)	124 (21)	2811 (522)
Dose 1																
	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	
Age - 18-29 Yrs	20 (4)	20 (4)	0 (0)	19 (7)	12 (4)	1 (1)	41 (9)	33 (5)	0 (0)	0 (0)	0 (0)	0 (0)	49 (11)	27 (7)	1 (0)	223 (52)
Age - 30-39 Yrs	34 (12)	25 (7)	0 (0)	19 (7)	13 (4)	0 (0)	71 (20)	37 (10)	0 (0)	0 (0)	0 (0)	0 (0)	55 (11)	36 (8)	0 (0)	290 (79)
Age - 40-49 Yrs	65 (14)	42 (6)	1 (0)	47 (10)	24 (2)	0 (0)	51 (14)	52 (6)	0 (0)	0 (0)	0 (0)	0 (0)	79 (16)	45 (10)	1 (0)	407 (78)
Age - 50-59 Yrs	50 (9)	35 (8)	0 (0)	45 (15)	37 (5)	2 (0)	93 (11)	60 (8)	2 (1)	0 (0)	0 (0)	0 (0)	57 (13)	47 (11)	0 (0)	428 (81)
Age - 60-69 Yrs	24 (4)	23 (5)	0 (0)	34 (5)	33 (7)	1 (0)	102 (24)	82 (10)	0 (0)	0 (0)	1 (1)	0 (0)	85 (10)	82 (11)	1 (1)	468 (78)
Age - 70-79 Yrs	13 (4)	4 (1)	0 (0)	18 (2)	12 (0)	0 (0)	47 (8)	61 (3)	1 (0)	0 (0)	0 (0)	0 (0)	42 (5)	58 (7)	1 (0)	257 (30)
Age - 80+ Yrs	3 (1)	0 (0)	0 (0)	5 (2)	8 (1)	0 (0)	17 (2)	23 (1)	0 (0)	0 (0)	0 (0)	0 (0)	17 (3)	21 (5)	0 (0)	94 (15)
Age Unknown																
Grand Total	225 (52)	150 (31)	1 (0)	197 (50)	146 (24)	6 (1)	441 (95)	365 (46)	15 (5)	0 (0)	1 (1)	0 (0)	464 (88)	371 (68)	100 (20)	2482 (481)
Dose 2																
	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	
Age - 18-29 Yrs	1 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	5 (1)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0)	0 (0)	10 (1)
Age - 30-39 Yrs	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (1)	0 (0)	0 (0)	8 (1)
Age - 40-49 Yrs	0 (0)	1 (0)	0 (0)	3 (1)	2 (0)	0 (0)	3 (0)	10 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (2)	3 (0)	0 (0)	26 (3)

Table 79 Thrombosis with Thrombocytopenia Syndrome Case Reports by age/gender, Dose, MHRA Case Classification and fatality (N)

All dose																
Age - 50-59 Yrs	1 (0)	3 (0)	0 (0)	2 (0)	3 (0)	0 (0)	4 (0)	13 (2)	0 (0)	0 (0)	0 (0)	0 (0)	6 (2)	5 (1)	0 (0)	37 (5)
Age - 60-69 Yrs	0 (0)	2 (0)	0 (0)	3 (0)	12 (0)	0 (0)	18 (0)	14 (0)	0 (0)	0 (0)	0 (0)	0 (0)	7 (2)	20 (4)	0 (0)	76 (6)
Age - 70-79 Yrs	1 (0)	3 (2)	0 (0)	4 (0)	11 (3)	0 (0)	9 (3)	23 (1)	0 (0)	0 (0)	0 (0)	0 (0)	7 (0)	8 (1)	0 (0)	66 (10)
Age - 80+ Yrs	1 (0)	2 (1)	0 (0)	3 (1)	3 (1)	0 (0)	10 (1)	8 (1)	0 (0)	0 (0)	0 (0)	0 (0)	6 (0)	2 (0)	0 (0)	35 (5)
Age Unknown																
Grand Total	5 (0)	11 (3)	0 (0)	20 (3)	33 (4)	0 (0)	53 (5)	79 (4)	1 (0)	0 (0)	0 (0)	0 (0)	35 (8)	45 (6)	23 (1)	305 (34)
Dose 3																
	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	
Age - 18-29 Yrs	0 (0)	0 (0)	0 (0)	1 (1)	1 (0)	0 (0)	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	5 (2)
Age - 30-39 Yrs	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	4 (2)
Age - 40-49 Yrs	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0)
Age - 50-59 Yrs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	1 (0)
Age - 70-79 Yrs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (1)	1 (0)	1 (1)
Age Unknown	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	1 (0)	2 (0)
Grand Total	0 (0)	2 (0)	0 (0)	1 (1)	1 (0)	0 (0)	3 (2)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	3 (0)	2 (1)	1 (0)	15 (5)

F Female; M Male; U Unknown

Events with fatal outcome

Eighteen percent (522/2811) of TTS cases reported fatal outcome. Age and gender stratification for fatal reports is presented in Table 80.

Table 80 Thrombosis with Thrombocytopenia Syndrome Case Reports by age/gender and fatality

Age group	Female N (fatal cases)	Male N (fatal cases)	Unknown Gender N (Fatal cases)	Grand Total
Age - 18-29 Yrs	138 (33)	99 (21)	2 (1)	239 (55)
Age - 30-39 Yrs	188 (53)	115 (29)	0 (0)	303 (82)
Age - 40-49 Yrs	254 (58)	180 (24)	2 (0)	436 (82)
Age - 50-59 Yrs	259 (50)	205 (36)	4 (1)	468 (87)
Age - 60-69 Yrs	273 (45)	272 (38)	2 (1)	547 (84)
Age - 70-79 Yrs	142 (22)	181 (18)	2 (0)	325 (40)
Age - 80+ Yrs	62 (10)	67 (10)	0 (0)	129 (20)
Age Unknown	132 (34)	97 (14)	135 (24)	364 (72)
Grand Total	1448 (305)	1216 (190)	147 (27)	2811 (522)

N Number, Yrs Years

TTO was available in 361 of the 522 fatal reports and ranged from 0 to 121 days with a median TTO of 11 days. Of the 521 fatal events, 481 fatal reports occurred after Dose 1, 34 fatal case reports occurred after Dose 2, 05 fatal cases after Dose 3 and there were one fatal case reports after Dose 4. The most frequently reported events of thrombosis in the fatal reports were: TTS (196), followed by (> 10), Cerebral venous sinus thrombosis (160), Pulmonary embolism (88), Thrombosis (72), Cerebral venous thrombosis (46), Portal vein thrombosis (38), Hemiparesis (37), Cerebrovascular accident (30), Cerebral thrombosis (29), Disseminated intravascular coagulation (25), Cerebral infarction (23), DVT (23), Superior sagittal sinus thrombosis (20), Haemorrhagic stroke (19), Transverse sinus thrombosis (18), Acute myocardial infarction (14), Mesenteric vein thrombosis (14), Ischaemic stroke (13), Peripheral artery thrombosis (11). In 306 out of 521 fatal reports (59%), there was a co-reported bleeding event from the narrow SMQ: Haemorrhage terms (excl. laboratory terms). Most common (>10) bleeding events included Cerebral haemorrhage (139), ITP (43), Haemorrhage intracranial (41), Subarachnoid haemorrhage (38), Disseminated intravascular coagulation (25), Haemorrhagic stroke (19), Haemorrhage (16), Petechiae (15), Contusion (13). Thirty-nine (38) case reports had the co-reported events from the HLT: Coagulopathies, including 25 cases with DIC.

Fatality/survival rate over time

Fatality/survival rate over time was calculated based on the case onset date. The onset date was not reported in 757 of the 2811 case reports, and for 160 case reports with fatal outcome. In cases where the onset date was not reported, date initially received by AstraZeneca was

used to calculate the reporting fatality/survival rate over time. Fatality/survival rate cumulatively for each month up to 28 December 2023 is presented in Table 81 and Figure 2.

The total number of fatal reports since August 2023 are decreasing compared to November 2022 to June 2023. There is an increased fatality rate in October 2023 (04 reported fatal events out of 05 reports) compared to the earlier months as there was a smaller number of cases reported. One of 04 cases (██████████) originated from UK with no reported vaccination dates, event onset dates, or time to event onset reported. Three cases originated from Australia and contained limited information with no reported vaccination dates, event dates, and information regarding time to event onset. The total number and percent of fatal reports has decreased, which suggests the effectiveness of the diagnostic and treatment guidelines implemented.

Table 81 TTS fatality/survival rate over time

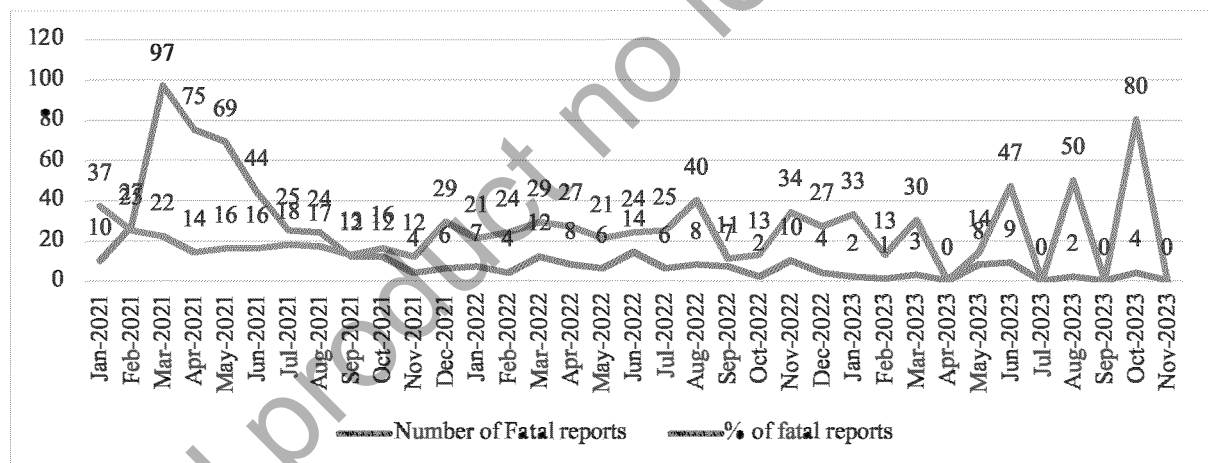
Case onset month ^a	Number of non-fatal reports	Number of Fatal reports	Grand Total	% of fatal reports
Jan-2021	17	10	27	37
Feb-2021	79	27	106	25
March 2021	342	97	439	22
April 2021	452	75	527	14
May 2021	359	69	428	16
June 2021	227	44	271	16
July 2021	117	25	142	18
August 2021	116	24	140	17
September 2021	83	12	95	13
October 2021	63	12	75	16
November 2021	30	4	34	12
December 2021	15	6	21	29
January 2022	27	7	34	21
February 2022	13	4	17	24
March 2022	29	12	41	29
April 2022	22	8	30	27
May 2022	22	6	28	21
June 2022	44	14	58	24
July 2022	18	6	24	25
August 2022	12	8	20	40
September 2022	58	7	65	11
October 2022	14	2	16	13
November 2022	19	10	29	34
December 2022	11	4	15	27
January 2023	4	2	6	33

Table 81 TTS fatality/survival rate over time

Case onset month ^a	Number of non-fatal reports	Number of Fatal reports	Grand Total	% of fatal reports
February 2023	7	1	8	13
March 2023	7	3	10	30
April 2023	1	0	1	0
May 2023	48	8	56	14
June 2023	10	9	19	47
July 2023	14	0	14	0
August 2023	2	2	4	50
September 2023	2	0	2	0
October 2023	1	4	5	80
November 2023	4	0	4	0
Grand Total	2289	522	2811	19

^a In cases where case onset date was not available, date initially received by AstraZeneca was used to calculate the reporting fatality/survival rate over time. TTS Thrombosis with thrombocytopenia syndrome.

Figure 2 TTS fatality/survival rate over time



Fatality rate over time by age group/gender for all cases is presented in Table 81 and fatality rate over time by age group/gender and doses (separately for all doses, Dose 1, and Dose 2) for confirmed/probable/possible cases is presented below.

Fatality rate in female vaccinees is higher (58%) compared to male (36%) for all cases and fatality rate in confirmed/probable/possible cases, is higher in female compared to male for all doses (63% vs 34%), Dose 1 (65% vs 32%) and Dose 3 (75% vs 25%) but for Dose 2, fatality rate in female is less than male (42% vs 58%); the reason for this difference might be cases received with Dose 2 are very little and this would increase the percentage markedly.

For all cases, highest fatality rate in female vaccinees was 17% in 30 to 39 years and 19% in 40 to 49 years age group, whereas in male vaccinees the highest fatality rate was 19% in 50 to 59 years and 20% in 60 to 69 years age group.

In confirmed/probable/possible cases, highest fatality rate in female vaccinees was 19% in 30-39 years, 40-49 years and 17% 50 to 59 years age groups (all doses) and 20 % in 30-39 years, 19% 40-49 years and 17% 50 to 59 years age groups (dose 1), 37% in 70-79 years age group (dose 2) and 66% in 30 -39 years age group (Dose 3), while in male vaccinees highest fatality rate in male vaccinees was 21% in 50-59 years and 19% 60-69 years (all doses) and 22% in 60 to 69 years age group (dose 1) and 54% in 70-79 years age group (dose 2). Fatality rate for some age groups/gender/months is increased compared to the previous period; however, reports received for these age groups/gender/months did not have onset dates of events and case received date was considered for analysis. This may be the reason for increased fatality rate, also cases received for these months are very little and this would increase the percentages markedly.

TTS reports after Dose 2 of VAXZEVRIA

A search of the AstraZeneca global safety database was undertaken to retrieve AE reports of thrombosis in combination with thrombocytopenia reported following administration of the Dose 2 of the VAXZEVRIA. The search encompassed all cases retrieved up to 28 December 2023. The search criteria mentioned above was used to identify TTS cases post Dose 2.

The cases of TTS following the Dose 2 were confirmed based on the dose number/information provided in the narrative, if the reports did not contain information on Dose 2, they were not included in the below analysis. The search identified 305 cumulative cases of TTS following the second dose of VAXZEVRIA. Time to onset was available in 231 of the 305 cases and ranged from 0 to 406 Days with a median TTO of 13.5 Days after 2nd dose. Time to onset by 14 Days, 21 Days, and 42 Days is presented in Table 73.

The majority of the 305 case reports of TTS following second dose occurred in male vaccinees (168, 55%). Of the 305 case reports of TTS following second dose, 113 were female (37%), and gender was unknown in 24 reports. The age range of vaccinees was from 22 to 95 years, age was not provided in 24 of the 305 reports. Median age was 65 years and 211 (69%) of the reports were in vaccinees > 50 years. Outcome in 87 cases were reported as Not recovered, 34 died, 24 Recovered, 80 Recovering, 10 Recovered with sequelae and Unknown in 70 reports.

These events included the following sites of thrombosis (≥ 5): Pulmonary embolism (124), DVT (71), TTS (60), Thrombosis (38), Cerebral venous sinus thrombosis (19), Cerebrovascular accident (17), Portal vein thrombosis (10), Embolism (10), Superior sagittal sinus thrombosis (6), Peripheral artery thrombosis (6), TTP (6), Mesenteric vein thrombosis (5).

In 67 out of 305 reports (22%) with Dose 2, there was a co-reported bleeding event from the narrow SMQ: Haemorrhage terms (excl. laboratory terms). The reported events (≥ 2) included: ITP (12), Haemorrhage (11), Contusion (9), Cerebral haemorrhage (8), TTP (6), Haemoptysis (6), Petechiae (4), Haemorrhagic stroke (3), Haematuria (2). There were two case report with the co-reported events from the HLT: Coagulopathies following Dose 2 with the event Coagulopathy (2) and Antiphospholipid syndrome (1).

TTS reports after Dose 3 of VAXZEVRIA

A search of the AstraZeneca global safety database was undertaken to retrieve AE reports of thrombosis in combination with thrombocytopenia reported following administration of the Dose 3 of the VAXZEVRIA as per the request received from PRAC (Procedure number: EMEA/H/C/PSUSA/00010912/202212). The search encompassed all cases retrieved up to 28 December 2023. The cases of TTS following the Dose 3 were confirmed based on the dose number/information provided in the narrative. Cumulatively there were 21 cases occurred after administration of a Dose 3/booster (either of AZD1222 or an mRNA vaccine): 15 after an VAXZEVRIA booster, and 6 after a mRNA booster. The 6 cases after an mRNA booster are not further discussed here as they do not concern the use of VAXZEVRIA as a booster. Of the 15 case reports of TTS following Dose 3/booster, 7 were female (40%), and 7 were male. The age range of vaccinees was from 21 to 74 years. Median age was 34 Days. Time to onset was available in 10 of the 15 cases and ranged from 1 to 60 days with a median TTO of 09 days after 3rd dose. Ten cases originated from Brazil and one case each from Ecuador, UK, Mexico, Italy and Germany. Outcome in 3 cases were reported as Not recovered, 3 Recovering, 2 recovered, 5 Fatal reports, 2 Unknown. The cases met the MHRA criteria confirmed 2, probable 2 (including 1 fatal case), possible 6 (including 3 fatal case) and criteria not met 5 (including 1 fatal case).

The events included the following sites of thrombosis: TTS (8), Thrombosis (4), Cerebral venous sinus thrombosis (3), Pulmonary embolism (3), Cerebral venous thrombosis (1), Transverse sinus thrombosis (1), Haemorrhagic stroke (1), Cerebral thrombosis (1), Venous thrombosis (1), Splenic infarction (1), Renal infarct (1). The co-reported bleeding event from the narrow SMQ: Haemorrhage terms (excl. laboratory terms). The reported events: Contusion (1), ITP (1), Heavy menstrual bleeding (1), Haematuria (1), Petechiae (1), Haemorrhage intracranial (1), Haemorrhagic stroke (1).

Summary of the fatal case report with details is presented below.

Case ID [REDACTED]: The spontaneous case concerned 22 years old female patient of unknown ethnic origin received from health professional in Brazil. The patient received 1st and 2nd dose Comirnaty. On 04 April 2022, the patient received booster dose of VAXZEVRIA. On 14 April 2022, the patient experienced loss of consciousness (preferred term: Loss of consciousness), hypotension (preferred term: Hypotension), abnormal platelets (preferred term: Platelet disorder) and brain thrombosis (preferred term: Cerebral thrombosis). It was not known whether an autopsy was performed.

AZ comments: The associated event hypotension could be considered as risk factor for event of loss of consciousness. TTO was within in the risk window (10 Days) for the safety topic. However, case has insufficient information on circumstances leading to the events, clinical course, any history of thrombosis/coagulopathy, patient's COVID-19 infection status, autopsy details with confirmed diagnosis on cause of death, complete etiological and diagnostic workup, the evaluation did not find evidence to suggest a causal relationship between the fatal events and VAXZEVRIA.

Case ID [REDACTED]: This spontaneous case concerned 28 years old male patient. Vaccination details for the dose 1 and dose 2 was not reported. On 03 June 2022, the patient received booster dose of VAXZEVRIA. On 10 June 2022, the patient complaining of intense headache and afterwards, radiating to the lumbar region. The patient was given morphine. The patient was referred for MRI which result showed thrombosis in the superior sagittal dural venous sinuses, left transverse and sigmoid vein, and in the internal jugular vein on that side. Brain parenchyma with preserved signal. The patient complains of paresthesia of the right upper limb and involuntary movements, requested cranial computed tomography that reveals an intraparenchymal hemorrhagic lesion in the left parietal region. Evolved with neurological worsening. He presented with intracranial bleeding requiring Oro Tracheal Intubation due to a lowered level of consciousness, evolving rapidly with anisocoria. On 12-Jun-2022, the patient was referred to the operating room to perform surgical decompression. Immunoglobulin and platelet blood transfusion were performed. He continued to be assisted by the hematology team. Assessed by the neuro on the 13-Jun-2022 with anisocoria on the right, he requested cranial computed tomography in an emergency with extensive areas of new hemorrhagic in relation to the previous exam. With a reserved prognosis and probable brain death protocol, pupils with fixed mydriasis. Off sedation to assess evolution. 14 June 2022, started brain death protocol.

AZ comments: The vaccinee died 11 Days from the date of vaccine administration. There was insufficient information on baseline health condition of the vaccinee before vaccination, medical history (such as antiphospholipid syndrome, cancer-associated thrombosis, and thrombocytopenia, disseminated intravascular coagulation), concurrent diseases and concomitant medications, circumstances leading to the event, autopsy report if any with a confirmed diagnosis of death.

Case ID [REDACTED]: This spontaneous case concerning a 38-year-old female patient of unknown ethnic origin received from health professional in Brazil. On 22 June 2022, the patient received VAXZEVRIA. On 02 July 2022, the patient experienced stroke hemorrhagic (preferred term: Haemorrhagic stroke) and thrombocytopenia (preferred term: Thrombocytopenia). On 03 July 2022, the patient experienced pulmonary embolism (preferred term: Pulmonary embolism). It was reported on an unspecified date, the patient died from the event of pulmonary embolism, stroke hemorrhagic and thrombocytopenia. On 04 July 2022, the patient was performed test PCR with result 219, test TOMOGRAPHY OF THE CHROMIUM with result Extensive decompressive craniectomy frontoparietal D. Hyperattenuating material compatible with hematic material in extra-axial situation located also in subdural region of cortical sulci and fissure sylviana on the right. presence of material hyperattenuating apparently parenchymatous in the depth of the right cerebral hemisphere. The remainder of the brain parenchyma is diffusely hypoattenuating with loss of distinction into three white and gray substances suggestive of diffuse hypoxic ischemic injury. Subfalcine herniation of the line structures median to the right at about 32mm to the level of the pellucid septum, noting transcranial brain herniation. Tapering of the ventricular system supra and infratentorial for hyperattenuating material in its interior compatible with hemoventri. Test CRANIAL TOMOGRAPHY CONTINUED with result Pneumoencephalal images on the right.

AZ comments: In this case has insufficient information on relevant family and medical history, concurrent diseases and concomitant medications, circumstances leading to the events, clinical course of the events, treatment given, autopsy report, the evaluation did not find evidence to suggest a causal relationship between the fatal events and VAXZEVRIA.

Case ID [REDACTED]: This spontaneous case concerned 37 years old female patient received from a health professional. The patient's past and current medical history included obesity (ongoing). No concomitant products were reported. The patient received VAXZEVRIA on 22 June 2022. On 30 June 2022, the patient experienced thrombosis syndrome with thrombocytopenia (preferred term: TTS). It was reported the patient was suffering from hemorrhagic cerebrovascular accident and morbid obesity. The patient's [REDACTED] refers to peeks and ecchymosis in UL and metrorragy outside the menstrual period (two days before the aggravation). The neurologist: diagnosis history: brain edema / subarachnoid hemorrhage / right brain middle artery aneurysm dengue (antigen ns1 07/02 - negative). exams for respiratory virus performed on 03 July 2022 still no result. id intracranial hypertension / ischemia of anterior cerebral artery and bilateral brain middle artery territories / sub arachnoid hemorrhage aggravated by plachetopenia. identified by doppler ultrasonography of UL: venous thrombosis to right subclavia vein, with normal arterial flow vascular surgery: deep venous thrombosis in upper right limb, with worse of edema and local cyanosis, signs of compartmental syndrome, signs of venolysis in upper right limb, antecubital edge. risk of loss of the upper right member 03 July 2022. diagnosis hypothesis: severe thrombocytopenia, hypernatremia, acute kidney failure, deep venous thrombosis, arterial ischemia with upper right limb compartment syndrome. brain edema with subarachnoid hemorrhage, vascular revaluation worse previous clinical picture, reduced flow arterial. fasciotomy with urgency at bedroom due to hemodynamic instability. On 04 July 2022 average general state, risk of death, neurological assessment on brain vitality. process of irreversible limb ischemia (lost, without vitality). severe plachetopenia. first clinical test for brain death started. 05 July 2022 severe metabolic acidosis, it was not possible to perform apnea test 06 July 2022 obit. there was no further information about this report.

AZ comments: Due to limited information on baseline health condition before vaccination, circumstances leading to the events, further risk factors, if any beyond conditions and diseases reported in medical history, concomitant medications, autopsy report with confirmed diagnosis, detailed aetiological and diagnostic work up, the evaluation did not find evidence to suggest a causal relationship between the events and AZD1222.

Table 82 Post-Marketing Cases of Thrombosis with Thrombocytopenia Syndrome Related to VAXZEVRIA COVID-19 Vaccine Booster

Case ID Country	Events (PT)	Age/Sex	Primary / Booster vaccine	Time to onset	MHRA case classification	Comment
	Cerebral venous sinus thrombosis; Immune thrombocytopenia; Cerebral venous thrombosis; Haemorrhage intracranial; Incorrect route of product administration; Seizure; Interchange of vaccine products	26/F	CoronaVac / AZD1222 (19 January 2022)	16 days	Criteria not met	This is a consumer report. Past drug therapy included COVID-19 vaccine (first 2 doses of the vaccine corresponded to the CoronaVac brand, without any problem) for prevention. On 19 January 2022, patient received Dose 3 of VAXZEVRIA . There is no radiological confirmation for thrombosis event.
	Pulmonary embolism; Sepsis; Pulmonary sepsis; Lung neoplasm malignant; Thrombocytopenia; Pyrexia; Respiratory rate increased	74/F	AZD1222 / AZD1222	Same day	Criteria not met	Regulatory report. No evidence of thrombocytopenia; considered to be a coding error and case was received from regulatory authority. Pulmonary embolism event was reported on same day of booster and in the context of pulmonary sepsis and malignant lung neoplasm. The patient outcome at the time of the report was not recovered.

Table 82 Post-Marketing Cases of Thrombosis with Thrombocytopenia Syndrome Related to VAXZEVRIA COVID-19 Vaccine Booster

Case ID Country	Events (PT)	Age/Sex	Primary / Booster vaccine	Time to onset	MHRA case classification	Comment
	Paralysis; Thrombosis; Speech disorder; Coordination abnormal; Muscular weakness; Diplopia; Petechiae; Contusion; Pallor; Heavy menstrual bleeding; Vision blurred; Thrombocytopenia; Dizziness; Nausea; Expired product administered; Incorrect route of product administration; Fatigue; Headache; Decreased appetite; Pain in extremity	46/F	AZD1222 / AZD1222	5 days	Possible	This is a consumer report. VAXZEVRIA Dose 1: 09 June 2021 VAXZEVRIA Dose 2: 03 August 2021 VAXZEVRIA Dose 3: 06 September 2021 There are events of medication error (subcutaneous route administration and expired product administered). The lot ID for reported Dose 2 and Dose 3 are same; hence, it cannot be confirmed as booster dose. There is no radiological confirmation for thrombosis event (site of thrombosis not reported), and the patient was treated with prednisolone for thrombocytopenia. No information on D-dimer and anti-PF4.
Italy	Thrombosis; Platelet count decreased; Off label use	NA/M	Unknown/ Unidentified AstraZeneca Product	Unknown	Criteria not met	Report was based on a social media post. There is very little information in this case. Not clear if this was VAXZEVRIA, as VAXZEVRIA is not used in Italy for booster dose. The patient died from the event of thrombosis during December 2021.

Table 82 Post-Marketing Cases of Thrombosis with Thrombocytopenia Syndrome Related to VAXZEVRIA COVID-19 Vaccine Booster

Case ID Country	Events (PT)	Age/Sex	Primary / Booster vaccine	Time to onset	MHRA case classification	Comment
	Venous thrombois; Pulmonary embolism, Thrombocytopenia	28/M	COMIRNATY / AZD1222 (03 March 2022)	2 days	Possible	This is a consumer report. Pfizer Dose 1: 11 August 2021 Pfizer Dose 2: 25 October 2021 AstraZeneca Dose 3: 03 March 2022 Venous thrombosis occurred 2 days after the Vaxzevria and pulmonary embolism occurred, 14 days after last dose. Events were confirmed by CT angiography of chest and abdominal aorta on 18 March 2022. Patient had history of DVT 14 months back, was put-on long-term anticoagulation with oral Rivaroxaban, which was stopped prior to the events. Normal D-dimer and negative PF4. Patient recovered from all events.
	Splenic infarction; Renal infarct; Thrombosis; Thrombosis with thrombocytopenia syndrome; Influenza; Haematuria; Dysuria; Back pain; Headache; Facial pain; Pyrexia; Abdominal pain lower	M/21	COMIRNATY/Vaxzevria	10 days	Probable	Spontaneous report. The vaccinee received First and second dose of Pfizer vaccine (dates unknown). AstraZeneca vaccine (Dose 3) received on 06 May 2022. CT scan abdomen revealed splenic infarction, renal infarct. Patient received Fondaparinux, Rivaroxaban and IVIg as treatment and was recovering.
Brazil	Pulmonary embolism; Haemorrhagic stroke; Thrombocytopenia	38 years /F	Vaxzevria booster	10 days	Possible	Spontaneous report. VAXZEVRIA received as Dose 3 on 22 June 2022. 10 days later developed pulmonary embolism, haemorrhagic stroke diagnosed by skull and chest CT. High D-dimer and anti PF-4 positive. Outcome was fatal.

Table 82 Post-Marketing Cases of Thrombosis with Thrombocytopenia Syndrome Related to VAXZEVRIA COVID-19 Vaccine Booster

Case ID Country	Events (PT)	Age/Sex	Primary / Booster vaccine	Time to onset	MHRA case classification	Comment
	Thrombosis with thrombocytopenia syndrome	32 years /M	Vaxzevria booster	7 days	Criteria not met	Spontaneous report. VAXZEVRIA received as Dose 4 on 25 June 2022. Previous doses were Coronavac/Coronavac/Pfizer. Symptoms began 7 days later with headache. Rapid neurological deterioration with seizures. CT skull revealed intracranial bleed. No radiological conformation of any cerebral venous sinus thrombosis or thrombosis at any other site. High D-dimer, PF 4 positive. Treated with IVIg. The patient outcome at the time of the report was not recovered.
Brazil	Thrombosis with thrombocytopenia syndrome	37 years /F	Vaxzevria booster	8 days	Possible	Spontaneous report. VAXZEVRIA received as Dose 4 on 22 June 2022. 8 days later developed thrombosis at multiple sites with complications. Outcome was fatal.
	Thrombosis with thrombocytopenia syndrome; Haemorrhoids; Headache; Pyrexia	41 years/M	Vaxzevria booster	N/A	Confirmed	This is a consumer report. VAXZEVRIA received as Dose 4 on 26 July 2022. Previous doses were with the Pfizer vaccine. Symptomatic 13 days later starting with headache. CT skull revealed CVST. High D-dimer, PF 4 positive. Treated with Rivaroxaban. Had intercurrent COVID-19 illness. Outcome was recovered.

Table 82 Post-Marketing Cases of Thrombosis with Thrombocytopenia Syndrome Related to VAXZEVRIA COVID-19 Vaccine Booster

Case ID Country	Events (PT)	Age/Sex	Primary / Booster vaccine	Time to onset	MHRA case classification	Comment
	Seizure; Cerebral thrombosis; acute respiratory distress syndrome; Thrombocytopenia; Vision blurred; Paraesthesia	20 years/M	Vaxzevria booster	13 days	Criteria not met	This is a consumer report. VAXZEVRIA received as Dose 1 on 16 June 2021. 2nd and 3rd doses were with Coronavac vaccine (dates unknown). 5 days after receiving VAXZEVRIA became symptomatic with blurred vision and paraesthesia. Later on, progressed to Cerebral venous thrombosis with intracranial bleed. During hospitalization, he had a lowered level of consciousness and required orotracheal intubation, which led to pulmonary complications. Anti PF4 positive. Treated with IVIg. Outcome unknown.
	Cerebral venous sinus thrombosis; Seizure; Thrombosis with thrombocytopenia syndrome; Interchange of vaccine products; Off label use	Unknown	AZD1222	14 days	Criteria not met	Spontaneous report. VAXZEVRIA received as Dose 3 on 19 January 2022. The 1st and 2nd vaccine shots were Sinovac. Insufficient information on complete demographics, outcome of the event, concomitant conditions and detailed diagnostic and etiologic workup.
	Cerebral venous sinus thrombosis; Cystitis; Transverse sinus thrombosis; Fibrin D dimer increased; Thrombocytopenia; Dysuria; Perineal pain; Testicular oedema; Urethritis; Chills; Abdominal pain lower; Headache; Pyrexia	M	AZD1222	Unknown	Confirmed	Spontaneous report. VAXZEVRIA received as Dose 3 on 14 February 2022. The vaccinee received primary vaccination series with Comirnaty. Concurrent conditions, relevant medical and family history, risk factors (hypercoagulability, ongoing infection), complete etiological work up not reported. Had radiologically confirmed CVST with high D-dimer and positive PF4. Outcome was recovered.

Table 82 Post-Marketing Cases of Thrombosis with Thrombocytopenia Syndrome Related to VAXZEVRIA COVID-19 Vaccine Booster

Case ID Country	Events (PT)	Age/Sex	Primary / Booster vaccine	Time to onset	MHRA case classification	Comment
[REDACTED] Brazil	Loss of consciousness; Hypotension; Platelet disorder; Thrombosis	22/F	AZD1222	10 days	Probable	Spontaneous report. First two doses of Pfizer vaccine. VAXZEVRIA received as Dose 3 on 04 April 2022. After 10 days developed the events. No radiological confirmation of site of thrombosis. High D-dimer and positive PF4. Outcome was fatal.
[REDACTED] Brazil	Thrombosis with thrombocytopenia syndrome	28/M	AZD1222	7 days	Possible	This is a spontaneous report. On 03 June 2022 patient took the 3rd dose of the AstraZeneca vaccine. Thrombosis at multiple sites was radiologically confirmed. Thrombocytopenia, Anti PF4 antibodies positive. D-dimer levels not reported, fibrinogen normal. Event had fatal outcome

CT Computed Tomography; CVST Cerebrovascular Venous and Sinus Thrombosis; F Female; M Male; PF4 Platelet Factor 4; PT Preferred Term

Literature

A periodic literature search of the databases in Embase, Insight Meme and PubMed was conducted for relevant articles on topic to review and understand the pathophysiology in association with VAXZEVRIA.

Richard et al 2024 studied that platelet factor 4 (PF4) binds and activates the thrombopoietin receptor (TPO), cellular myeloproliferative leukemia protein (c-Mpl), on platelets. This leads to the activation of Janus kinase 2 (JAK2) and phosphorylation of signal transducer and activator of transcription (STAT) 3 and STAT5, leading to platelet aggregation. Inhibition of the c-Mpl–JAK2 pathway inhibits platelet aggregation to PF4, VITT sera, and the combination of PF4 and IgG isolated from VITT patient plasma. To investigate this mechanism of activation the authors measured tyrosine phosphorylation of whole cell lysates by western blotting using the anti-phosphotyrosine monoclonal antibody. PF4 stimulated a concentration-dependent increase in tyrosine phosphorylation of a prominent doublet at 95 kDa. Analysis by mass spectrometry revealed the presence of a signal transducer and activator of transcription (STAT) 5a/b peptide phosphorylated. These findings were confirmed by western blot analysis using a phosphospecific antibody to STAT5a/b. STAT3 was also identified by mass spectrometry and shown to be phosphorylated on Tyr704 using a phosphospecific antibody. The JAK2 inhibitor ruxolitinib inhibits platelet activation by PF4. The author used a concentration of ruxolitinib (100 nM) that had no effect on platelet activation by CRP or thrombin to minimize off-target effects. In high-responding donor platelets, ruxolitinib inhibited aggregation by PF4 (50 µg/mL) and TPO (100 ng/mL) and blocked potentiation of aggregation to a subthreshold concentration of CRP by PF4 (10 µg/mL). The same concentration of ruxolitinib also inhibited phosphorylation of STAT3 and STAT5a/b by PF4 and TPO. In the context of VITT, binding of PF4 to c-Mpl might increase the functional affinity of immune complexes for platelet binding and increase the avidity of the antibody-FcγRIIA interaction. These findings may have a similar relevance for HIT, where, in addition, there may be synergy with the activation of platelet endothelial aggregation receptor 1 (PEAR1) by heparin.

Warkentin et al 2023 report the development of symptomatic adenovirus infection in a 5-year-old boy and a 58-year-old woman. Both patients had nasopharyngeal swab samples that were positive for human adenovirus and negative for 18 other pathogens, including severe acute respiratory syndrome coronavirus 2, as determined with the BioFire Respiratory 2.1 Panel (bioMérieux), a PCR-based multiplexed nucleic acid test. Both patients had fever, with gastrointestinal symptoms in the child and respiratory symptoms in the adult. These symptoms were followed 5 to 6 days later by severe thrombocytopenia in both patients, coagulopathy (hypofibrinogenemia in both patients and a greatly elevated d-dimer level in the child [d-dimer levels were not measured in the adult]), and thrombotic events (fatal cerebral venous sinus thrombosis in the child and multiple arterial strokes, ST-segment elevation myocardial infarction, and multiple deep-vein thromboses in the adult). Neither patient had been previously exposed to heparin. Using multiple anti-PF4 assays, the author found VITT like antibodies to PF4 in serum samples obtained from both patients.

The author suggested that a life-threatening, prothrombotic anti-PF4 disorder with clinical and serologic features resembling VITT can be triggered by symptomatic human adenovirus infection. PF4 has been shown to bind to adenovirus through charge complementarity, which provides a plausible explanation for how adenovirus infection and adenoviral vector vaccines might rarely trigger an anti-PF4 disorder.

AstraZeneca Comment: The above articles provide potential hypotheses for mechanism of TTS with VAXZEVRIA; however, these hypotheses have not been confirmed. Further evaluation is required to better characterize and confirm the mechanism of TTS with VAXZEVRIA.

CVST with thrombocytopenia

Of the 2811 thrombosis with thrombocytopenia case reports reviewed cumulatively, the reported venous thrombotic sites included CVST (HLT: Cerebrovascular venous and sinus thrombosis) in 720 (25%) cases. Of these 720 cases, 454 (63%) were in females, 251 (35%) occurred in males, and in 2% gender was unknown.

In 223 of the 720 (31%) of the CVST with Thrombocytopenia cases were fatal. CVST with thrombocytopenia cases by age group/gender/dose and fatality are provided.

Table 83 Cerebral venous sinus thrombosis with Thrombocytopenia Case Reports by age/gender

Age group	Female N (fatal)	Male N (fatal)	Unknown N (fatal)	Grand Total
Age - 18-29 Yrs	55 (13)	52 (11)	1 (0)	108 (24)
Age - 30-39 Yrs	84 (36)	46 (18)	0 (0)	130 (54)
Age - 40-49 Yrs	117 (36)	46 (12)	0 (0)	163 (48)
Age - 50-59 Yrs	73 (19)	46 (17)	0 (0)	119 (36)
Age - 60-69 Yrs	69 (19)	30 (9)	0 (0)	99 (28)
Age - 70-79 Yrs	16 (9)	4 (2)	0 (0)	20 (11)
Age - 80+ Yrs	2(0)	3(0)	0(0)	5(0)
Age Unknown	38(14)	24(3)	14(5)	76(22)
Grand Total				
Dose 1				
Age - 18-29 Yrs	53(12)	51(11)	1(0)	105(23)
Age - 30-39 Yrs	83(35)	45(18)	0(0)	128(53)
Age - 40-49 Yrs	113(34)	40(12)	0(0)	153(46)
Age - 50-59 Yrs	71(19)	43(15)	0(0)	114(34)
Age - 60-69 Yrs	68(19)	25(8)	0(0)	93(27)
Age - 70-79 Yrs	16(9)	3(1)	0(0)	19(10)
Age - 80+ Yrs	1(0)	3(0)	0(0)	4(0)
Age Unknown	36(13)	21(3)	13(5)	70(21)
Grand Total				
Dose 2				
Age - 18-29 Yrs	1(1)	1(0)	0(0)	2(1)
Age - 30-39 Yrs	1(1)	0(0)	0(0)	1(1)
Age - 40-49 Yrs	3(1)	6(0)	0(0)	9(1)
Age - 50-59 Yrs	2(0)	3(2)	0(0)	5(2)

Age - 60-69 Yrs	1(0)	5(1)	0(0)	6(1)
Age - 70-79 Yrs	0(0)	1(1)	0(0)	1(1)
Age - 80+ Yrs	1(0)	0(0)	0(0)	1(0)
Age Unknown	2(1)	3(0)	0(0)	5(1)
Grand Total				
Dose 3				
Age - 18-29 Yrs	1(0)	0(0)	0(0)	1(0)
Age - 30-39 Yrs	0(0)	1(0)	0(0)	1(0)
Age - 40-49 Yrs	0(0)	0(0)	0(0)	0(0)
Age - 50-59 Yrs	0(0)	0(0)	0(0)	0(0)
Age - 60-69 Yrs	0(0)	0(0)	0(0)	0(0)
Age - 70-79 Yrs	0(0)	0(0)	0(0)	0(0)
Age - 80+ Yrs	0(0)	0(0)	0(0)	0(0)
Age Unknown	0(0)	0(0)	1(0)	1(0)
Grand Total	1(0)	1(0)	1(0)	3(0)

Reporting rates for CVST with thrombocytopenia

Reporting rates for CVST in combination with thrombocytopenia across age groups based on the data from the UK and EEA by risk window of 21 Days and 42 Days are provided in Table 84; reporting rate is also stratified by Dose 1, and Dose 2.

The reporting rate of CVST in combination with thrombocytopenia in the UK was higher across the age groups when compared to the BG rate except for reports in vaccinees aged > 65 years (risk window 21 days), aged > 50 years (risk window 42 days) and with Dose 2.

The reporting rate of CVST in combination with thrombocytopenia in the EEA was higher when compared to the BG rate in vaccinees aged < 70 years with all doses. In the EEA the reporting rate of CVST in combination with thrombocytopenia with Dose 2 was higher than the BG rate for vaccinees aged < 49 years, however reporting rate in age group > 50 years was less compared to the BG rate.

The observed versus expected analyses for TTS (including CVST) and CVST with thrombocytopenia are presented in Table 85. Background rates for TTS were derived from MarketScan (US claims) data, using OHDSI-aligned code lists and definitions for TTS.

Algorithm 2 for TTS uses updated OHDSI-aligned code lists and washout periods (previously patients with thrombosis in the 2 years prior to 2019 were excluded). The results of the observed versus expected analyses suggests that observed cases of CVST with thrombocytopenia are more than expected for all age stratifications.

Table 84 Reporting rate for CVST and thrombocytopenia (UK and EEA data) by risk window of 21 days

UK 21 Days RW								
Age Group	Total Exposed	Cases within Risk Window of 21 days	Confirmed, probable and possible cases within Risk Window of 21 days	Reporting Rate (per million)	Reporting Rate (per million) for Confirmed, probable and possible cases	Background Rate (per million) ^a	Rate relative to Background (per million)	Rate relative to Background (per million) for Confirmed, probable and possible cases
All Dose (UK)								
Age - 18-39 Yrs	5227125	47	43	8.99	8.23	0.1	8.89	8.13
Age - 40-49 Yrs	8954709	62	54	6.92	6.03	0.1	6.82	5.93
Age - 50-64 Yrs	17999174	58	53	3.22	2.94	0.2	3.02	2.74
Age - > 65 Yrs	13443624	7	7	0.52	0.52	0.2	0.32	0.32
Age Unknown	3294137	8	7	2.43	2.12	-	-	-
Grand Total	48918769	182	164	3.72	3.35	0.1	3.62	3.25
Dose 1 (UK)								
Age - 18-39 Yrs	2663686	47	43	17.64	16.14	0.1	17.54	16.04
Age - 40-49 Yrs	4535864	59	52	13.01	11.46	0.1	12.91	11.36
Age - 50-64 Yrs	9060897	56	52	6.18	5.74	0.2	5.98	5.54
Age - > 65 Yrs	6737698	6	6	0.89	0.89	0.2	0.69	0.69
Age Unknown	1723525	7	6	4.06	3.48	-	-	-

Table 84 Reporting rate for CVST and thrombocytopenia (UK and EEA data) by risk window of 21 days

UK 21 Days RW								
Age Group	Total Exposed	Cases within Risk Window of 21 days	Confirmed, probable and possible cases within Risk Window of 21 days	Reporting Rate (per million)	Reporting Rate (per million) for Confirmed, probable and possible cases	Background Rate (per million) ^a	Rate relative to Background (per million)	Rate relative to Background (per million) for Confirmed, probable and possible cases
Grand Total	24721670	175	159	7.08	6.43	0.1	6.98	6.33
Dose 2 (UK)								
Age - 18-39 Yrs	2558509	0	0	0	0	0.1	-0.1	-0.1
Age - 40-49 Yrs	4412378	3	2	0.68	0.45	0.1	0.58	0.35
Age - 50-64 Yrs	8921359	2	1	0.22	0.11	0.2	0.02	-0.09
Age - > 65 Yrs	6679268	1	1	0.15	0.15	0.2	-0.05	-0.05
Age Unknown	1566438	1	1	0.64	0.64	-	-	-
Grand Total	24137952	7	5	0.29	0.21	0.1	0.19	0.11
All Dose (EEA)								
Age - 18-49	11827734	123	72	10.4	6.09	0.07	10.33	6.02
Age - 50-59	6495374	26	19	4	2.93	0.16	3.84	2.77
Age - 60-69	20461213	49	29	2.39	1.42	0.4	1.99	1.02
Age - 70-79	8193743	6	3	0.73	0.37	0.47	0.26	-0.1
Age - 80+	1165347	1	0	0.86	0	0	0.86	0

Table 84 Reporting rate for CVST and thrombocytopenia (UK and EEA data) by risk window of 21 days

UK 21 Days RW								
Age Group	Total Exposed	Cases within Risk Window of 21 days	Confirmed, probable and possible cases within Risk Window of 21 days	Reporting Rate (per million)	Reporting Rate (per million) for Confirmed, probable and possible cases	Background Rate (per million) ^a	Rate relative to Background (per million)	Rate relative to Background (per million) for Confirmed, probable and possible cases
Age Unknown	8441	5	4	592.35	473.88	-	-	-
Grand Total	48151852	210	127	4.36	2.64	-	-	-
Dose 1 (EEA)								
Age - 18-49	6434510	120	70	18.65	10.88	0.07	18.58	10.81
Age - 50-59	3518799	26	19	7.39	5.4	0.16	7.23	5.24
Age - 60-69	10521781	46	29	4.37	2.76	0.4	3.97	2.36
Age - 70-79	4176155	6	3	1.44	0.72	0.47	0.97	0.25
Age - 80+	596132	1	0	1.68	0	0	1.68	0
Age Unknown	4187	4	4	955.34	955.34	-	-	-
Grand Total	25251564	203	125	8.04	4.95	-	-	-
Dose 2 (EEA)								
Age - 18-49	5385769	3	2	0.56	0.37	0.07	0.49	0.3
Age - 50-59	2972927	0	0	0	0	0.16	-0.16	-0.16
Age - 60-69	9934975	3	0	0.3	0	0.4	-0.1	-0.4
Age - 70-79	4014635	0	0	0	0	0.47	-0.47	-0.47

Table 84 Reporting rate for CVST and thrombocytopenia (UK and EEA data) by risk window of 21 days

UK 21 Days RW								
Age Group	Total Exposed	Cases within Risk Window of 21 days	Confirmed, probable and possible cases within Risk Window of 21 days	Reporting Rate (per million)	Reporting Rate (per million) for Confirmed, probable and possible cases	Background Rate (per million) ^a	Rate relative to Background (per million)	Rate relative to Background (per million) for Confirmed, probable and possible cases
Age - 80+	567777	0	0	0	0	0	0	0
Age Unknown	3931	0	0	0	0	-	-	-
Grand Total	22880014	6	2	0.26	0.09	-	-	-

CVST Cerebrovascular Venous and Sinus Thrombosis; EEA European Economic Area; RW Risk Window; UK United Kingdom

Table 85 Observed versus Expected Analysis for CVST+TCP

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	Observed/Expected ratio (95% CI)	Conclusion
CVST-TCP - Overall	14	0.25	466115644	421	44.67	9.42 (8.55 - 10.37)	Observed significantly > expected
CVST-TCP - Overall	21	0.25	466115644	496	67	7.4 (6.77 - 8.08)	Observed significantly > expected
CVST-TCP - Overall	42	0.25	466115644	531	134	3.96 (3.63 - 4.31)	Observed significantly > expected
CVST-TCP - Overall (RW14 + Unk TTO)							
CVST-TCP - Overall (RW14 + Unk TTO)	21	0.25	466115644	496	67	7.4 (6.77 - 8.08)	Observed significantly > expected
CVST-TCP - Overall (RW42 + Unk TTO)	42	0.25	466115644	531	134	3.96 (3.63 - 4.31)	Observed significantly > expected

Table 85 Observed versus Expected Analysis for CVST+TCP

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	Observed ratio (95% CI)	Conclusion
Observed Versus Expected analysis for CVST+TCP by age group (EU/UK/Brazil/Australia)							
CVST-TCP - 18-49	14	0.17	110094983	255	7.17	35.56 (31.33 - 40.21)	Observed significantly > expected
CVST-TCP - 50-59	14	0.39	58336094	73	8.72	8.37 (6.56 - 10.53)	Observed significantly > expected
CVST-TCP - 60-69	14	0.33	57960860	63	7.33	8.59 (6.6 - 11)	Observed significantly > expected
CVST+TCP:70+	14	0.24	32376365	13	2.98	4.36 (2.32 - 7.46)	Observed significantly > expected
CVST-TCP - 18-49	21	0.17	110094983	291	10.76	27.04 (24.03 - 30.34)	Observed significantly > expected
CVST-TCP - 50-59	21	0.39	58336094	94	13.08	7.19 (5.81 - 8.79)	Observed significantly > expected
CVST-TCP - 60-69	21	0.33	57960860	76	11	6.91 (5.44 - 8.65)	Observed significantly > expected
CVST+TCP:70+	21	0.24	32376365	18	4.47	4.03 (2.39 - 6.36)	Observed significantly > expected
CVST-TCP - 18-49	42	0.17	110094983	307	21.52	14.27 (12.71 - 15.95)	Observed significantly > expected
CVST-TCP - 50-59	42	0.39	58336094	101	26.16	3.86 (3.14 - 4.69)	Observed significantly > expected
CVST-TCP - 60-69	42	0.33	57960860	84	21.99	3.82 (3.05 - 4.73)	Observed significantly > expected
CVST+TCP:70+	42	0.24	32376365	20	8.94	2.24 (1.37 - 3 Days)	Observed significantly > expected

Background event rates per 1M PY per 42 days from Truven Market Scan-2019.

CI Confidence Interval; CVST Cerebral Venous Sinus Thrombosis; E Expected; O Observed; TCP Thrombocytopenia

Summary

The analysis of thrombosis in combination with thrombocytopenia following the booster dose of VAXZEVRIA showed that the rate of events was extremely low and lower than after administration of the first dose and second dose. The majority of the vaccinees who experienced TTS events post dose 2 were male (55% vs 42%) and were older (65 years vs. 53 years) compared to first dose recipients, whereas post dose 3 the distribution of events in male and female was roughly equal with median age of 34 years. The median time to onset was similar (13 Days vs 12 Days and 9 Days). Of these 720 CVST cases, 453 (63%) were in females, 251 (35%) occurred in males, and in 2% gender was unknown.

Overall, the most common thrombosis events were Cerebral venous sinus thrombosis, DVT, Pulmonary embolism, DVT, Portal vein thrombosis, and thrombosis.

Overall, there were more fatal reports for TTS within 14 and 21 Days. Seventy-five percent of the fatal report occurred with 14 Days compare to 65% for all cases and 89% of the fatal report occurred with 21 Days compare to 81% for all cases. The highest number of fatal reports occurred due to HLT of Cerebrovascular venous and sinus thrombosis. Cerebral haemorrhage was the most common bleeding event associated with fatal event.

The arterial events were reported highest in the age group of 50-59 and 60-69. The distribution of events in male and female was roughly equal. The mixed or the combined arterial and venous was equally distributed in age group 30-39, 40-49, 50-59 and 60-69 and the distribution of cases in female and male was roughly equal. The venous events were reported highest in the age group of 40-49, 50-59 and 60 – 69 years. The occurrence in female was higher than in the male.

Overall, there were information on platelet count was available in (66%) of case reports, PF-4 antibodies were positive in 26% reports, negative in 23% reports, unknown or pending in 51% case reports, D-dimer levels were reported in 39% of the case reports, however, in many reports the units were not specified. The total number of confirmed cases were (14%), probable cases were (14.4%), possible cases were (34.3%), unlikely (0.03%) and criteria not met cases were (37%).

The most common confounding factors in descending order of frequency in all 2811 cases were autoimmune conditions, malignancy, history of heparin, obesity, and concomitant use of contraceptives. The most common confounding factors in the confirmed reports were history of heparin use and malignancy. The dates of heparin administered were not reported in all cases.

Conclusion

Based on currently available data, no new safety information concerning TTS was identified. The current risk minimisation measures described in the product information are considered adequate.

No new or emerging concern regarding TTS has been identified with booster doses of AZD1222. Based on the review of available safety data, there is no indication suggesting that the safety profile of an AZD1222 booster after a primary series with another vaccine would be different with respect to TTS from that of a first vaccine dose of AZD1222.

The topic 'thrombosis in combination with thrombocytopenia/ TTS will continue to be closely monitored as part of AstraZeneca's ongoing surveillance activities.

.

16.3.3 New information on other potential risks not categorised as important

The AESIs for VAXZEVRIA and associated PTs are listed in Appendix 7.

Adverse Event of Special Interest listed in Appendix 7 for VAXZEVRIA have been included for an O/E analysis for this PBRER and results are provided in Appendix 8 (O/E Analyses). Following an agreement with the MHRA, the frequency of the O/E analyses have been reduced from biweekly to 6-monthly aligned with PBRER.

16.3.4 New information on other identified risks not categorised as important

No new information relevant to any other identified risks not categorised as important has been identified during the reporting period.

16.3.5 Update on missing information

No new information relevant to the previously recognised missing information of has been identified during the reporting period. Detailed information regarding missing information is provided in Section 16.4.3.

16.3.5.1 Use of VAXZEVRIA in pregnant and breastfeeding women

16.3.5.1.1 Use of VAXZEVRIA in pregnant women

Review of Cases

Reports of pregnancy were retrieved from the ASTRAZENECA Global Safety Database using VAXZEVRIA and ASTRAZENECA customized 'PSUR pregnancy' Business Objects Report which includes the following search criteria:

The field Pregnant is marked as YES or Events code to one of the MedDRA (Version 26.1) SOCs: Congenital, familial and genetic disorders, Pregnancy, puerperium and perinatal conditions or Events code to the MedDRA High-level Group Term: Foetal and neonatal investigations or Events code to one of the MedDRA High-level Terms: Induced abortion complications, Induced abortions or Events code to one of the MedDRA Preferred Terms (PTs): Aborted pregnancy, Amastia, Amnioscopy, Amnioscopy abnormal, Amnioscopy normal, Ectopic pregnancy termination, External cephalic version, Pregnancy of partner, Pregnancy test positive, Pregnancy test urine positive, Hyperplasia adrenal and Macroorchidism. Cases describing Pregnancy with adverse neonatal outcomes are included below.

Clinical trial

Data from Study C-Viper: D8110C00003

A total of 720 study participants who received at least one dose of VAXZEVRIA have enrolled in the C- Vaccines International Pregnancy Exposure Registry (VIPER) as of 31 May 2023 (DLP). Of note, 90 study participants have completed the study.

Cumulatively in the homologous population, 411 out of 611 study participants (67.3%) reported at least one AE. Cumulatively, 1498 AEs were reported any time post-vaccination in the homologous population. The most commonly reported AEs were pain in extremity, fatigue, and chills. Cumulatively in the heterologous population, 95 of the 109 study participants (87.2%) reported at least one AE. Cumulatively, 328 AEs have been reported in the heterologous population. The most commonly reported AEs were pain in extremity, fatigue, and headache.

Cumulatively in the homologous population, 441 AEs were reported for 204 of 343 delivered infants and in utero fetuses (59.8%) of study participants. The most commonly reported AEs were COVID-19, pyrexia, and nasopharyngitis. Cumulatively in the heterologous population, 170 AEs were reported for 67 of 97 delivered infants and in utero fetuses (69.1%) of study participants. The most commonly reported AEs were large for dates baby, COVID-19, and breech presentation.

Cumulatively in the homologous population, 137 SAEs were reported in 103 of the 611 study participants (mothers) (16.9%), and 155 SAEs were reported in 100 of the 343 delivered infants and in utero fetuses (29.2%) of the study participants. The most commonly reported SAEs in the mothers were prolonged labour, gestational diabetes, and abortion spontaneous. The most commonly reported SAEs in the infants / fetuses were breech presentation, premature baby, and foetal growth restriction. Cumulatively in the heterologous population, 46 SAEs were reported in 39 of the 109 study participants (mothers) (35.8%) and 60 SAEs were reported in 43 of the 97 delivered infants and in utero fetuses (44.3%) of the study participants. The most commonly reported SAEs in the mothers were gestational diabetes and prolonged labour. The most commonly reported SAEs in the infants / fetuses were breech presentation and jaundice neonatal.

Cumulatively, the most commonly reported protocol-specified obstetric outcomes in the homologous population were “caesarean delivery and COVID-19” and neonatal outcomes were “COVID-19, preterm baby, and neonatal infections”.

Cumulatively, the most commonly reported protocol-specified obstetric outcomes in the heterologous population were caesarean delivery, COVID-19, and gestational diabetes. During the current reporting period, the reported protocol-specified neonatal outcomes were COVID-19 and preterm baby. Cumulatively, the most commonly reported protocol-specified neonatal outcomes were COVID-19, neonatal infections, and major congenital malformations.

The assessment of the safety data and outcomes data for study participants treated with VAXZEVRIA and their infants / fetuses did not reveal any new safety signals or concerns.

Data from pooled data analysis (COV001, COV002, COV003 and COV005)

From pooled data analysis, 102 pregnancies in 100 participants had been reported in the AZD1222 group and 87 pregnancies in 83 participants had been reported in the control group. In the AZD1222 group, there were 9 terminations, 15 miscarriages, 71 births, and 6 pregnancies with unknown outcome reported. In the control group, there were 10 terminations, 16 miscarriages, 54 births, and 7 pregnancies with unknown outcome reported. A review of the pregnancy exposure reports did not raise any safety concerns.

Post-marketing data

Interval Review (29 December 2022 – 28 December 2023)

During the reporting period, 715 case reports were retrieved using the above search strategy. However, 32 case reports were excluded as these cases were non-valid (ie, duplicate cases or invalid cases) and 54 were excluded as the cases were not pregnancy case reports which were retrieved due to the broad nature of the search strategy (congenital anomalies etc.). The remaining 629 cases were considered for further analysis. Of the 629 case reports, 371 reports included pregnancy/breastfeeding reports with other co-reported AEs and 258 reports without other AEs. Of the 629 case reports of exposure to VAXZEVRIA during or before pregnancy/breastfeeding, 358 reports were from interventional clinical trials, 226 post-marketing studies and 45 were from spontaneous sources. Of the 629 reports, 333 reports were MC (57 serious and 276 non-serious). Pregnancy outcomes was reported in 295 case reports were: 32 spontaneous abortions (SAB), 1 with therapeutic abortion, 1 with abnormal maternal outcome (premature rupture of membranes leading to abnormality in unborn baby PT: Foetal disorder), 5 still birth and 10 elective abortions, 124 healthy babies, 122 non-healthy babies, and outcome was unknown in 334 cases.

In 122 cases reported with pregnancy outcome as non-healthy babies' information on foetus is available in only 35 cases (excluding cases mentioning c-section, male/female neonate without any details). In 21 cases of the 35 cases, babies were pre-term (1 had cleft lip and palate), 4 cases reported infections (Bronchiolitis, Respiratory syncytial virus, Skin, Sinus, Streptococcus/bacterial infections), 2 babies failed hearing test and 1 had speech delay, 2 babies reported cardiac disorders (low heart rate and arrhythmia), 1 baby developed congenital anomalies (amelia syndrome), and singular events of neonatal jaundice, glucose-6-phosphate dehydrogenase deficiency and syphilis was reported.

Cumulative Review (through 28 December 2023)

Cumulatively, 6673 case reports were retrieved using the above search criteria. However, 852 case reports were excluded as these cases were non-valid or retrieved due to broad nature of search criteria (ie, duplicate cases, or invalid cases). The remaining 5821 cases were considered for further analysis. Of the 5821 case reports, 4844 case reports included pregnancy/breastfeeding reports with other co-reported AEs and 977 reports without other AEs. Of the 5821 case reports of exposure to VAXZEVRIA during or before pregnancy/breastfeeding, 1359 reports were from interventional clinical trials, 3341 post-marketing studies and 1121 spontaneous. Of these 5821 reports, 1484 reports were MC (386 serious and 1098 non-serious respectively).

Spontaneous Abortion – Interval Review

A total of 32 SAB was received during this interval, all of which were consumer reports. Most of the cases (50%, 16/32) from US Study: D8110C00001 and 4 cases each from UK and Belgium, 2 cases each from Norway, Australia, Germany and 1 case each from Brazil and Spain.

Age was reported in all cases; median age was 33 years (range: from 23 to 43). In 7 cases, gestation week related information was available. In 1 case sonography showed intrauterine gestational sac with 3 mm embryo without a heartbeat, in 1 one case there was no heartrate or flow, with little amniotic fluid with maximum lodge 40mm spill *in-utero* at 21 weeks and in 3 cases there was no visualization of gestational sac and discrete amorphous echoes. In the remaining 3 cases, no details were available.

Spontaneous Abortion – Cumulative Review

A total of 484 pregnancy cases reported SAB. A total of 73.1% (354 out of 484) were reports from consumers and 26.9% (130 out of 484) MC. Around 59.5% (288/484) of the cases were reported from UK. Age was reported in 412 of the 484 case reports; median age was 34.0 years (range: from 23 to 46 years, ie, 28 reports in women aged < 25 years, 197 reports in women aged 26 to 35 years and 185 reports were in women aged > 36 years). In 224 of the 484 reports, gestational age of exposure was unknown; in the remaining 240 reports, SAB was occurred in the 1st trimester of pregnancy.

Observed Vs. Expected Analysis – Spontaneous abortion

The IRs for SAB were calculated based on the reported rates by Hemminki and Forssas 1999 data on conceptions among women in England and Wales, 2018 from the UK Office of National Statistics (Conceptions in England and Wales 2018) to estimate the rates of SABs per 100,000 women years.

Vaccine administration data based on the age and gender is only available from UK and the below analysis was based on case reports from UK. The observed versus expected analysis of SABs with DLP 28 December 2023 showed that observed cases occurred significantly less frequently than expected for overall and for different age stratifications from UK. A summary of SAB observed versus expected analysis is presented in Table 86. Conservatively, the exposure for global reports (44,83,06,152) is based on doses administered in 13 markets as explained in Section 8 until December 2022.

Table 86 Spontaneous Abortion Observed Versus Expected Analysis (UK cases only)

Age group (years)	IR/100,000 PY	Risk Window	Exposure from UK	Observed Cases	Expected Cases	Ratio	Interpretation
18 to 24	1780.8	60	498587	3	1458.57	0 (0 - 0.01)	Observed significantly < expected
25 to 29	1437.5	60	610901	19	1442.61	0.01 (0.01 - 0.02)	Observed significantly < expected
30 to 34	1447	60	842004	37	2001.49	0.02 (0.01 - 0.03)	Observed significantly < expected
35 to 39	864.6	60	1050964	45	1492.7	0.03 (0.02 - 0.04)	Observed significantly < expected
40 to 44	223.3	60	2041971	28	749.05	0.04 (0.02 - 0.05)	Observed significantly < expected
18 to 24 plus Unk TTO	1780.8	60	498587	9	1458.57	0.01 (0 - 0.01)	Observed significantly < expected
25 to 29 plus Unk TTO	1437.5	60	610901	25	1442.61	0.02 (0.01 - 0.03)	Observed significantly < expected
30 to 34 plus Unk TTO	1447	60	842004	62	2001.49	0.03 (0.02 - 0.04)	Observed significantly < expected
35 to 39 60 plus Unk TTO	864.6	60	1050964	71	1492.7	0.05 (0.04 - 0.06)	Observed significantly < expected
40 to 44 60 plus Unk TTO	223.3	60	2041971	40	749.05	0.05 (0.04 - 0.07)	Observed significantly < expected

Table 86 Spontaneous Abortion Observed Versus Expected Analysis (UK cases only)

Age group (years)	IR/100,000 PY	Risk Window	Exposure from UK	Observed Cases	Expected Cases	Ratio	Interpretation
All ages	995.3	60	7418105	150	38018.38	0 (0 - 0)	Observed significantly < expected
All ages plus Unk TTO	995.3	60	7418105	252	38018.38	0.01 (0.01 - 0.01)	Observed significantly < expected

IR, Incidence Rate; PY, Person Years; TTO, Time to onset; UK, United Kingdom; Unk, Unknown.

For the observed versus expected analysis of Gestational diabetes, please see Appendix 8.

Conclusion

From the data identified during the reporting period, and also taking into account the cumulative experience, no causal relationship could be established between Abortion spontaneous and VAXZEVRIA. Pregnancy and Abortion spontaneous will continue to be kept under close surveillance by AstraZeneca.

Adverse Maternal Outcomes – Interval and Cumulative Review

Maternal outcomes that are part of the AE of Special Interest concept of “Pregnancy outcome – maternal” (as presented in the RMP) are shown in Table 87.

Table 87 Adverse Maternal Outcomes – Interval and Cumulative Period

PT	Event Count (Interval)	Event Count (Cumulative)
Amniotic cavity infection	0	1
Caesarean section	2	12
Eclampsia	1	5
Gestational diabetes	7	41
Placenta praevia	1	7
Pre-eclampsia	8	28
Premature labour	0	110
Uterine rupture	0	3
Grand Total	19	107

PT Preferred Term.

The most common relevant risk factors reported in the cases included: previous history of gestational diabetes, increased BMI, hypertension, tobacco use, substance and alcohol use, multigravida, diabetes, history of SAB and stillbirth, Factor V Leiden mutation, previous “high risk pregnancy”, history of kidney disease, Fabry’s disease, suspected COVID-19, asthma, polycystic ovaries, and dengue fever. No safety concern was identified from the review of these reported PTs.

Conclusion

From the data identified and analysed during the reporting period, and also taking into account the cumulative experience, no causal relationship could be established between adverse maternal outcomes and VAXZEVRIA. Pregnancy and adverse maternal outcomes will continue to be kept under close surveillance by AstraZeneca.

Co-reported Adverse Events in the Pregnancy Cases - Interval Review

Of the 629 pregnancy case reports, 371 cases had co-reported AEs in both mothers and infants. Most of the AEs reported in these cases were known reactogenicity events (i.e., headache, pyrexia, fatigue, chills, myalgia, nausea, pain in extremity and arthralgia). There were 110 cases with 399 AEs that occurred in the neonatal population, the top 4 AEs being: maternal exposure during pregnancy (92), pyrexia (26) and nasopharyngitis and cough (11, each). There was no trend or signal observed from these AEs reported from the pregnancy cases.

Other co-reported Adverse Events in the Pregnancy Cases – Cumulative Review

Of the 5821 case reports, 4844 cases had co-reported AEs in both mothers and infants. Most of the AEs reported in these cases were known reactogenicity events (headache, pyrexia, fatigue, chills, myalgia, nausea, pain in extremity and arthralgia). There were 408 cases with 1307 AEs that occurred in the paediatric population, the top 4 AEs being: exposure via breast milk (149), maternal exposure during pregnancy (125), foetal exposure during pregnancy (96) and Pyrexia (83). There was no trend or signal seen from these AEs reported from the pregnancy cases.

Abnormal Neonatal Outcomes – Cumulative and Interval Review

In order to appropriately assess all cases reported to the company with any congenital anomaly or adverse neonatal outcome, a search cumulatively and during the reporting period of this PBRER was done with the following MedDRA (version 26.1) PTs: “Congenital musculoskeletal disorder of limbs; Congenital musculoskeletal disorder of skull; Congenital musculoskeletal disorder of spine; Congenital female genital tract fistula; Oculo-digito-oesophageal-duodenal syndrome; Congenital musculoskeletal disorder of head and neck;

Macrophthalmos; Congenital female reproductive tract disorder; Congenital musculoskeletal disorder; Congenital laryngeal malformation; Athelia; Congenital vocal cord paralysis; Congenital subglottic stenosis; Congenital vena cava stenosis; Aphallia; Congenital connective tissue disorder; Congenital musculoskeletal disorder of trunk; Congenital anisocoria; Congenital lip pits; Pleural malformation; Arhinencephaly; Acrocephalosyndactyly; Amniotic band syndrome; Anencephaly; Annular pancreas; Anomalous pulmonary venous connection; Anophthalmos; Anorectal malformation; Anotia; Aorticopulmonary septal defect; Arnold-Chiari malformation; Arteriovenous malformation; Atrial septal defect; Atrioventricular septal defect; Auditory neuropathy spectrum disorder; Brain malformation; Breast malformation; Cardiac septal defect; Cataract congenital; Cerebral arteriovenous malformation haemorrhagic; Cerebral cavernous malformation; Cerebrovascular arteriovenous malformation; Choanal atresia; Cleft lip; Cleft lip and palate; Cleft palate; Cloacal exstrophy; Coarctation of the aorta; Congenital absence of bile ducts; Congenital aortic valve stenosis; Congenital arterial malformation; Congenital cerebral haemangioma; Congenital coronary artery malformation; Congenital cystic kidney disease; Congenital diaphragmatic hernia; Congenital ectopic bladder; Congenital eye disorder; Congenital eyelid malformation; Congenital foot malformation; Congenital genital malformation; Congenital genital malformation female; Congenital genital malformation male; Congenital hand malformation; Congenital hearing disorder; Congenital heart valve disorder; Congenital heart valve incompetence; Congenital hydrocephalus; Congenital hydronephrosis; Congenital intestinal malformation; Congenital jaw malformation; Congenital joint malformation; Congenital large intestinal atresia; Congenital lymphoedema; Congenital megacolon; Congenital mitral valve incompetence; Congenital mitral valve stenosis; Congenital nose malformation; Congenital oesophageal stenosis; Congenital oral malformation; Congenital pulmonary artery anomaly; Congenital pulmonary valve atresia; Congenital rubella infection; Congenital rubella syndrome; Congenital skin disorder; Congenital small intestinal atresia; Congenital syphilis; Congenital tricuspid valve atresia; Congenital vesicoureteric reflux; Conjoined twins; Constricted ear deformity; Craniorachischisis; Craniosynostosis; Cryptorchism; Deaf mutism; Deafness congenital; Death neonatal; Developmental glaucoma; Developmental hip dysplasia; Double outlet right ventricle; Duodenal atresia; Dysmorphism; Ear malformation; Ebstein's anomaly; Encephalocele; Epispadias; Exomphalos; Fallot's tetralogy; Foetal alcohol syndrome; Foetal anticonvulsant syndrome; Foetal distress syndrome; Foetal growth restriction; Foetal malformation; Gastrointestinal arteriovenous malformation; Gastrointestinal malformation; Gastroschisis; Genitalia external ambiguous; Haemangioma congenital; Haemangioma of retina; Haemorrhagic arteriovenous malformation; Hepatic arteriovenous malformation; Heterotaxia; Holoprosencephaly; Hydrops foetalis; Hypoplastic left heart syndrome; Hypoplastic right heart syndrome; Hypospadias; Iniencephaly; Interruption of aortic arch; Intestinal atresia; Kidney malformation; Limb reduction defect; Lissencephaly; Low birth weight baby; Malformation biliary; Malformation venous; Microcephaly; Microencephaly;

Microphthalmos; Microtia; Mitral valve atresia; Neural tube defect; Oesophageal atresia; Parachute mitral valve; Patent ductus arteriosus; Polydactyly; Porencephaly; Premature baby; Pulmonary aplasia; Pulmonary artery atresia; Pulmonary artery stenosis congenital; Pulmonary malformation; Pulmonary valve stenosis congenital; Pyloric stenosis; Rectal atresia; Renal aplasia; Renal arteriovenous malformation; Renal dysplasia; Renal failure neonatal; Renal hypoplasia; Respiratory tract malformation; Retinal arteriovenous malformation; Schizencephaly; Skeletal dysplasia; Skin malformation; Spina bifida; Spina bifida cystica; Spina bifida occulta; Spleen malformation; Stillbirth; Syndactyly; Talipes; Thyroid malformation; Tracheo-oesophageal fistula; Transposition of the great vessels; Truncus arteriosus persistent; Umbilical malformation; Univentricular heart; Urethral valves; Urinary tract malformation; VACTERL syndrome; Vascular malformation; Vein of Galen aneurysmal malformation; Venolymphatic malformation; Ventricular septal defect; Vallecular cyst; Foetal vascular malperfusion; Beaver tail liver; Congenital ectopic spleen; Congenital pulmonary airway malformation; Vertebral artery fenestration; Foetal cardiac function test abnormal; Lymphatic malformation; Megalencephaly; Mitral valve dysplasia; Congenital umbilico-enteric fistula”.

Cumulatively, 195 cases reporting any PTs (outlined as above) from the concept of pregnancy outcomes - “Neonates” were reported since launch until the DLP of this PBRER. Upon further review, 88 of these cases were acquired conditions and/or presented in elderly age or adults and not congenital malformations and hence not included for further review.

During the reporting period of this PBRER until 28 December 2023, 29 cases were reported among this concept of pregnancy outcomes - “Neonates”. Upon further review of 29 cases (containing 38 neonatal outcome events) reported among neonatal age or case reports linked to a neonate or a pregnancy product, such cases were therefore included in this section.

Premature baby (15), Low birth weight baby (6), Foetal growth restriction (3), Cleft lip (2), Developmental hip dysplasia (2), Cleft palate (2), Foetal distress syndrome (1), Congenital syphilis (1), Atrial septal defect (1), Congenital cystic kidney disease (1), Congenital hydronephrosis (1), Congenital hydrocephalus (1), Haemangioma congenital (1), Patent ductus arteriosus (1) and Congenital hydronephrosis (1).

The above 29 cases were described in use of VAXZEVRIA in pregnant women. Review of these 29 cases with adverse neonatal outcomes received during the reporting period did not highlight any new significant safety concerns. The majority of cases were either confounded or contained limited information to ascribe an appropriate causal relationship to VAXZEVRIA (Case IDs: [REDACTED]).

AstraZeneca Comment: Due to confounders in maternal history (including but not limited to breech presentation; the bacteria treponema pallidum being passed from mother to child during fetal development or at birth; diabetes and the primary reason for C-section was reported to be pre-eclampsia) and limited information on complete demographics of vaccinee, baseline health condition before vaccination, relevant medical history, obstetric history, relevant family history, concurrent diseases, concomitant medications, details of the event, further circumstances surrounding the event, outcome of the event, further risk factors (such as chromosomal abnormalities, cerebral anoxia, severe maternal malnutrition and chronic conditions, smoking, alcohol and drugs exposure, maternal infections such as toxoplasmosis, CMV, rubella, varicella and zika virus), genetic factors, other congenital abnormalities such as family history of hypospadias and detailed diagnostic and etiologic workup (physical examination, neurological, genetics testing, imaging studies such as Ultrasound and X-ray), the evaluation did not find evidence to suggest a causal relationship between all neonatal outcomes and VAXZEVRIA.

Conclusion

From the data identified during the reporting period, and also taking into account the cumulative experience, no causal relationship could be established between these events reported in neonates and VAXZEVRIA. Pregnancy and neonatal outcomes will continue to be kept under close surveillance by ASTRAZENECA.

Literature review – Pregnancy

A periodic literature search of the databases in Embase, Insight Meme and PubMed was conducted for relevant articles on topic in association with VAXZEVRIA.

The search did not yield any articles that were considered relevant for further evaluation and presentation.

Summary

In summary, the cumulative and periodic reviews up and until 28 December 2023 of all reports of exposure to VAXZEVRIA during pregnancy did not identify any new safety concerns for the mother or baby. The reported AEs are similar between the pregnant and non-pregnant populations. The results of the O/E analyses for SAB (UK reports) suggest that observed cases are less than would be expected in the unvaccinated pregnant women.

Conclusion

Based on these interval and cumulative reviews of the currently available data, it is ASTRAZENECA's opinion that no updates to product labelling or RMP are warranted. Use of

VAXZEVRIA during pregnancy remains as Missing information for the product and is closely monitored.

16.3.5.1.2 Use of VAXZEVRIA in Breastfeeding women

Breastfeeding cases were retrieved from the AstraZeneca customized 'PSUR pregnancy' Report by filtering for breastfeeding related PTs (Exposure via breast milk, Maternal exposure during breast feeding).

Interval Period (29 December 2022 to 28 December 2023)

During the interval period, there were 22 reports pertaining to infant exposure to VAXZEVRIA during breastfeeding. Overall, 6 serious cases (a consumer report) were reported. Within these 22 reports, there were 35 events in infants following breastfeeding. Events occurring with a frequency of 2 or more in paediatric cases are milk allergy (4), pyrexia (2) and suspected COVID-19 (2). No safety concern was identified.

There were no fatal cases reported within the infant lactation cases. Outcomes of these 22 cases were: Not recovered (6), Recovered (6), Recovering (1) and Unknown (9).

Of the interval review of reports of VAXZEVRIA exposure during breastfeeding retrieved from the ASTRAZENECA Global Safety Database, there was limited information to suggest any reasonable association between exposure to VAXZEVRIA via breastfeeding and adverse outcomes in the neonates. No safety relevant literature relating to VAXZEVRIA, and breastfeeding was identified during the reporting period.

Cumulative Review (29 December 2020 to 28 December 2023)

Cumulatively, there were 177 reports pertaining to infant exposure to VAXZEVRIA during breastfeeding. Overall, 61 cases were serious (of which 5 were MC). Within these 61 reports, there were 556 events in infants following breastfeeding. Most frequently reported PTs in these cases is pyrexia (50), diarrhoea (20), somnolence and malaise (11, each). No safety concern was identified.

Adverse Events in Maternal Vaccinees

Interval Period (29 December 2020 to 28 December 2023)

During the interval period, there were 8 reports pertaining to exposure to VAXZEVRIA whilst lactating, one of which was serious consumer report. Within these 8 reports, there were 94 events in maternal vaccinees. Of these 94 events, 77 were serious adverse events. Events occurring with a frequency of 3 or more are shown in Table 88. No safety concern was identified.

Table 88 Adverse Events in Maternal Vaccinees (with a Frequency of ≥ 3)

Preferred Term	Non-serious	Serious	Total
Pyrexia	2	1	3

There were no fatal cases reported. Outcomes of these 31 cases were: Recovered (2), Not recovered (1) and Unknown (5).

Of the interval review of reports of exposure of maternal vaccinees to VAXZEVRIA retrieved from the AstraZeneca Global Safety Database, there was limited information to suggest any reasonable association between exposure to VAXZEVRIA and adverse outcomes in the maternal vaccinees.

Section 4.6 of the VAXZEVRIA CDS includes the following text on breastfeeding:

Anti-SARS-CoV-2 S antibodies are excreted in breast milk of mothers vaccinated with VAXZEVRIA. In animal studies, lactational transfer of anti-SARS-CoV-2 S antibodies from maternal female mice to pups was observed. It is unknown whether the vaccine itself is excreted in human milk.

In animal studies no quantifiable levels of the vaccine were detected in the mammary gland in female mice.

Available non-clinical, clinical and post-marketing data do not suggest a risk to breastfed newborns/infants.

Conclusion

From the data identified during the reporting period, and also taking into account the cumulative experience, there is no new safety information, or a safety concern identified with the exposure to VAXZEVRIA during pregnancy or while breast feeding. Use of VAXZEVRIA in pregnant and breastfeeding women/ Use during pregnancy and while breastfeeding will continue to be considered as Missing information for VAXZEVRIA.

Use of VAXZEVRIA in pregnant and breastfeeding women / Use during pregnancy and while breastfeeding will be primarily investigated in the ongoing non-interventional pregnancy Registry Study (D8110C00003) of women exposed to VAXZEVRIA immediately before or during pregnancy as part of the C-VIPER Registry Consortium.

More detailed information is provided in Section 16.4.3.1.

16.3.5.2 Use of VAXZEVRIA in subjects with severe immunodeficiency

Vaccines may be less effective in severely immunocompromised individuals, as the vaccinees weakened immune system may not mount a sufficient response. Additionally, immunocompromised individuals may also be at a greater risk of morbidity and mortality from vaccine-preventable disease, and consequently this population has been identified as a priority group for initial vaccination in several jurisdictions. Although there is no evidence that the safety profile of VAXZEVRIA in this population will be different than that of the general population, given the paucity of data, the possibility cannot be excluded.

WHO recommends that the primary vaccine series in moderately to severely immunocompromised persons (ICP) should be extended to include an additional dose for all COVID-19 vaccines. On the basis of available evidence, the additional dose in an extended primary series should be given at least 1 month and within 3 months after the primary series in order to increase protection for immunocompromised persons. A homologous additional dose in an extended primary series should currently be considered standard practice, but alternative heterologous platforms for the additional dose may also be considered, taking into account current vaccine supply, vaccine supply projections, and other access considerations WHO interim guidance 2021.

Review of Cases

A cumulative search (up to 28 December 2023) of the AstraZeneca Global Safety Database was undertaken for AE reports received for VAXZEVRIA in subjects with medical history of severe immunodeficiency and in immunocompromised patients, using the criteria mentioned in Appendix 12.

Of note, it should be noted that the limitations of spontaneous data, as in most of the reports date of diagnosis or medical histories of IC conditions were not provided; therapy dates and duration of concomitant immunosuppressive agents were also not available.

The search of the AstraZeneca Global Safety database identified a cumulative total of 52581 cases from all sources, reported in subjects with severe immunodeficiency and in immunocompromised patients in association with VAXZEVRIA. Most of the reports were from post-marketing sources including 94 % (49401) spontaneous cases, 5% (2813) other non-interventional studies.

Of the 52581 cases, 74% (38716) were reported in females, 24% (12648) were in males and gender was not reported in the remaining 2% (1217) of cases. Age was reported in 48921 case reports and in 53 % of the cases the reported age was ≥ 50 years. Case reports by age and sex are provided in below Table 89.

Table 89 Age group and Sex in Immunocompromised groups

Age group/Gender	Female	Male	Gender unknown	Grand Total
Age < 17 Years	79 (59.4%)	45 (33.8%)	9 (6.8%)	133
Age - 18-29 Years	3313 (77%)	913 (21.2%)	78 (1.8%)	4304
Age - 30-39 Years	5131 (77.7%)	1360 (20.6%)	112 (1.7%)	6603
Age - 40-49 Years	7795 (78.8%)	1962 (19.8%)	138 (1.4%)	9895
Age - 50-59 Years	8758 (76.5%)	2502 (21.9%)	184 (1.6%)	11444
Age - 60-69 Years	7300 (71.3%)	2799 (27.3%)	140 (1.4%)	10239
Age - 70-79 Years	3326 (62.5%)	1904 (35.8%)	89 (1.7%)	5319
Age - 80+ Years	564 (57.3%)	407 (41.4%)	13 (1.3%)	984
Age Unknown	2450 (66.9%)	756 (20.7%)	454 (12.4%)	3660
Grand Total	38716 (73.6%)	12648 (24.1%)	1217 (2.3%)	52581

The most frequently reported (>100) events in immunocompromised group are provided in Table 90. There is no clinically meaningful trend seen in these events and they are similar to the events observed for VAXZEVRIA in the general vaccinated population.

Table 90 Most frequently reported events (>100) in the IC group

Event (PT)	Non-serious	Serious	Total
Headache	6790	11261	18051
Pyrexia	5530	8498	14028
Fatigue	4272	7742	12014
Chills	3579	6208	9787
Nausea	2528	5269	7797
Myalgia	2803	4113	6916
Arthralgia	2272	3794	6066
Dizziness	1592	3411	5003
Pain in extremity	2089	2856	4945
Pain	1644	2405	4049
Malaise	1630	2158	3788
Influenza like illness	1696	1465	3161
Dyspnoea	866	2115	2981
Vomiting	806	2025	2831
Diarrhoea	797	1520	2317
Tremor	366	1611	1977
Paraesthesia	757	1175	1932
Asthenia	883	994	1877

Table 90 Most frequently reported events (>100) in the IC group

Event (PT)	Non-serious	Serious	Total
Hyperhidrosis	470	1396	1866
Rash	744	982	1726
Pruritus	775	924	1699
Migraine	308	1328	1636
Decreased appetite	422	1147	1569
Injection site pain	835	728	1563
Chest pain	342	1172	1514
Influenza	356	1015	1371
Palpitations	334	1024	1358
Peripheral swelling	427	865	1292
Back pain	391	889	1280
Cough	450	806	1256
COVID-19	580	626	1206
Vaccination site pain	851	332	1183
Abdominal pain upper	277	890	1167
Lymphadenopathy	373	788	1161
Abdominal pain	387	770	1157
Hypoaesthesia	405	749	1154
Feeling cold	340	689	1029
Oropharyngeal pain	304	689	993
Illness	154	824	978
Lethargy	211	651	862
Erythema	435	411	846
Pulmonary embolism		832	832
Muscle spasms	229	550	779
Contusion	382	388	770
Insomnia	249	507	756
Eye pain	195	543	738
Tinnitus	230	506	736
Asthma	199	514	713
Chest discomfort	224	483	707
Neck pain	208	492	700
Limb discomfort	364	328	692
Muscular weakness	184	482	666
Tachycardia	231	429	660

Table 90 Most frequently reported events (>100) in the IC group

Event (PT)	Non-serious	Serious	Total
Vision blurred	189	462	651
Somnolence	292	335	627
Interchange of vaccine products	606	17	623
Urticaria	302	311	613
Vertigo	230	359	589
Feeling hot	263	322	585
Heart rate increased	186	383	569
Swelling	225	334	559
Feeling abnormal	207	342	549
Confusional state	102	444	546
Deep vein thrombosis		537	537
Epistaxis	263	271	534
Musculoskeletal stiffness	189	344	533
Syncope	97	430	527
Thrombocytopenia		492	492
Thrombosis	68	413	481
Off label use	422	57	479
SARS-CoV-2 antibody test negative	469	8	477
Ear pain	108	344	452
Hot flush	147	303	450
Abdominal discomfort	137	290	427
Nasopharyngitis	166	259	425
Body temperature increased	266	148	414
Hypertension	141	271	412
Hypersensitivity	145	264	409
Heavy menstrual bleeding	155	252	407
Dizziness postural	74	331	405
Tenderness	188	211	399
Dysgeusia	163	229	392
Bone pain	154	226	380
Rash erythematous	172	199	371
Night sweats	78	286	364

Table 90 Most frequently reported events (>100) in the IC group

Event (PT)	Non-serious	Serious	Total
Rhinorrhoea	136	226	362
Herpes zoster	135	226	361
Neuralgia	91	261	352
Rash pruritic	154	182	336
Cold sweat	68	254	322
Tension headache	76	244	320
Anxiety	86	234	320
Photophobia	84	232	316
Wheezing	77	221	298
Psoriasis	135	155	290
Peripheral coldness	89	200	289
Cerebrovascular accident		287	287
Joint swelling	86	199	285
Balance disorder	80	203	283
Condition aggravated	102	179	281
Injection site mass	85	192	277
Visual impairment	94	180	274
Menstruation delayed	156	118	274
Arthritis	73	199	272
Thirst	82	188	270
Vaccination site erythema	184	82	266
Disturbance in attention	96	169	265
Rheumatoid arthritis	60	203	263
Swelling face	80	178	258
Injection site erythema	166	89	255
Vaccination site swelling	193	60	253
Burning sensation	102	148	250
Inflammation	83	166	249
Menstruation irregular	117	130	247
Seizure		241	241
Dry mouth	73	167	240
Haemorrhage	67	172	239
Ageusia	94	144	238
Loss of consciousness	36	198	234

Table 90 Most frequently reported events (>100) in the IC group

Event (PT)	Non-serious	Serious	Total
Pain of skin	63	164	227
Head discomfort	83	144	227
Blood pressure increased	85	142	227
Muscle fatigue	43	178	221
Gait disturbance	77	137	214
Maternal exposure during breast feeding	69	140	209
Hallucination	31	178	209
Injection site swelling	153	55	208
Drug ineffective	72	135	207
Feeling of body temperature change	68	139	207
Application site pain	192	14	206
Menstrual disorder	113	89	202
Vaccination failure	22	178	200
Lip swelling	61	138	199
Anaphylactic reaction		198	198
Brain fog	44	153	197
Paraesthesia oral	82	114	196
Renal pain	42	148	190
Dehydration	33	156	189
Petechiae	87	101	188
Immunisation reaction	161	27	188
Pneumonia	12	175	187
Hypotension	53	134	187
Dyspepsia	48	130	178
Body temperature	36	141	177
Injection site reaction	80	94	174
Rash macular	87	80	167
Haematoma	107	60	167
Heart rate	26	141	167
Vaginal haemorrhage	67	99	166
Swollen tongue	52	106	158
Discomfort	89	69	158
Colitis ulcerative	27	131	158

Table 90 Most frequently reported events (>100) in the IC group

Event (PT)	Non-serious	Serious	Total
Depression	35	122	157
Immune thrombocytopenia		156	156
Presyncope	52	102	154
Memory impairment	45	109	154
Flushing	42	111	153
Maternal exposure during pregnancy	80	72	152
Inappropriate schedule of product administration	103	49	152
Disorientation	24	128	152
Sinus headache	32	119	151
Axillary pain	44	106	150
Muscle twitching	63	86	149
Abdominal distension	48	101	149
Guillain-Barre syndrome		148	148
Sleep disorder	61	85	146
Nervousness	29	117	146
Anosmia	66	80	146
Transient ischaemic attack		145	145
Nasal congestion	53	92	145
Weight decreased	41	103	144
Injection site inflammation	137	7	144
Eczema	58	86	144
Oedema peripheral	67	76	143
Skin burning sensation	46	96	142
Poor quality sleep	37	104	141
Hypoaesthesia oral	62	79	141
Platelet count decreased	32	108	140
Sinus pain	22	117	139
Blister	54	85	139
Constipation	38	99	137
Depressed mood	31	106	137
Alopecia	45	92	137

Table 90 Most frequently reported events (>100) in the IC group

Event (PT)	Non-serious	Serious	Total
Amnesia	25	112	137
Dysmenorrhoea	42	94	136
Eye swelling	37	98	135
Taste disorder	63	71	134
Death		134	134
Cluster headache	33	100	133
Oral herpes	50	82	132
Rash papular	52	78	130
Pain in jaw	26	104	130
Injection site warmth	71	59	130
Atrial fibrillation	14	116	130
Myocardial infarction		128	128
Lymph node pain	35	93	128
Restlessness	41	86	127
Sweating fever	16	110	126
Mouth ulceration	46	80	126
Dry skin	40	85	125
Sinusitis	32	89	121
Infection	29	91	120
Fall	25	95	120
Pallor	34	83	117
Parosmia	52	65	117
Breast pain	50	67	117
Vaccination site reaction	104	12	116
Joint stiffness	35	81	116
Cellulitis	22	94	116
Skin warm	48	67	115
Musculoskeletal chest pain	31	84	115
Lower respiratory tract infection	21	94	115
Dysarthria	6	109	115
Angioedema		115	115
Vaccination site mass	47	66	113
Sneezing	43	69	112

Table 90 Most frequently reported events (>100) in the IC group

Event (PT)	Non-serious	Serious	Total
Pharyngeal swelling	34	78	112
Mobility decreased	39	69	108
Mental fatigue	9	99	108
Adverse drug reaction	28	77	105
Eye pruritus	31	73	104
Fibromyalgia	21	83	104
Diplopia	21	83	104
Vaccination site warmth	56	47	103
Pericarditis	12	91	103
Sensitive skin	28	74	102
Crohn's disease	19	83	102
Injection site pruritus	57	44	101
Urinary tract infection	35	65	100
Neuropathy peripheral	20	80	100
Facial pain	23	77	100
Gastrointestinal pain	21	79	100

IC Immunocompromised; PT Preferred term

Outcome of all events is provided below.

- Died 650
- Not recovered 23397
- Recovered 25923
- Recovered with sequelae 2358
- Recovering 18513
- Unknown 16503

Cumulatively there were 650 deaths out of 52581 case reports. Out of the 650 reports with fatal outcome, age of vaccinee was reported in 618 reports and in 557 (85.6%) of the reports the vaccinee age was ≥ 50 years (median age 74 years). Most frequently (≥ 20) reported events (PTs) with fatal outcome were: Death: 133; Pulmonary embolism: 58; Dyspnoea: 41; COVID-19: 36; Cardiac arrest: 30; Myocardial infarction: 27; Vaccination failure: 26; Cerebral haemorrhage: 25; COVID-19 pneumonia: 24; Cerebrovascular accident: 23; Thrombocytopenia: 23; Sudden death: 22; Pneumonia: 20; Multiple organ dysfunction syndrome: 20; Headache: 17; Thrombosis: 15; Vomiting: 15; Fatigue: 15; Cerebral venous sinus thrombosis: 13; Cardio-respiratory arrest: 13; Acute myocardial infarction: 12; DVT: 12;

Nausea: 11; Sepsis: 11; ITP: 11; AE following immunisation: 10; Respiratory failure: 10; and Cough: 10.

Review of AESI and COVID-19 Events in IC group

A total of 7396 cases reported AESIs (see appendix 07 for list of AESIs). Most frequently reported AESI was Embolic and thrombotic events (Thrombosis) (2137 events), Anaphylaxis (547 events), Immune-mediated neurological conditions (1372 events) and Thrombocytopenia including ITP (704 events). COVID-19 events (from COVID-19 SMQ) were reported in 1167 case reports and outcome of in 65 (5.6%) out of 1167 case reports were fatal.

No signals or safety concerns were identified based on the review of events reports in this population.

Review of Literature

Evidence on the safety of VAXZEVRIA in immunocompromised (IC) individuals is identified as an area of missing information in the European Union (EU) RMP. There are currently no published systematic literature reviews (SLRs) of observational studies including AEs of VAXZEVRIA in immunocompromised individuals. Therefore, AstraZeneca has conducted a systematic review to assess the frequency of AEs reported by authors of included studies recorded up to one year following administration of VAXZEVRIA in patients taking immunosuppressant medications and/or with primary immunodeficiency.

The search was performed using Embase and InsightMeme and the World Health Organization (WHO) COVID-19 Research Database, grey literatures using medRxiv (ordered by “Best Match”) and the COVID-19 Rapid Evidence Reviews platform by McMaster University to identify literature articles on “Immune and associated conditions” disease following the use of VAXZEVRIA, from 01 January 2021 to 05 February 2023, using the following search terms.

'azd-1222' OR 'azd 1222' OR 'azd1222' OR 'covid-19 vaccine astrazeneca' OR VAXZEVRIA /exp OR VAXZEVRIA OR 'chadox1 ncov 19'/exp OR 'chadox1 ncov 19' OR 'covishield' OR ('astrazeneca' NEAR/2 'covid-19 vaccine') OR 'chadox1-s', 'immunocompromised patient'/exp OR 'immunocompromised patient' OR 'immunocompromise*' OR 'immunosuppressed' OR 'immunosuppress*' OR 'immunogenicity', 'hematologic malignancy'/exp OR 'h?ematologic malignancies' OR 'haematologic cancer*' OR 'haematologic neoplasm' OR 'leukemia'/exp OR 'leukemia' OR 'lymphoma'/exp OR 'lymphoma':ti,ab OR 'adenolymphoma' OR 'lymphocytic' OR 'Hodgkin disease'/exp OR 'myeloma'/exp OR 'myeloma':ti,ab OR 'myeloplaxoma' OR 'blood cancer':ti,ab OR 'chemotherapy'/exp OR 'cancer chemotherapy'/exp OR 'immunotherapy'/exp OR 'immunotherap*':ti,ab OR 'solid malignant neoplasm'/exp OR 'solid malignant neoplasm' OR 'chronic lymphatic leukemia'/exp OR 'chronic leukemia', 'heart

transplantation'/exp OR 'intestine transplantation'/exp OR 'kidney transplantation'/exp OR 'liver transplantation'/exp OR 'lung transplantation'/exp OR 'pancreas transplantation'/exp OR ([{'solid organ' OR 'kidney' OR 'heart' OR 'liver' OR 'intestine*' OR 'lung' OR 'pancreas*'} NEAR/2 'transplant*']:ti,ab), 'chimeric antigen receptor t-cell immunotherapy'/exp OR 'chimeric antigen receptor t-cell and immunotherapy' OR 'car-t therapy' OR 'adoptive cellular immunotherap*':ti,ab OR 'hematopoietic stem cell transplantation'/exp OR 'hematopoietic stem cell transplant*' OR 'hematopoietic stem cell therapy' OR 'hematopoietic stem cell transplant*' OR 'hsc therapy' OR 'hsc transplant*', 'human immunodeficiency virus'/exp OR 'human immunodeficiency virus infection'/exp OR (hiv:ti,ab OR 'human immunodeficiency virus':ti,ab) AND (advanced:ti,ab OR 'un-treated':ti,ab OR 'untreated':ti,ab), 'steroid'/exp OR ('steroid*' OR 'corticosteroid*' OR 'glucocorticoid*'):ti,ab OR 'alkylating agent'/exp OR 'alkylating agent':ti,ab OR 'antimetabolite'/exp OR 'antimetabolite*':ti,ab OR 'tumor necrosis factor inhibitor'/exp OR ('anti TNF alpha*' OR 'anti tumor necrosis factor agent*' OR 'TNF alpha inhibitor*' OR 'TNF inhibitor*' OR 'tumor necrosis factor alpha inhibitor*'):ti,ab OR 'biological therapy'/exp OR 'bacteriotherapy'/exp OR 'cell therapy'/exp OR 'enzyme therapy'/exp OR 'molecular therapy'/exp OR 'stem cell mobilization'/exp OR ('biologics' OR 'bacteriotherap*' OR 'cell therap*' OR 'enzyme therap*' OR 'molecular therap*'):ti,ab OR 'disease modifying antirheumatic drug'/exp OR ('disease modifying anti-rheumatic' OR 'disease modifying antirheumatic' OR DMARD):ti,ab, 'end stage renal disease'/exp OR 'stage 5 renal disease*' OR ('dialysis'/exp AND 'late stage kidney disease'), 'immune deficiency'/exp OR 'immune deficienc*' OR 'DiGeorge syndrome'/exp OR 'Wiskott Aldrich syndrome'/exp OR 'immune deficiency'/exp OR 'primary immunodeficiency' OR 'primary immune deficiency' OR 'DiGeorge syndrome':ti,ab OR 'Wiskott Aldrich syndrome':ti,ab, ('case control study'/de OR 'clinical article'/de OR 'cohort analysis'/de OR 'comparative effectiveness'/de OR 'comparative study'/de OR 'controlled study'/de OR 'cross sectional study'/de OR 'diagnostic test accuracy study'/de OR 'evidence based medicine'/de OR 'human'/de OR 'logistic regression analysis'/de OR 'longitudinal study'/de OR 'major clinical study'/de OR 'medical record review'/de OR 'meta analysis'/de OR 'multicentre study'/de OR 'multicentre study topic'/de OR 'normal human'/de OR 'observational study'/de OR 'pilot study'/de OR 'postmarketing surveillance'/de OR 'prospective study'/de OR 'quality control'/de OR 'questionnaire'/de OR 'retrospective study'/de OR 'systematic review'/de OR 'telephone interview'/de), ('case control study'/de OR 'clinical article'/de OR 'cohort analysis'/de OR 'comparative effectiveness'/de OR 'comparative study'/de OR 'controlled study'/de OR 'cross sectional study'/de OR 'diagnostic test accuracy study'/de OR 'evidence based medicine'/de OR 'human'/de OR 'logistic regression analysis'/de OR 'longitudinal study'/de OR 'major clinical study'/de OR 'medical record review'/de OR 'meta analysis'/de OR 'multicentre study'/de OR 'multicentre study topic'/de OR 'normal human'/de OR 'observational study'/de OR 'pilot study'/de OR 'post-marketing surveillance'/de OR 'prospective study'/de OR 'quality control'/de OR 'questionnaire'/de OR 'retrospective study'/de OR 'systematic review'/de OR 'telephone interview'/de) AND ('article'/it OR 'article in press'/it OR 'preprint'/it OR 'review'/it)

The search identified 18 studies that involved 13,497 participants who were considered immunocompromised, with 10,124 (75%) receiving at least one dose of VAXZEVRIA and of these, 7,201 (71%) received the homologous primary series. AEs were reported in relation to a total of 17,075 doses of VAXZEVRIA (9,589 first doses, 7,201 second doses, and 295 not specified). Overall, 11,385 AEs were reported after any dose of VAXZEVRIA, 8,295 (73%) after the first dose, 3,087 (27%) after two doses, and three (0.03%) AEs where the dose was not specified. Most (87% of all AEs reported after any dose) reported AEs in the included studies were categorised as “general” AEs, followed by the musculoskeletal system (5%), neurological (4%), and gastrointestinal (3%). There was significant heterogeneity in the time from vaccine dose administration to AEs reporting across the included studies (two Days to one year). Half (n=9) of the included studies used a control group, but only six (33%) of these studies reported measures of association between VAXZEVRIA and reported AE, and only four (22%) studies measured and adjusted for the impact of potential confounding. Only one included study was deemed of “good” quality with 14 (78%) rated as “fair” quality and three studies (17%) categorized as “poor” quality.

Frequency of AEs Reported in Immunocompromised Individuals Following the Administration of VAXZEVRIA

Overall, authors of the included studies reported 11,385 AEs after any dose of VAXZEVRIA, 8,295 (73%) after the first dose, 3,087 (27%) after two doses, and three (0.03%) AEs where the dose was not specified. The full list of AEs by SOC and number of doses can be found in Table 91. Most reported AEs (86.9% of all AEs reported after any dose) in the included studies were categorised as “general” AEs, followed by the musculoskeletal system (5.4%), neurological (4.4%), and gastrointestinal (2.7%). The list of AEs included under “General” AEs is available in Table 91.

Table 91 Adverse Events Reported by Authors of Included Studies by SOC And In Relation to the Number of Doses of VAXZEVRIA in Immunocompromised Individuals

SOC	After first dose		After two doses		After any dose ^a	
	Frequency	Proportion of events	Frequency	Proportion of events	Frequency	Proportion of events
General ^b	7195	86.7%	2693	87.2%	9890	86.9%
Musculoskeletal system	435	5.2%	175	5.7%	610	5.4%
Neurologic	393	4.7%	106	3.4%	499	4.4%
Gastrointestinal	232	2.8%	73	2.4%	305	2.7%
Other system	2	0.0%	30	1.0%	32	0.3%
Renal	17	0.2%	-	0.0%	17	0.1%
Respiratory	8	0.1%	4	0.1%	12	0.1%

Skin	6	0.1%	3	0.1%	9	0.1%
Circulatory system/ Haematological	5	0.1%	2	0.1%	8	0.1%
Cardiovascular system	1	0.0%	1	0.0%	2	0.0%
Immunological	1	0.0%	0	0.0%	1	0.0%

^a Includes first doses, second doses and doses from studies not specifying the relation between the AEs and the number of dose.

^b Some studies reported "Any adverse events" and were categorized as general
SOC: System Organ Class

Regarding the general adverse effects after any dose of VAXZEVRIA reported by the authors of the included studies, the most frequently reported after the "Any AE" categories, were injection site pain (388 events reported per 10,000 doses), fatigue (334 events reported per 10,000 doses), and pyrexia (221 events reported per 10,000 doses). Other reported general AEs included chest pain (8 events per 10,000 doses), and anaemia (2 event per 10,000 doses). One death was also reported in an individual eight days after receiving a second dose of VAXZEVRIA. This person had a history of both severe aortic stenosis and aortic insufficiency and had stopped taking all the cardiac medications against the treating physician's advice. The patient passed away at home after developing cardiac decompensation with pleural effusion and lower limb oedema. The authors attributed the death to pre-existing left ventricular dysfunction resulting from aortic stenosis.

Regarding musculoskeletal system AEs, myalgia (165 events per 10,000 doses) and musculoskeletal pain (107 events per 10,000 doses) were commonly reported. Arthralgia (55 events per 10,000 doses) and back pain (28 events per 10,000 doses) were uncommonly reported AEs.

On neurological AEs reported by authors after any dose, headache was commonly reported at 194 events per 10,000 doses. Dizziness (39 events per 10,000 doses), lethargy (35 events per 10,000 doses), and insomnia (20 events per 10,000 doses) were uncommonly reported AEs. For gastrointestinal AEs, the most frequent was diarrhoea (85 events per 10,000 doses), followed by nausea/vomiting (63 events per 10,000). No studies reported GBS.

Subgroup Analysis of AEs Reported by Immunocompromised Groups

Immunocompromised or immunosuppressed individuals were defined as those that had one or more of the following:

- 1 Solid tumours or haematological malignancies, including chronic lymphocytic leukaemia.
- 2 Solid organ transplant +/- receiving immunosuppressive therapy.
- 3 Chimeric antigen receptor T-cell or haematopoietic stem cell transplant

- 4 Moderate or severe primary immunodeficiency and/or acquired immunodeficiency.
- 5 Advanced or untreated HIV.
- 6 Active treatment with any of the following: high-dose corticosteroids, alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, or tumour-necrosis factor inhibitors.
- 7 Late- or end-stage kidney disease and receiving dialysis.

Patients with solid tumours or haematological malignancies represented nearly half (48%; n=6,536) of the total IC participants, followed by those on active treatment with immunosuppressive drugs (26%), individuals with solid organ transplant (10%), participants with moderate or severe primary immunodeficiency and/or acquired immunodeficiency (7.5%), late- or end-stage kidney disease and receiving dialysis (7%) and participants on chimeric antigen receptor T-cell or haematopoietic stem cell transplant (0.6%) (Table 92). None of the included studies reported AEs following VAXZEVRIA vaccination in patients with advanced or untreated HIV (Table 92).

Table 92 Description of Immunocompromised Groups

IC subgroups	No. of IC (%)	VAXZEVRI A 1st dose	VAXZEVRIA 2nd dose*	VAXZEVRI A Any dose [‡]
Solid tumours or haematological malignancies, including chronic lymphocytic leukaemia	6,536 (48.4%)	5,765	4,426	10,222
Solid organ transplant	1,379 (10.2%)	860	831	1,691
Chimeric antigen receptor T-cell or haematopoietic stem cell transplant	80 (0.6%)	80	53	133
Moderate or severe primary immunodeficiency and/or acquired immunodeficiency	1,008 (7.5%)	1,008	713	1,721
Advanced or untreated human immunodeficiency virus	0	0	0	0
Active treatment with immunosuppressive drugs ^{&}	3,523 (26.1%)	1,060	843	2,167
Late- or end-stage kidney disease and receiving dialysis	971 (7.2%)	816	335	1,151
Total	13,497	9,589	7,201	17,085

IC, Immunocompromised

[&]Active immunosuppressive treatment with any of the following: high-dose corticosteroids, alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, or tumour-necrosis factor inhibitors.

*This is a subgroup of those who have been vaccinated with a first dose of VAXZEVRIA, in some studies it is explicitly reported or is an inclusion criterion (eg, full standardised vaccination schedule) and in others it is not specified but is the general vaccination scheme.

*Some studies do not report vaccination by dose and report AEs after at least one dose of AZ vaccine or do not specify.

Solid Tumours or Haematological Malignancies, Including Chronic Lymphocytic Leukaemia

Seven studies including a total of 6,536 participants with solid tumours or haematological malignancies, including chronic lymphocytic leukaemia were identified. Of these, 88% (n=5,765) received a first VAXZEVRIA dose and of those, 76% (n=4,426) completed the homologous primary series. A total of 5,910 AEs were reported by authors in this group with two studies accounting for 98.6% of all the AEs (n=5,831) (Deng et al 2022, Pakvisal et al 2022). Among all the reported AEs, 87% were general AEs (n=5,1274), 5% were in the musculoskeletal system (n=321), 4% were neurological (n=256), and 3% were gastrointestinal (n=192). Among this group, one cardiovascular event and three circulatory system or haematological AEs were reported by Walle et al 2022.

In Walle et al 2022 nine patients with advanced solid tumours undergoing combined immune-checkpoint inhibitors (ICIs) completed the full-standardized two vaccines scheme, and two patients received only the first VAXZEVRIA. One patient with a history of severe aortic stenosis and insufficiency, died after cardiac decompensation following eight Days after the administration of two doses of VAXZEVRIA. One event of blood corticotropin decrease (very rare) four weeks after the second VAXZEVRIA vaccination dose and two thrombocytopenia events (rare), after first and second VAXZEVRIA doses respectively were reported by authors. In this study, the following AEs-related to Intracavernosal Injection (ICI)-therapy were collected after a longer FU (median FU of 24 weeks after first dose): three anaemias (rare), one ileus (very rare), two muscular weakness (rare), one cholangitis infective (very rare), two blood creatinine increase (rare), dry skin and eczema (very rare).

In the study conducted by Pakvisal et al 2022, 399 solid malignancy patients on active cancer treatment received the first dose of VAXZEVRIA vaccine. Of these, 92.5% (n=369/399) received a second dose of VAXZEVRIA. 7.5% of participants (n=30/399) did not receive the second dose at 8–10 weeks later due to either cancer-related deaths (n = 7) or loss to FU. A total of 2,979 AEs were reported by authors, 75% were general, 10% were musculoskeletal system AEs and included myalgia and back pain, 8% were neurological with headache being the more frequent, and 6% were gastrointestinal, which included nausea/vomiting and diarrhoea. In Deng et al 2022, 2,852 AEs were reported, and all were general.

Solid Organ Transplant

Five studies including 1,379 patients with solid organ transplants were identified. Of these, 62% (n=860) received a first VAXZEVRIA dose and 96.6% (n=831) completed the homologous two dose vaccination scheme (Table 92). A total of 850 AEs were reported by authors in this group, two studies accounted for 80% of all the AEs (n=683). Among all the AEs, 94% were general AEs (n=803), 2% were neurological (n=20) and 2% were renal (n=15). One circulatory system or haematological AE was reported in one study Watcharananan et al 2022.

Watcharananan et al 2022 included 83 kidney transplant recipients who received two doses of VAXZEVRIA, and AEs were measured three Days after each dose. Body ache, local reaction of the injection site, fever and headache were the most frequently reported AEs, which ranged from 5-10% after the receipt of any dose. High blood pressure was reported in one patient within 3 Days after receiving VAXZEVRIA. It is unclear if high blood pressure was self-reported or measured at the time of FU when the blood test was performed. The study by Ajlan et al 2022 reported on 148 organ transplant recipient subjects who received two doses of VAXZEVRIA and AEs reported seven Days after the receipt of any dose. Bell's palsy and dermatitis were collected for other COVID-vaccines but not for VAXZEVRIA. In the study conducted by Chen et al 2022., 30 kidney transplant recipients were vaccinated with at least one dose of VAXZEVRIA, and 15 patients experienced (50%) deterioration in renal function (measured by a fluctuation in serum creatinine levels) within two months after vaccination. The mean change in creatinine levels were $6.06 \pm 10.17\%$.

Chimeric Antigen Receptor T-Cell or Haematopoietic Stem Cell Transplant

One study with 80 patients with chimeric antigen receptor T-cell or haematopoietic stem cell transplants was identified. In this study, all patients received a first dose of VAXZEVRIA (n=80) and 66% completed the full standardised vaccination schedule (n=53). A total of 43 events were recorded, all were general (Table 92).

Moderate or Severe Primary Immunodeficiency and/or Acquired Immunodeficiency

One study with 1,008 patients with moderate or severe primary immunodeficiency and/or acquired immunodeficiency was identified. In this study, all patients received a first dose of VAXZEVRIA and 70% completed the full standardised vaccination schedule (n=713). A total of 754 events were recorded, all were general (Table 92).

Active Treatment with Immunosuppressive drugs

Four studies with 3,432 individuals on active immunosuppressive treatment with any of the following: high-dose corticosteroids, alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, or tumour-necrosis factor inhibitors were identified. Of these, 31%

received a first VAXZEVRIA dose (n=1,060) and 79.5% (n=843) completed the homologous two dose vaccination scheme (Table 92). A total of 634 AEs following VAXZEVRIA vaccination were reported by authors, with one study accounting for 83% of all the AEs (n=529). Among all the AEs, 94% were general AEs (n=596), 5% were other systems (n=29), and one circulatory system AE was reported in one study (Table 92 and Appendix G).

Czarnowska et al 2022 included a total of 264 individuals with MS, treated with disease modifying therapies from 19 Polish MS centres who received at least one dose of VAXZEVRIA and one pro-thrombotic complication was recorded in a 42-year-old female after receiving the two doses of AstraZeneca vaccine. Chanprapaph et al 2022., studied adverse reactions events after two doses of VAXZEVRIA in individuals with psoriasis receiving methotrexate (n=39) and individuals with autoimmune bullous disease receiving steroid-sparing agents (n=37), prednisolone (n=42) and rituximab (n=15). Thirty Days after the receipt of second dose (n=133), 29 up titration of immunosuppressants for disease control (therapy change) were reported by authors. In the study conducted by Szebeni et al 2022, 20 patients with autoimmune and inflammatory rheumatic and musculoskeletal diseases on active immunosuppressive treatment, received a first and second dose of VAXZEVRIA. Two events of cough and one event of rhinorrhoea were reported by authors after the first dose. Following the second dose of VAXZEVRIA, two rhinorrhoea and one cough events were reported. Less than five AEs were reported per dose, three malaise, two chills and one event each of fever, myalgia, arthralgia and headache. Cough was reported in two patients and rhinorrhoea was reported in one patient after dose one and two patients after dose two.

Late- or end-stage Kidney Disease and Receiving Dialysis

Four studies with 971 individuals with late- or end-stage kidney disease and receiving dialysis were identified. Of these, 84% received a first VAXZEVRIA dose (n=816) and 41% (n=335) completed the homologous two dose vaccination scheme (Table 92). A total of 3,194 AEs following VAXZEVRIA were reported, with two studies accounting for 81% of all the AEs (n=2584). Among all the AEs, 80% were general AEs (n=2,567), 9% were musculoskeletal system AEs (n=281), 7% were neurological (n=222), and three circulatory system AEs were reported in one study (Table 92 and Appendix G).

In Yang et al 2022 270 adults with end-stage renal disease on haemodialysis received two doses of the VAXZEVRIA and AEs were collected on day two and on day seven. Five participants had AEs, including herpes zoster (HZ) reactivation (n=1) in the right leg five Days after vaccination and acute vascular access site thrombosis (n=3). Chest pain/tightness was self-reported (n=13), injection site induration (n=52), thirst (n=63), and insomnia (n=34) were reported.

Table 93 AEs Reported by Authors of Included Studies Grouped by System Organ Class and Immunocompromised Groups

IC category	CV	CS	Gastr.	Imm.	MS	Neur.	OS	Renal	RS	Skin	Gen.	Grand Total
Solid tumours or haematological malignancies, including chronic lymphocytic leukaemia	1	4	192	3	321	256	2	2	1	4	5,127	5,910
Solid organ transplant	1	NK	6	1	4	20	NK	15	NK	0	803	850
Chimeric antigen receptor T-cell or haematopoietic stem cell transplant	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	43	43
Active treatment with any of the following*	NK	1	NK	0	4	1	29	NK	3	NK	596	634
Moderate or severe primary immunodeficiency and/or acquired immunodeficiency	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	754	754
Late- or end-stage kidney disease and receiving dialysis	NK	3	107	NK	281	222	1	NK	8	5	2,567	3,194
Total	2	8	305	4	610	499	32	17	12	9	9,890	11,385

High-dose corticosteroids, alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, or tumour-necrosis factor inhibitors. Legend:

IC, Immunocompromised; NK, Not Known; CV, Cardiovascular System; CS, Circulatory System; Eye, Eye Disorder; Gastr., Gastrointestinal; Imm Immunological; MS Musculoskeletal System; Neur Neurological; OS Other System; RS, Respiratory System; Gen General.

Association Between VAXZEVRIA and AEs in Individuals Taking Immunosuppressant Medications and/or With Primary Immunodeficiency

Half (n=9) of the included studies used a control group. However, three of these studies reported no measure of association between VAXZEVRIA and reported AEs. Of the six studies (Table 93) that did report measures of association, Chen et al 2022 compared the deterioration in renal function in kidney transplant recipients after administration of different COVID-19 vaccines (VAXZEVRIA, Moderna COVID-19 Vaccine, Comirnaty BioNTech Pfizer Vaccine, and MVC COVID-19 Vaccine) and found no significant differences.

Ajlan et al 2022 and Haase et al 2022 also compared IC individuals vaccinated with VAXZEVRIA and Comirnaty and show mixed results. In individuals with solid organ transplants in Ajlan et al 2022 AEs were more frequent in the Comirnaty group, especially after the second dose. In the case of Haase et al 2022, in patients on haemodialysis, the occurrence of local and systemic reactions and medication use was reported more frequently after the first dose of VAXZEVRIA.

Deng et al 2022, Pakvisal et al 2022 and Wang et al 2022 [A] compared the frequency of AEs from VAXZEVRIA with healthy controls. Deng et al 2022 evaluated different IC populations and presented ORs adjusted for sex, age group, indigenous status, clinic type, jurisdiction, prior history of anaphylaxis, and underlying medical conditions for the outcome variable "any adverse event". Overall, numbers were very low after the first dose and high with second dose. In the case of individuals receiving chemotherapy or radiotherapy, the adjusted OR after the first dose was 0.90 (95% CI 0.70-0.91) and after the second dose was 1.40 (95% CI 1.14-1.68). Individuals with organ transplant recipient on immunosuppressive therapy had an aOR of 0.75 (95% CI 0.62-0.90) after the first dose and 1.47 (95% CI 1.17-1.81) after the second dose. Individuals with a diagnosis of non-haematological malignancies in the last 12 months had an aOR of 0.92 (95% CI 0.85-0.99) after the first dose and 1.29 (95% CI 1.15-1.43) after the second dose. For individuals with haematological malignancies diagnosed in the past five years only the aOR after the second dose was significant (aOR: 2.33; 95% CI 2.03-2.66), as for individuals with primary or acquired immunodeficiency (aOR: 2.24; 95% CI 1.89-2.63). In contrast Pakvisal et al 2022, Wang et al 2022 [A] reported lower numbers of AEs for both the first and second dose in IC individuals (solid cancer patients who were actively receiving cancer treatments and patients with end-stage renal disease [ESRD] receiving dialysis respectively). All significant associations reported in the included studies are presented in the data extraction table in the supplementary material.

Discussion

There were 18 studies that met the eligibility criteria and were included for synthesis. The included studies involved 13,497 participants with immunosuppression, with 10,124 (75%) receiving at least one dose of VAXZEVRIA and of these, 7,201 (71%) received the

homologous primary series. Overall, AEs were reported in relation to a total of 17,075 doses of VAXZEVRIA. Only one study was classified as good quality, the rest were either of fair or poor quality.

Overall, authors of the included studies reported 11,385 AEs after any dose of VAXZEVRIA, 8,295 after the first dose, 3,087 after two doses, and three AEs where the dose was not specified. Most of the overall AEs (86.9% of all AEs reported after any dose) in the included studies were categorised as “general” AEs, followed by the musculoskeletal system (5.4 %), neurological (4.4%), and gastrointestinal (2.7%).

Common AEs reported by authors following VAXZEVRIA were injection site pain, fatigue, pyrexia and injection site tenderness (pyrexia and injection site tenderness were uncommon after dose two). Anaemia was rare (unknown after second dose) and death was very rare (one person after second dose). Among musculoskeletal system AEs, common AEs were myalgia and musculoskeletal pain (musculoskeletal pain was uncommon after dose two). Arthralgia or back pain were uncommon. In the neurologic group, headache was common, and dizziness, lethargy and insomnia were uncommon (lethargy and insomnia were not known after dose two), somnolence was rare and hypoaesthesia was very rare after first dose and unknown after second dose.

The distribution of patients among IC categories was heterogenous. Seven studies including almost half of the IC population were conducted in patients with solid tumours or haematological malignancies, including chronic lymphocytic leukaemia.. Five studies including 10% of participants were conducted in solid organ transplants patients. Four studies including more than 25% of patients were conducted in individuals on active immunosuppressive treatment. This SLR did not identify any study reporting AEs following VAXZEVRIA in individuals with advanced or untreated HIV. One study in patients with moderate or severe primary immunodeficiency and/or acquired immunodeficiency represented 7% of the population and the same study was conducted in individuals with chimeric antigen receptor T-cell or haematopoietic stem cell transplant. Four studies with late- or end-stage kidney disease and receiving dialysis were identified, representing 7% of all IC individuals.

The association between VAXZEVRIA and AEs reported by authors in IC groups was reported only in six studies and yielded mixed results. It was therefore not possible to draw any conclusion on a potential association between Vaxzervria and AEs. Three studies compared VAXZEVRIA with different COVID-19 vaccines and found inconclusive results in patients with kidney transplants, solid organ transplants and haemodialysis. Deng et al 2022, Pakvisal et al 2022 and Wang et al 2022 [A], compared the frequency of AEs to healthy controls. In Deng et al 2022. Ae reported by study authors were significantly associated after the second dose of VAXZEVRIA in multiple IC groups, but this difference was not reported in Pakvisal et al 2022, Wang et al 2022 [A].

The SLR provided the first descriptive synthesis of AEs following vaccination with VAXZEVRIA in IC populations. Common AEs reported by study authors following VAXZEVRIA were general, involving injection site pain and tenderness, fatigue and pyrexia. The association between VAXZEVRIA and AEs reported by study authors in IC groups was reported only in six studies and yielded mixed results. It was therefore not possible to draw any conclusions on a potential association between VAXZEVRIA and AEs. There was considerable heterogeneity and few studies accounted for key confounders. Only one study was classified as good quality, the rest were either of fair or poor quality, hence, results should be interpreted with caution given the heterogeneity and limitations described. The AEs reported were similar to those seen in immunocompetent recipients, although reported with varying frequencies. No new AEs of concern were reported.

Conclusions

This cumulative review of the Use of VAXZEVRIA in subjects with severe immunodeficiency/Use in immunocompromised patients did not indicate any new safety concerns.

The review and analysis of the available literature did not highlight any particular safety concerns with VAXZEVRIA when used in immunocompromised patients (ICPs). The safety data in ICPs have generally been consistent with those observed for the Non-ICPs. There were no articles identified with a specific reference to any new safety concerns associated with VAXZEVRIA. Overall, the review of the currently available data did not reveal any new safety information in immune-compromised individuals that has not been identified in the overall population.

AstraZeneca will continue to monitor safety information in vaccinees with severe immunodeficiency and in immunocompromised patients as part of the routine safety surveillance activities for VAXZEVRIA and take further actions as deemed appropriate.

16.3.5.3 Use of AZD1222 in subjects with severe and/or uncontrolled underlying disease /Use in frail patients with co-morbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorder)

Subjects with severe and/or uncontrolled underlying diseases are potentially at risk of developing a more severe manifestation of COVID-19 and, as a consequence, have been included as a priority group for initial vaccination in several jurisdictions. Although there is no evidence that the safety profile of VAXZEVRIA in this population will be different to that of the general population, given the paucity of data, the possibility cannot be excluded.

Indicators of frailty used in the review of cases were defined in the protocol for the VAXZEVRIA PASS: A post-authorisation/post-marketing observational study to evaluate the

association between exposure to VAXZEVRIA and safety concerns using existing secondary health data sources. This protocol was approved by EMA on 27 January 2022, as no FU questionnaires are sent for this missing information concept, no scale of frailty was used for the assessment of the spontaneous cases. Rather, a case narrative text search of VAXZEVRIA reports in the AstraZeneca global safety database using the parameters for each indicator of frailty in Table 94 was used to identify cases for review in the sub-sections below:

Table 94 Indicators of Frailty

Frailty Indicator	Search Parameter
Frailty	“Frailty” “Bedridden”
Dispensing of or reimbursement for durable medical equipment (eg, wheelchairs, home oxygen)	“oxygen” “O2” “scooter” “walker” “wheelchair” “wheel-chair”
Residence in long-term facility or nursing home	“long term” “nursing home” “skilled care” “skilled-care”
Hip fracture	“hip fracture” “fractured hip” “broken hip” “hip broken”
Palliative care	“palliative” “hospice” “palliate”
Metastatic cancer	“metastatic” “metastasis” “metastases” “metastasise” “cancer spreading” “cancer spread”
Cachexia	“cachexia” “wasting” “waste”

Table 94 Indicators of Frailty

Frailty Indicator	Search Parameter
Dementia	“dementia” “Alzheimer” “memory” “cognitive” “cognition”
Pressure ulcers	“ulcer”
Bladder incontinence	“bladder” “urine” “leak”

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database through 28 December 2023 was undertaken to review AEs reported after vaccination with VAXZEVRIA in individuals identified as having severe and/or uncontrolled underlying disease or were identified as frail. All the categories are described below:

16.3.5.3.1 Frailty

Reporting Period (28 December 2022 to 28 December 2023)

The search identified a total of 55 cases (98.2% spontaneous cases, 1.8 % noninterventional/post-marketing cases) for the topic use of VAXZEVRIA in individuals with frailty_ frail.

Of the 55 cases, 33 (60) were reported in females, 18 (32.7%) in males and gender was not reported in the remaining 4 (7.3%) case. Age ranged from 18 years to <65 years in 47.3% (26), and 27.3% (15) in 65+ years. In 13 (23.6%) cases the age was reported as unknown. Of the 55 reports, 25.5% (14) were MC, with remaining 74.5% (41) being consumer reports.

Of these 55 cases, 48 (87.3%) were serious, reported seriousness criteria were medically important (34), disability (22), hospitalization (15), life threatening (6), and death (4). Cases may have met more than one criterion for seriousness. The remaining 7 (13.4%) reports were non-serious.

The top 20 reported PTs were Fatigue (38), Headache (25), Bedridden (23), Pyrexia (19), Rash (22), Tinnitus (20), COVID-19 (18), Colitis ulcerative (17), Pain (17), Loss of personal independence in daily activities (16), Pulmonary embolism (13), Palpitations (12), Stress (12), Impaired quality of life (12), Pain in extremity (12), Arthralgia (11), Arthritis (11), Cardiac murmur (11), Cerebrovascular accident (11), Confusional state (11), Drug ineffective (11),

Haematochezia (11), Migraine (11), Pulmonary embolism (11), Somnolence (11), Weight decreased (11).

Of the 55 cases, there were 4 (8%) cases with fatal outcome reported during this period. The assessment of these 4 fatal case reports are presented below:

Case ID [REDACTED]: This MC case concerns 52 years old patient of unknown age and gender. The patient's medical history included back pain, anal fissure, tonsillectomy and adenoidectomy (dates not reported). No concomitant products were reported. On an unknown date after vaccination, vaccinee experienced ADEM. After two months was diagnosed with and pulmonary embolism. On an unknown date, the patient experienced meningoencephalitis, chronic respiratory failure, pneumonia recurrent, thrombocythemia and respiratory failure type 2. Patient passed away on 87 due to pulmonary embolism and DVT. An autopsy was performed but no detailed report was available.

AstraZeneca Comment: In this case an autopsy was performed however the autopsy result was not provided and the events ADEM, encephalitis, respiratory failure, chronic respiratory failure, pneumonia, pneumothorax, thrombocytosis and fatal events of DVT and pulmonary embolism were not listed in the company CDS. The cause of death was reported as DVT and pulmonary embolism, which could be in association with each other. There was insufficient information on nature and circumstances leading to the events, relevant family history, concomitant medications, possible risk factors, detailed etiologic and diagnostic workup, the evaluation did not find evidence to suggest a causal relationship between the events and AZD1222.

Case ID [REDACTED]: This MC case concerns a female patient born in 1954 of Unknown ethnicity. The patient's past and current medical history included osteoarthritis, stomach ulcer, skin cancer, acute hepatitis, depressive disorder, hiatus hernia, hallux valgus and hysterectomy. No concomitant products were reported. The patient received VAXZEVRIA on 25 February 2021. On an unknown date, the patient suffered from stroke (preferred term: Cerebrovascular accident), systemic coagulopathy (preferred term: Coagulopathy), colitis (preferred term: Colitis), intracerebral haemorrhage (preferred term: Cerebral haemorrhage), cerebral venous sinus thrombosis (preferred term: Cerebral venous sinus thrombosis), vaccine-induced thrombocytopenia and thrombosis (preferred term: TTS), diverticulitis (preferred term: Diverticulitis), pyelophletis in the portal vein (preferred term: Portal vein phlebitis), brain infarct (preferred term: Cerebral infarction). acute thrombosis (preferred term: Thrombosis), anaemia (preferred term: Anaemia), pulmonary emboli (preferred term: Pulmonary embolism), photophobia (preferred term: Photophobia), true thrombocytopenia (low platelets) (preferred term: Thrombocytopenia), sinus symptoms (preferred term: Sinusitis), the feeling of pressure (preferred term: Discomfort), gastroenteritis (preferred term: Gastroenteritis) and confused (preferred term: Confusional state). On an unknown date, the

patient experienced agitated (preferred term: Agitation). The outcome of the event(s) of diverticulitis, pyelophletis in the portal vein, brain infarct, acute thrombosis, anaemia, pulmonary emboli, photophobia, true thrombocytopenia (low platelets), sinus symptoms, the feeling of pressure, gastroenteritis, confused and agitated was unknown. The patient died from the event of stroke, systemic coagulopathy, colitis, intracerebral haemorrhage, cerebral venous sinus thrombosis and vaccine-induced thrombocytopenia and thrombosis on 16 March 2022. An autopsy was not performed. The cause of death was vaccine-induced thrombocytopenia and thrombosis, stroke, systemic coagulopathy, colitis, intracerebral haemorrhage and cerebral venous sinus thrombosis.

AstraZeneca Comment: Events of Thrombosis (Preferred terms: Pulmonary embolism, Cerebral venous sinus thrombosis, Thrombosis, Cerebral infarction, Cerebrovascular accident, TTS) in combination with Thrombocytopenia (Preferred term: TTS and Thrombocytopenia) is listed in the company CDS of AZD1222. however, as the SAEs cerebral venous sinus thrombosis, TTS has been reported with the seriousness criteria of death the event is considered unlisted. This case is MC. Concomitant skin cancer could be confounding factor. Due to limited information on patient's age, start date of AZD1222, events onset date, circumstances leading to the events, clinical course, treatment provided, further relevant medical history, risk factors, other concurrent diseases, concomitant medications, relevant family history, status of underlying comorbidities, complete etiologic and diagnostic workup, the evaluation did not find evidence to suggest a reasonable possibility of a causal relationship between events and AZD1222.

Case ID [REDACTED] This consumer report concerning a female patient of Unknown ethnic origin. No concomitant products were reported. On 27 January 2021, the patient received first dose of VAXZEVRIA. On 27 January 2021, the patient experienced arm paralysis (preferred term: Monoplegia), tiredness (preferred term: Fatigue) and weakness (preferred term: Asthenia). On 07 February 2021, the patient experienced ischemic heart disease (preferred term: Myocardial ischaemia). On an unknown date, the patient experienced heart attack (preferred term: Myocardial infarction). After the heart attack, a stent was placed on 03 February 2021. The patient died from the event of ischemic heart disease on 07 February 2021. An autopsy was not performed. The cause of death was ischemic heart disease.

AstraZeneca Comment: This case report concerns a female patient with reported fatal outcome of the events as reported- Myocardial ischaemia, Monoplegia and Myocardial infarction, that are not listed in the company CDS of AZD1222. The cause of death was reported as ischemic heart disease. Due to limited information on baseline health condition before vaccination, circumstances leading to the events, further risk factors, if any beyond conditions and diseases reported in medical history, concomitant medications, autopsy report

with confirmed diagnosis, detailed aetiological and diagnostic work up, the evaluation did not find evidence to suggest a causal relationship between the events and AZD1222.

Case ID [REDACTED]: this is consumer report concerning a male patient of Unknown ethnic origin. The patient's past and current medical history included type 1 diabetes mellitus. No concomitant products were reported. On 04 February 2021, the patient received dose one of VAXZEVRIA. On 19 April 2021, the patient received dose two of VAXZEVRIA. During October 2021, the patient received Booster- same brand as primary vaccine VAXZEVRIA. On 06 February 2021, the patient experienced rash trunk (preferred term: Rash). On 05 February 2022, the patient experienced SARS-COV-2 infection (preferred term: COVID-19). On an unknown date, the patient experienced skin peeling (preferred term: Skin exfoliation), liver failure (preferred term: Hepatic failure), kidney failure (preferred term: Renal failure), bedridden (preferred term: Bedridden), unable to urinate (preferred term: Urinary retention), sepsis (preferred term: Sepsis). Action taken with both the doses of VAXZEVRIA and booster dose of VAXZEVRIA was not applicable. The outcome of the events of rash trunk, skin peeling, liver failure, kidney failure, bedridden and unable to urinate was unknown. The patient died from the event of sars-cov-2 infection, sepsis on 15 February 2022. The cause of death was sars-cov-2 infection and sepsis. Autopsy performed was unknown.

AstraZeneca Comment: Fatal events of Sepsis and COVID-19 and non-fatal events of Bedridden, Renal failure, Hepatic failure, Skin exfoliation and Urinary retention are not listed in company CDS of AZD1222. The cause of death was reported as Sepsis and Sars-cov-1 infection. Type 1 diabetes mellitus could be considered as a risk factor to the events of Sepsis, Renal failure and COVID-19. Sepsis, Renal failure, Hepatic failure, Skin exfoliation and Rash could be in association with each other. Current pandemic situation of COVID-19 could contribute to the event of COVID-19. Due to limited information on nature and circumstances leading to the events, relevant family history, concomitant medications, possible risk factors, detailed etiologic and diagnostic workup, the evaluation did not find evidence to suggest a causal relationship between the events and AZD1222.

Cumulative Review (28 December 2020 to 28 December 2023)

The search of the AstraZeneca global safety database identified a cumulative total of 1592 cases (98.4% spontaneous cases, 01% non-interventional/post-marketing cases, and 0.6% literature) for the topic use of VAXZEVRIA in individuals with frailty.

Of the 1592 cases, 1201 (75.5%) were reported in females, 333 (20.9%) in males and gender was not reported in the remaining 58 (3.6%) of cases. Age ranged from 18 years to <65 years in 64% (1019), 65+ years in 22.2% (353), 0 to <18 years in 0.1% (1), in adult 0.4% (6), and in elderly 0.5% (8). In 12.9% (205) cases the age was reported as unknown. Of the 1592 reports, 17% (269) were MC, with remaining 83% (1323) being consumer reports.

Of these 1592 cases, 1144 (72%) were serious, reported seriousness criteria were medically important (840), disability (331), hospitalization (171), life threatening (66), and death (144). Cases may have met more than one criteria for seriousness. The remaining 448 (28.14%) reports were non serious.

The top 20 reported PTs were Pyrexia (747), Headache (727), Fatigue (638), Bedridden (601), Chills (474), Nausea (433), Myalgia (337), Dizziness (332), Pain (284), Malaise (274), Arthralgia (259), Pain in extremity (214), Asthenia (209), Vomiting (196), Dyspnoea (161), Decreased appetite (158), Hyperhidrosis (141), Influenza like illness (114), Diarrhoea (113), Tremor (108). Outcome was reported as fatal for 144 (9.04%) cases, of which 4 were reported during the interval period, as described in the previous section.

16.3.5.3.2 Hip Fracture

Search Strategy

A cumulative and periodic search of the global safety database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited reporting and literature) for the topic use of VAXZEVRIA in individuals with Hip fracture.

Reporting Period (28 December 2022 to 28 December 2023)

The search identified a total of 14 case reports (71.4% from the study D8110C00001 and 28.6% of spontaneous cases in frail vaccinees with hip fracture who received VAXZEVRIA.

Of the 14 cases, 46.2% (6) were reported in females, 53.8% (7) in males and gender was not reported in the remaining one case. Age ranged from, 18 to <65 years in 14.3% (2), 65+ years in 85.7%. The majority of cases 78.6% (11) were consumer reports with the remaining 21.4% (3) cases being MC.

All the 14 cases were serious, reported seriousness criteria were medically important (2), hospitalization (13), disability (2) and Death and Life Threatening (1, each). Cases may have met more than one criterion for seriousness. The most frequently co-reported AEs with hip fracture are Arthralgia (3), Fatigue (2), neck pain (2), paraesthesia (2) and abnormal loss of weight (2) and the remaining events were reported singularly.

One case was reported with fatal outcome. In this case, 64-year-old male patient was paralyzed on one side due to the infarction in the brain stem. One month before his death (approximately 6 months from infarction), vaccinee he broken his hip due to a cramp. This case has limited information on the clinical course of the event, medical history, concurrent diseases concomitant medications, diagnostic workup, autopsy findings to perform a comprehensive causality assessment.

Upon review of the cases retrieved during reporting interval, no trend or pattern was observed.

Cumulative Review (28 December 2020 to 28 December 2023)

The search of the AstraZeneca Global Safety Database identified a cumulative total of 43 (76.7% spontaneous cases and 23.3% from the study D8110C00001) cases in frail vaccinees with hip fracture who received VAXZEVRIA.

Of the 43 cases, 61.9% (26 cases) were reported in females, 35.7% (15 cases) were in males and in 1 one case gender was not reported. Age ranged from 18 years to <65 years in 29.2%, 65+years in 70.7% and gender was not reported in 2 cases.

The majority of reports cases 23 (53.5%) were from consumers with the remaining 20 (46.5%) cases being MC. Of these 43 cases, 36 (83.7%) were serious, reported seriousness criteria were medically important (19), disability (6), hospitalization (22), life threatening (3), and death (6). Cases may have met more than one criterion for seriousness. The remaining 7 (16.3%) reports were non serious.

The most frequently co-reported AEs with Hip fracture are Headache (9), Arthralgia (8), Pyrexia and Fatigue (7, each), Pain in extremity (6), Dizziness and Fall (5, each). There were 6 fatal cases reported cumulatively in individuals with hip fracture.

16.3.5.3.3 Cachexia

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited reporting and literature) for the topic use of VAXZEVRIA in cachexic individuals.

Reporting Period (28 December 2022 to 28 December 2023)

The search identified a total of 9 cases (8 spontaneous cases and 1 cases from Study D8110C00001) for the topic, use of VAXZEVRIA in cachexic individuals.

Of the 9 cases, 5 (55.6%) cases were reported in females and 5 (44.4%) in males. Age ranged from 18 years to <65 years in 4 (57.1%) cases, 2 (42.8%) in 65+ years, and in 2 cases the age was reported as unknown. Of the 9 reports, 33.3% (3) were MC, with remaining 66.7% (6) being consumer reports.

All these 9 cases were serious, reported seriousness criteria were medically important (3), hospitalization (6), disability (5), and life threatening (2). Cases may have met more than one criterion for seriousness. The most frequently reported AEs in these cases are fatigue and muscle atrophy (4, each) and Dizziness, Headache and Malaise (3, each). None of the cases were reported with fatal outcome.

There were no fatal cases reported.

Cumulative Review (29 December 2020 to 28 December 2023)

The search of the AstraZeneca Global Safety Database identified a cumulative total of 226 cases (98.7% spontaneous cases, 0.9% literature and 0.4% from study D8110C00001) for the topic, use of VAXZEVRIA in cachexic individuals. Of the 226 reports, 22.6% (51) were MC, with remaining 77.4% (175) being consumer reports.

Of the 226 cases, 125 (55.7%) were reported in females, 94 (42.3%) in males and gender was not reported in the remaining 5 cases. Age ranged from 18 years to <65 years in 78.1% (161), 65+ years in 21.9% (45), and unknown in 20 cases.

Of these 226 cases, 73.5% (166) were serious, reported seriousness criteria were medically important (95), hospitalization (61), disability (41), life threatening (17), and death (11). Cases may have met more than one criterion for seriousness. The remaining 60 (26.5%) reports were non serious. The mostly frequently reported events were related reactogenicity related events (

The top 30 reported events were Headache (69), Fatigue (57), Pyrexia (45), Muscle atrophy (44), Dizziness (39), Myalgia (38), Muscular weakness (34) and Chills (30). There were 11 (4.9%) fatal cases reported cumulatively in individuals with cachexia.

16.3.5.3.4 Bladder Incontinence

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited and literature) for the topic use of VAXZEVRIA in individuals with underlying Bladder incontinence.

Reporting Period (28 December 2020 to 28 December 2023)

The search identified a total of 359 case reports (54.9% spontaneous cases, 19.5% literature, 7.2% non-interventional/post-marketing, 0.3 % from the study D7220C00001 and 18.1% from study D8110C00001) in individuals with underlying bladder incontinence who received VAXZEVRIA. The majority of cases 79.7% (229) were consumer reports with the remaining 36.2% (130) cases being MC.

Of the 359 cases, 115 cases were reported in females, 166 in males and gender was not reported in the remaining 3 cases. Age ranged from, 18 to <65 years in 59.6% (214), 65+ years in 30.4% (109) cases; in 2 cases reported in infants and age was not reported in the remaining 334 cases.

Of these 359 cases, 315 (87.7%) were serious. The most frequently co-reported AEs are Headache (69), Fatigue (63), Pyrexia (53), myalgia and nausea (40), dizziness (36), paraesthesia (34) and Pain in extremity (32).

The outcome of the case was reported as fatal in 22 cases (6.1%) of the cases. The age of the vaccinees with fatal outcome ranged between 36-92 years (median 57). The cause of death in most of the cases are due to cardio-respiratory events (MI, Cardio-respiratory arrest, cardiac disorder, COPD), TTS and embolic and thromboembolic events (such cerebrovascular accident, cerebral haemorrhage, cerebral venous sinus thrombosis etc.). There were 05 cases where a fatal event occurred after 1st dose of vaccine and 1 case after 2nd dose, limited information was available in the remaining 16 cases.

Based on the review of data received during the reporting interval no specific trend or pattern of events were observed.

Cumulative Review (28 December 2020 to 28 December 2023)

The search of the AstraZeneca Global Safety Database identified a cumulative total of 5471 cases (94.1% spontaneous cases, 4.2% cases from literature and 1.7% cases from Clinical trials. Most of these cases 73.2% were reported as serious. The most frequently reported events are reactogenicity related events such as Headache (1565), Pyrexia (1287), Fatigue (1164), Chills (823), Nausea (770) and Myalgia (617).

Around 192 cases were reported with fatal outcome. The cause of death in these cases were mostly due to cardio-respiratory events (MI, Cardio-respiratory arrest, cardiac disorder, COPD), TTS and embolic and thromboembolic events (such cerebrovascular accident, cerebral haemorrhage, cerebral venous sinus thrombosis etc.). No specific trend or pattern was observed.

16.3.5.3.5 Dementia

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited and literature) for the topic of use of VAXZEVRIA in individuals with Dementia.

Reporting Period (29 December 2022 to 28 December 2023)

The search identified a total of 373 case reports (86.1% spontaneous, 4% literature, 6.7% noninterventional/ post-market and 3.2% from study D8110C00001) in individuals with underlying dementia who received VAXZEVRIA. The gender of vaccinees was reported in 361 cases, 62% were females and 38% were males vaccinees. The age was reported in 319 cases and majority of cases (67.3%) were reported in adults and in 21.1% were in elderly age

group. The age of the vaccinees ranges between 20-96 years (median 55 years). Majority of the cases reports 249 (66.8%) were from consumer reports and 124 cases (33.2%) are MC. The most frequently co-reported events in the dementia cases are Fatigue (181); Headache (152); Memory impairment (152); Disturbance in attention (97); Dizziness (96); Amnesia (87); Arthralgia (87); Cognitive disorder (83); Pyrexia (83) and COVID-19 (80).

Of the 373 cases, 318 (85.3%) were reported as serious and 16 cases were reported with fatal outcome (3 adults and 2 unknown and 11 elderly vaccinees). The age of the vaccinees was available in 14 cases and ranges between 34-96 years (median age 55 years). In Six cases, vaccinees, patient had history of dementia. The most common cause of death reported as TTS and cardio-respiratory events (COPD, sudden cardiac death, Cerebral artery embolism). Of the 3 adults vaccinees reporting dementia, 1 vaccinee was diagnosed with glioblastoma 14 Days after vaccination, 1 reported fatal cerebral haemorrhage. These two cases had limited to perform a comprehensive medical assessment. Third case with history of craniocerebral trauma, hypertension, atherosclerosis and in this case cause of death was unknown.

Cumulative Review (29 December 2020 to 28 December 2023)

The search of the AstraZeneca Global Safety Database identified a cumulative total of 3906 cases (95.7% spontaneous, 2.5% non-interventional/post-marketing, 1.4% from literature and 0.4% from the study D8110C00001 and 1 (0.0%) case each from COV003 and Indian Council of Medical Research (ICMR)/SII-AZD-COVID-19/2020) in individuals with dementia who received VAXZEVRIA. The age of the vaccinees was reported in 3557 cases and 66.3% of the cases were reported in adults and 35.6% of the cases reported in elderly vaccinees. The age of vaccinees ranges between 18-103 years (median 57 years). About 76.7% of the cases were consumer reports and the remaining 23.3% of the cases were MC. Majority of the cases (72.5%) reported as serious.

Most frequently co-reported AEs in the cases with dementia are Fatigue (1354); Headache (1351); Memory impairment (1345); Pyrexia (834); Amnesia (805); Dizziness (739); Myalgia (559); Nausea (540); Cognitive disorder (532) and Disturbance in attention (520). Outcome of the cases was reported fatal in around 5.6% of the cases. In most of the cases where the cause of death is reported, they were mostly due to cardiovascular complications. Overall no trend or pattern was observed.

16.3.5.3.6 Residence in long-term facility or nursing home

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited and literature) for the topic use of VAXZEVRIA in Residence in long-term facility or nursing home.

Reporting Period (29 December 2022 to 28 December 2023)

The search identified a total of 155 case reports in vaccinees in Residence in long-term facility or nursing home who received VAXZEVRIA (39.4% spontaneous, 47.1% non-interventional/post-market, 12.9% from literature and 0.6% from study D8110C00001). The majority of reports 106 (68.4%) were MC with the remaining 49 cases (31.6%) from consumers.

Of the 155 cases, 53.7% (80) were reported in females, 46.3% (69) in males. The gender was not reported in 6 cases. Age ranged from 18 to <65 years in 83.2% (129) cases; 65+ years in 8.4% (12) reports and in 13 cases age was not reported.

Of these 155 cases, 82 (52.9%) were serious and most of the events in these cases are Fatigue (15), Dyspnoea (11), Arthralgia (10), COVID-19 (10), Dizziness (10) and Nausea, Paraesthesia and Tinnitus (8, each). Around 2.6% of the cases were reported with fatal outcome. In two cases, patient died of multiple organ failure, in one case due to respiratory arrest and COVID-19 infection and in the other case due to CVST, cerebral haemorrhage. In two cases, medical history such as Hypertension; Hyperlipidaemia; Cerebrovascular accident; Type 2 diabetes mellitus confounded the causality assessment. The other two cases had very limited information on medical history, concomitant medications, clinical course of the events and autopsy findings to perform a comprehensive causality assessment.

Cumulative Review (29 December 2020 to 28 December 2023)

The search of the AstraZeneca global safety database identified a cumulative total of 1067 cases (84.1% spontaneous, 8.6% non-interventional/post-marketing, 7.1% literature and 0.1% from study COV002 and 0.1% from study D8110C00001) in Residence in long-term facility or nursing home.

Of the 1067 cases, 62.6% (637) were reported in females, 37.4% (381 cases) in males and gender was not reported in the remaining 49 cases. Age was reported in 962 cases, and it ranged between 20-101 years (median 54 years). The majority of reports 786 (73.7%) were from consumers with the remaining 281 cases (26.3%) being MC.

Of the 1067 cases, 897 (84.1%) were serious and most frequently co-reported events are Headache (194), Fatigue (189), Pyrexia (119), Pain in extremity (95), Dizziness (93), Nausea (92) and Dyspnoea (85). Outcome was reported as fatal in 69 cases (6.5%). In most of the cases where the cause of death is reported, they were mostly due to cardiovascular complications. Overall, no trend or pattern was observed.

16.3.5.3.7 Metastatic Cancer

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited reporting and literature) for the topic use of VAXZEVRIA in individuals with metastatic cancer.

Reporting Period (29 December 2022 to 28 December 2023)

The search identified a total of 59 case reports in vaccinees with metastatic cancer who received VAXZEVRIA (44.1% spontaneous, 5.1% from literature, 3.4% from study D7220C00001 and 47.5% from study D8110C00001). The majority of reports 44 (74.6%) were MC and remaining 15 cases (25.4%) from consumers. Of the 59 cases, 45.8% (27) were reported in females, 54.2% (32) in males. Age ranged from 18 to <65 years in 46.6% (27) cases; 65+ years in 53.4% (31) reports and age was not reported in one case.

Of these 59 cases, 58 (98.3%) were serious and most frequently co-reported AEs in these cases are fatigue, pancreatic carcinoma metastatic and prostate cancer metastatic (4 cases, each). The remaining 1 (1.7%) case was reported as non-serious.

Outcome of 17 cases (28.8% of the cases) was reported as fatal. The age of these vaccinees ranged between 46-83 years (median 69 years). In 12 cases, vaccinees had a medical history of metastasis/neoplasm and the cause of death in majority of the cases were related to disease progression and cardiovascular complications. No specific trend or pattern was observed.

Cumulative Review (29 December 2020 to 28 December 2023)

The search of the AstraZeneca Global Safety Database identified a cumulative total of 494 cases (89.3% spontaneous, 1.4% non-interventional/post-marketing, 2.2% literature, 1.0% from the study COV002, 0.4% from study D7220C00001 and 5.7% from study D8110C00001) in individuals with metastatic cancer who received VAXZEVRIA. Majority of the cases 210 (42.5%) were MC and the remaining 57.5% (284) were from consumers. Of the 494 cases, gender of the vaccinees was available in 487 cases (56.9% were females and 43.1% were males). The age of the vaccinees was reported in 467 cases and it ranges between 20-95 years.

Of these 494 cases, 427 (86.4%) were serious and the frequently co-reported events in these cases are Headache (57), Pulmonary embolism (56), Pyrexia (51), Fatigue (48), Thrombocytopenia (43), Dyspnoea (38), Chills (32) and Nausea (28).

The outcome of the events was reported as fatal in 78 cases (15.8%). The cause of death in these cases were mostly related to metastasis/neoplasm progression. Overall, no specific trend or pattern was observed.

16.3.5.3.8 Supplementary Oxygen Use

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited reporting and literature) for the topic use of VAXZEVRIA in individuals with frailty_Oxygen (periodic search) and frailty_Supplementary Oxygen Use (cumulative search).

Reporting Period (29 December 2022 to 28 December 2023)

The search identified a total of 267 case reports (46.8% spontaneous, 9% literature, 5.2% non-interventional/post-marketing, 1.1% each from study D7220C00001 and 37.8% from study D8110C00001) for the topic use of VAXZEVRIA in individuals with frailty_Oxygen. Majority of the cases 65.2% were MC and 34.8% of cases were consumer reports.

Of the 267 cases, 129 (48.3%) were reported in females, 138 (51.7%) in males. The age of the vaccinees were reported in 248 cases (ranges between 20-96 years; median 59 years).

The events frequently co-reported in these cases with oxygen saturation decreased are Fatigue (35), Dyspnoea (31), COVID-19 (24), Headache (24), Pyrexia (24), Paraesthesia and Pulmonary embolism (20, each). Of these 267 cases, 257 (96.3%) were serious and the outcome of the event was reported as fatal in 38 cases (14.2%). The age ranged between 30 to 96 years with a median of 65 years. The cause of the death was majorly due to cardiovascular complications.

Upon review of cases received during the reporting interval, no specific trend or pattern was observed.

Cumulative Review (29 December 2020 to 28 December 2023)

The search of the AstraZeneca Global Safety Database identified a cumulative total of 4679 cases (92.4% spontaneous, 3.4% literature, 1.2% non-interventional/post-marketing, and 2.7% from study D8110C00001, 0.1% from studies D7220C00001 and D8111C00013, and 1 case each from studies COV002, COV003, D8111C00003, D8111C00010, and ICMR/SII-AZD-COVID-19/2020) for the topic use of VAXZEVRIA in individuals with frailty_Supplementary Oxygen Use. The majority of the cases (46.6%) were MC and the remaining 53.4% were consumer reports. Of the 4679 cases, 65.8% of cases are serious and 5.4% (357) of the cases were reported with fatal outcome.

The events frequently co-reported in these cases with oxygen saturation decreased are Pyrexia (1190), Headache (1041), Dyspnoea (941), Oxygen saturation decreased (767), Fatigue (699), Chills (524), Myalgia (501), Dizziness (465) and Nausea (460). Overall, no trend was observed.

16.3.5.3.9 Palliative Care

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited reporting and literature) for the topic use of VAXZEVRIA in individuals with Palliative care needs.

Reporting Period (29 December 2022 to 28 December 2023)

The search identified a total of 11 case reports (36.4 % Spontaneous and 63.6% from study D8110C00001) for the topic use of VAXZEVRIA in individuals with Palliative care needs. Majority of the cases (81.8%) cases were MC and remaining 18.2% were consumer reports.

Of the 11 cases, 4 (36.4%) were reported in females, 6 (50.0%) in males and gender was not reported in the remaining 1 case. The age of the vaccinees was reported in 10 cases and it ranged between 58-92 years (median 70 years). All 11 cases were reported with serious AEs and 19 events were reported with singularly.

Of the 11 cases, there were 7 (63.4%, 2-Initial and 5-Follow-up) cases with fatal outcome reported during this period. Age of the 7 vaccinees who died ranged from 62 and 92 years with a median of 79 years. The reported PTs for the 7 fatal cases were Toxic shock syndrome staphylococcal, Cholangiocarcinoma, COPD, Guillain-Barre syndrome, Acute respiratory failure, Cardiac failure congestive, Cerebrovascular accident, Blood pressure increased, Seizure and Pneumonia (2). The 6 fatal cases outcome occurred after the 1st dose of vaccine and the remaining 1 case fatal outcome occurred after the 2nd dose.

Upon review of the data received during the reporting period, no specific patten or trend was observed.

Cumulative Review (29 December 2020 to 28 December 2023)

The search of the AstraZeneca Global Safety Database identified a cumulative total of 132 cases (85.6% spontaneous, 6.1% literature, 0.8% non-interventional/post-marketing, 5.3% from study D8110C00001, 1.5% from study COV002 and 0.8% from study COV003) for the topic use of VAXZEVRIA in individuals with Palliative care needs. Of the 132 reports, 59.1% (78) were MC, with remaining 40.9% (54) being consumer reports.

Of the 132 cases, 61 (46.9%) were reported in females, 69 (53.1%) in males and gender was not reported in the remaining 2 cases. Age of the vaccinees was reported in 126 cases (ranges between 23-100 years). The median age of the vaccinees was 77 years.

Of these 132 cases, 129 (97.7%) were serious and the most frequently reported AEs in these cases are Cerebrovascular accident (16), Death, Dyspnoea and Malaise (14, each), Headache (11), Pyrexia, Cerebral haemorrhage and thrombocytopenia (9, each). There were 75 (57.3%)

fatal cases reported cumulatively in individuals with palliative care needs, of which 7 cases were reported during the interval period, as described in the previous section. Overall, no specific trend or pattern was observed.

16.3.5.3.10 Pressure Ulcers

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited reporting and literature) for the topic use of VAXZEVRIA in individuals with pressure ulcers.

Reporting Period (29 December 2022 to 28 December 2023)

The search identified a total of 195 case reports (68.8% spontaneous, 9.6% literature, 6.4% non-interventional/post-marketing, 14.6 from study D8110C00001 and 0.6% from study D7220C00001 for the topic use of VAXZEVRIA in individuals with pressure ulcers.

Of the 195 cases, 120 (62.5%) were reported in females, 72 (37.5%) in males and gender was not reported in the remaining 2 cases. Age of the vaccinees was reported in 174 cases and age ranges between 18-89 years (median 55 years). Of the 195 reports, 52.8% (103) were MC, with remaining 47.2% (92) being consumer reports.

Of the 195 cases, 71.3% of cases were reported with serious AEs. The most frequently reported AEs in these cases Pyrexia (56), Headache (51), Fatigue (48), Pain in extremity (36), Colitis ulcerative (35), COVID-19 (29), Myalgia (29), Pain (29) and Palpitations (27).

Of the 195 cases, there were 7 (3.6%) (initial – 2, follow-up -5) cases with fatal outcome reported during this period. Age of the 4 vaccinees who died ranged from 46 to 76 years with a median of 64 years. Age was not reported for the two cases. The reported PTs (1 each) for the 7 fatal cases were AEFI, Cerebral venous sinus thrombosis, TTS, Cardio-respiratory arrest, Cerebral haemorrhage, Guillain-Barre syndrome Paraesthesia and Intestinal infarction.

Upon review of the data received during the reporting period, no specific pattern or trend was observed.

Cumulative Review (29 December 2020 to 28 December 2023)

The search of the AstraZeneca Global Safety Database identified a cumulative total of 4415 cases (95.3% spontaneous, 2.8% non-interventional/post-marketing, 1.3% literature, 0.5% from study D8110C00001 and 1 case each from studies COV001, COV002, COV003, D7220C00001 and ICMR/SII-AZD-COVID-19/2020) for the topic use of VAXZEVRIA in individuals with pressure ulcers. Majority of the cases (78.4%) were consumer reports and 21.6% were MC. Gender of the vaccinees was reported in 4310 cases and 72.1% were females

and 27.9% were males. Of these 4415 cases, 2476 (55.6%) were serious and 64 (0.8%) cases were reported with fatal outcome.

The most frequently reported AEs in these cases with underlying peptic ulcers are Pyrexia (1173), Headache (1428), Fatigue (1020), Mouth ulceration (979), Chills (744), Myalgia (598), Nausea (582) and Arthralgia (500). Overall, no specific trend or pattern was observed.

Overall Conclusion

This review of the cumulative and periodic data in individuals with frailty, severe and/or uncontrolled underlying disease and comorbidities did not reveal any new safety concern. There was no increase in events seriousness (for all discussed topics) or severity.

In individuals with frailty, there was an increase of 4 fatal cases (2 new, 2 follow-ups) reported cumulatively from the previous PBRER (144) covering the previous period (28 December 2022). On review, there were no significant safety concerns identified.

In individuals with dispensing of or reimbursement for durable medical equipment, there was an increase of 38 fatal cases (6 new, 36 follow-ups) reported cumulatively from the previous PBRER (361) covering the previous period (28 December 2022). On review, there were no significant safety concerns identified.

In summary, no abnormal trends or significant new safety concerns were identified in the interval period with respect to the cumulative data. Majority of the AEs reported in patients with frailty and/or uncontrolled underlying disease were either related or heavily confounded by patients' medical history and underlying disorders or were consistent with the known safety profile of the vaccine.

This cumulative and periodic review of currently available data from the use of VAXZEVRIA in subjects with frailty, severe and/or uncontrolled underlying diseases and comorbidities did not identify any new safety concerns.

This topic will continue to be considered missing information and will be kept under close surveillance by AstraZeneca.

Use of VAXZEVRIA in subjects with severe or uncontrolled underlying disease/Use in frail patients will be investigated primarily in the ongoing non-interventional post-marketing observational study using existing secondary health data sources (D811110R00002 [US] and D81111R00006 [EU/UK]) study of subgroups exposed to VAXZEVRIA. Refer to Appendix 4 for additional details.

More detailed information is provided in Section 16.4.3.3 .

16.4 Characterisation of risks

At the end of the reporting period, the VAXZEVRIA safety specification (presented in the global AstraZeneca Core RMP, Version no. 9.0, dated 03 March 2023) included the following important identified and important potential risks, and missing information (see Table 95). Characterisations of the safety concerns are presented in Sections 16.4.1, 16.4.2 and 16.4.3 respectively.

Table 95 Summary of safety concerns – AstraZeneca Core Risk Management Plan for VAXZEVRIA (Version no. 9.0, dated 03 March 2023)

Risk Category	Safety concern
Important identified risks	Thrombosis in combination with thrombocytopenia
Important potential risks	Cerebrovascular venous sinus thrombosis without thrombocytopenia
	Immune mediated neurological conditions
Missing information	Use of VAXZEVRIA in pregnant and breastfeeding women
	Use of VAXZEVRIA in subjects with severe immunodeficiency
	Use of VAXZEVRIA in subjects with severe and/or uncontrolled underlying disease

In the following sections, detailed information is given on the important identified and potential risks, and missing information included in Table 95 above.

16.4.1 Important identified risks

The following safety concern is considered as important identified risk:

16.4.1.1 Thrombosis in combination with thrombocytopenia

Table 96 Important identified risk - Thrombosis in combination with thrombocytopenia

Characterisation	Summary
Frequency	There were no reports of thrombosis concurrent with thrombocytopenia in the VAXZEVRIA clinical development programme. Very rare events of serious thrombosis concurrent with thrombocytopenia (including fatal events), have been observed following vaccination with VAXZEVRIA during post authorisation use. The majority of the events occurred within the first 21 days following vaccination and some events had a fatal outcome. The reporting rates after the second dose are lower compared to after the first dose.

Table 96 *Important identified risk - Thrombosis in combination with thrombocytopenia*

Characterisation	Summary
Potential mechanisms	The exact mechanism of thrombosis concurrent with thrombocytopenia following immunisation with VAXZEVRIA is unknown. Several hypothetical biologic mechanisms have been proposed to explain the pathophysiology of thromboembolic events with thrombocytopenia following vaccination Greinacher et al 2021 (NEJM). Among them a study by (Baker et al 2021) proposes an interaction between the ChAdOx1 vaccine vector used in VAXZEVRIA and PF4; however, it is unknown if the adenoviral ChAdOx1 interaction with PF4 is actually platelet activating or thrombogenic (causal of blood clots). Greinacher et al 2021 (NEJM) suggested that ChAdOx1 itself or proteins contained within the vaccine can bind to PF4 to form immune complexes which may drive a B-cell response causing high-titer anti-PF4 antibodies resulting in TTS. However, none of these hypotheses have been confirmed.
Risk group or risk factors	There are no known risk factors for the development of thrombosis with thrombocytopenia following vaccination.
Preventability	Prevention of thrombosis concurrent with thrombocytopenia in the context of COVID-19 vaccination is currently unknown. As described in Section 4.4 of the CDS, HCPs should be alert to the signs and symptoms of thromboembolism (TE) and thrombocytopenia, as well as coagulopathies. Vaccinated individuals should be instructed to seek immediate medical attention if they develop symptoms such as a severe or persistent headaches, blurred vision, confusion, seizures, shortness of breath, chest pain, leg swelling, leg pain, persistent abdominal pain, or unusual skin bruising and/or petechia a few days after vaccination.
Impact on the risk-benefit balance of the product	Thrombosis with thrombocytopenia is a potentially life-threatening event if not recognised or managed appropriately, may result in persistent or significant disability or incapacity. Thrombosis with thrombocytopenia requires immediate medical intervention.
Public health impact	The public health benefit of vaccination is considered to outweigh the very rare occurrence of these events.

CDS Core Data Sheet; of COVID-19 Coronavirus Disease Of 2019; HCP Healthcare Professional; TTO Time To Onset

16.4.2 Important potential risks

The following 2 safety concerns are considered as important potential risks:

- Immune-mediated neurological conditions (Section 16.4.2.1)
- Cerebrovascular venous sinus thrombosis (CVST) without thrombocytopenia (Section 16.4.2.2)

16.4.2.1 Immune-mediated neurological conditions

Table 97 *Important potential risk - Immune mediated neurological conditions*

Characterisation	Summary
Frequency	Overall, in clinical studies there were no clinically meaningful imbalances in the incidence of neurological AESIs. In the US study, neurologic or neuroinflammatory AESIs were reported in 0.6% (121/21,587 participants) in the VAXZEVRIA (formerly AZD1222) group and 0.4% (48/10,792 participants) in the placebo group. In the pooled Oxford studies as of 07 December 2020, neurologic or neuroinflammatory AESIs were reported in 0.7% (81/12,282 participants) in the VAXZEVRIA (formerly AZD1222) group and 0.8% (90/11,963 participants) in the control group. Furthermore, in the pooled Oxford studies no clinically meaningful imbalance was noted in the incidence of AESIs of neuroinflammatory disorders, which were reported in 7 participants (0.1%) in the VAXZEVRIA (formerly AZD1222) group and 4 participants (< 0.1%) in the control group in the pooled safety dataset (any dose group). Of these, the most frequently reported events were nonserious AEs of facial paralysis occurred in 4 participants in the VAXZEVRIA (formerly AZD1222) group and 3 participants in the control group. In the US study, there were 5 nonserious AEs of facial paralysis, all in the VAXZEVRIA (formerly AZD1222) group. In the US study, there was 1 SAE of a demyelinating event: a participant in the VAXZEVRIA (formerly AZD1222) group had an AE initially reported as Guillain-Barre syndrome, which was subsequently diagnosed as an SAE of CIDP. In the pooled Oxford studies, there were 3 SAEs of demyelinating events: 2 cases in the VAXZEVRIA (formerly AZD1222) group (1 case of transverse myelitis, and 1 case of multiple sclerosis in a participant with pre-existing, but previously unrecognised, multiple sclerosis), and 1 case of myelitis in the control group.
Potential mechanisms	Several hypothetical biologic mechanisms have been proposed to explain the pathophysiology of neurologic adverse reactions following immunisation; most involve the concept of autoimmunity and the possibility that the vaccine's immunostimulatory effect results in an aberrant immunologic response (Stratton et al 1994)
Risk groups or risk factors	There are no known risk factors for the development of immune-mediated neurological conditions following vaccination.

Table 97 *Important potential risk - Immune mediated neurological conditions*

Characterisation	Summary
Preventability	Prevention of immune-mediated neurological conditions in the context of SARS-COV-2 vaccination is unknown.
Impact on the risk-benefit balance	Severe immune-mediated neurological conditions, if not recognised or managed appropriately, may result in persistent or significant disability or incapacity.
Public health impact	Immune-mediated neurological disorders are very rare, and as such the public health benefit of vaccination is considered to outweigh the very rare potential occurrences of such events.

AESI Adverse Event of Special Interest; SARS-COV-2 Severe Acute Respiratory Coronavirus 2; SAE Serious Adverse Event; US United States

16.4.2.2 Cerebrovascular venous sinus thrombosis (CVST) without thrombocytopenia

Table 98 *Important potential risk - Cerebrovascular venous sinus thrombosis (CVST) without thrombocytopenia*

Characterisation	Summary
Frequency	There were no reports of CVST identified in the VAXZEVRIA (formerly AZD1222) group in the US study (D8110C00001 [DCO: 15 March 2021] and D8111C00002 [DCO: 10 January 2021]), and in the pooled Oxford studies (COV001, COV002, COV003 and COV005; DCO: 07 December 2020). In the post-marketing setting, CVST without thrombocytopenia have been reported very rarely following vaccination with VAXZEVRIA.
Potential mechanisms	The exact mechanism of CVST without thrombocytopenia following administration with VAXZEVRIA is unknown.
Risk groups or risk factors	There are no known risk factors for the development of CVST without thrombocytopenia following vaccination.
Preventability	Prevention of CVST without thrombocytopenia in the context of COVID-19 vaccination is currently unknown. The events of CVST without thrombocytopenia can be fatal and may require different treatment approaches than thrombosis in combination with thrombocytopenia.
Impact on the risk-benefit balance of the product	CVST without thrombocytopenia is a potentially life-threatening event, and if not recognised or managed appropriately, may result in persistent or significant disability or incapacity, and hence requires immediate medical intervention.
Public health impact	The public health benefits of vaccination are considered to outweigh the very rare occurrence of these events.

COVID-19 Coronavirus Disease of 2019; CVST- Cerebral Venous Sinus Thrombosis; DCO Data Cut Off

16.4.3 Missing information

The following 3 safety concerns are considered as missing information:

- Use of VAXZEVRIA in pregnant and breastfeeding women (Section 16.4.3.1)
- Use of VAXZEVRIA in subjects with severe immunodeficiency (Section 16.4.3.2)
- Use of VAXZEVRIA in subjects with severe and/or uncontrolled underlying disease (Section 16.4.3.3)

16.4.3.1 Use of VAXZEVRIA in pregnant and breastfeeding women

Evidence source

As per the VAXZEVRIA CDS Section 4.6, data from more than 400 case reports of pregnant women or women who became pregnant after receiving VAXZEVRIA do not suggest unusual patterns of pregnancy complications or foetal/neonatal outcomes. No increased risk of maternal thrombosis in combination with thrombocytopenia has been observed. Preliminary non-clinical safety studies have not indicated any concern to date, and available non-clinical, clinical and post-marketing data do not suggest a risk to breastfed newborns/infants. As VAXZEVRIA is intended for use in mass vaccination campaigns in a large proportion of the global population, the collection of pregnancy and infant outcomes data with the aim of further characterising the safety profile in this population, is still considered necessary.

Population in need of further characterisation

Although there are data in the post-marketing setting in pregnant and breastfeeding women, use of VAXZEVRIA in pregnant and breastfeeding women will continue to be investigated in the ongoing PASS (EAS, a post-marketing observational study using existing secondary health data sources, and a pregnancy registry).

16.4.3.2 Use of VAXZEVRIA in subjects with severe immunodeficiency

Evidence source

Vaccines may be less effective in severely immunocompromised subjects, as the vaccinees weakened immune system may not mount a sufficient response; however, immunocompromised individuals may also be at greater risk of morbidity and mortality from vaccine-preventable disease, and consequently this population have been identified as a priority group for initial vaccination in several jurisdictions following vaccine availability.

Although there is no evidence that the safety profile of this population receiving VAXZEVRIA will be different to that of the general population, given the paucity of data, the possibility cannot be excluded.

Population in need of further characterisation

Use of VAXZEVRIA in subjects with severe immunodeficiency will continue to be investigated in the ongoing PASS and additional Pharmacovigilance activity (a post-marketing observational study using existing secondary health data sources and SLR).

16.4.3.3 Use of VAXZEVRIA in subjects with severe and/or uncontrolled underlying disease

Evidence source

Subjects with severe and/or uncontrolled underlying disease are potentially at risk of developing a more severe manifestation of COVID-19, and as a consequence have been included as a priority group for initial vaccination in several jurisdictions following vaccine availability. Although there is no evidence that the safety profile of this population receiving VAXZEVRIA will be different to that of the general population, given the paucity of data, the possibility cannot be excluded.

Population in need of further characterisation

Use of VAXZEVRIA in patients with severe and/or uncontrolled disease will continue to be investigated in the ongoing PASS program (post-marketing observational study using existing secondary health data sources).

16.5 Effectiveness of risk minimisation

No information on the effectiveness of risk minimisation activities relevant to the benefit-risk assessment became available during the reporting period.

17 BENEFIT EVALUATION

17.1 Important baseline efficacy/effectiveness information

At the beginning of the reporting period, VAXZEVRIA was authorised for the prevention of COVID-19 in adults.

VAXZEVRIA is able to elicit a strong immune response against all variants up to and including earlier omicron variants and is thus capable of preventing serious symptomatic infections with SARS-COV-2, the causative agent of COVID-19, a life-threatening disease, particularly in older age groups.

VAXZEVRIA has been shown to be efficacious in preventing severe disease, avoiding hospitalization and death.

A summary of the information supporting the efficacy and effectiveness in this authorised indication is provided in the sections below.

17.2 Newly identified information on efficacy/effectiveness

New information on the efficacy/effectiveness of VAXZEVRIA in the approved indication of prevention of COVID-19 in adults that became available during the reporting period is focused on the Omicron variant.

During the reporting period, data analyses for Oxford studies data was conducted by AstraZeneca to estimate the efficacy of VAXZEVRIA against Omicron variant of concern. As described in detail in section 13 there were no new clinical trial efficacy data available during the reporting period.

17.3 Vaccine effectiveness against SARS-CoV-2 Omicron variant

Real world studies have demonstrated high vaccine effectiveness (VE) of a 2-dose primary series vaccination with AZD1222 against earlier Omicron variants (up to and including BA4/5) in a variety of settings and populations, particularly with regard to prevention of severe disease. The range of VE in studies focused on severe outcomes in a general adult population (≥ 18 years and/or an older population (≥ 65 years) during a period when Omicron was the dominant variant was presented in the previous PBRER. As of 03 March 2023, the European Centre for Disease Prevention and Control announced there are currently no SARS-CoV-2 variants meeting the Variant of Concern criteria, and Omicron is listed as a Variant of Interest being monitored (ECDC 2023).

Additional studies that have been published during the reported period, whereby vaccine effectiveness of VAXZERVIA, amongst other vaccines, against the omicron variant are presented below.

The Vaccine Study COvid-19 (VASCO) is a large population- based prospective cohort study with a 5-year FU, conducted in the Netherlands (Huiberts AJ et al 2023). The study was started during the initiation of the COVID-19 vaccination program and between the 03 May 2021 and 15 December 2021, 45,552 community-based adults aged 18 to 85 years participated. In this study participants received primary vaccination series with two doses of VAXZEVRIA or vaccinated with alternative available vaccines such as Comirnaty (BioNTech/Pfizer), Spikevax (Moderna) or Jcovden (Janssen). In addition, they also received one booster vaccinations. The paper provides collective information about vaccine effectiveness and reports that Vaccine Effectiveness in the Omicron era was substantially lower than those in the Delta period and estimated to have been 46% (95%CI 21.7-62.7), decreasing to 25% (25% (95% CI 7.7-39.1) 18-23 weeks after completion of the primary vaccination series. VE increased to 57% (95% CI 51.9- 62.3) < 6 weeks after booster vaccination and decreased to 31% (95% CI 16.6-43.5) at 18-23 weeks For the participants aged ≥ 60 years, the VE against Omicron infection within 6 weeks after the second booster vaccination was 50% (95% CI 34.0-62.1). This paper did not provide effectiveness information against severe infection or hospitalization.

A test-negative case-control study (Sritipsukho et al 2023) was conducted in Thailand to obtain real-life Vaccine Effectiveness data against the Omicron variant between 01 January 2022 to 15 June 2022 when the Omicron variant was the dominant variant (97-100%). Primary series vaccine regimens during the initial period mainly included two-dose CoronaVac (4 weeks apart between the two doses) and two-dose ChAdOx1 nCoV-19 (12 weeks apart between the two doses). The two-dose BNT162b2 (4 weeks apart between the two doses) became available later. The booster doses of the vaccines included one dose of ChAdOx1 nCoV-19 or one to two doses of BNT162b2 given at 3–6 months after the primary series or after the last dose of the previous vaccines. Of the 7971 vaccinated individuals, 3104 (38.9%) were cases and 4867 (61.1%) were controls and none of these individuals had prior COVID-19. For the two dose vaccine regimens received by 2363 individuals, 1209 (51.2%) received ChAdOx1 nCoV-19 vaccine. For the three dose regimens, received by 3100 individuals, 1387 (44.7%) received a two dose ChAdOx1 nCoV-19 plus one BNT162b2 booster. The Vaccine Effectiveness of the ChAdOx1 nCoV-19 vaccine was associated with an overall vaccine effectiveness of 38% (95% CI 13-56) though for a period ≤ 90 days since the last dose, vaccine effectiveness was substantially higher at 61% (41-74%). Thereafter, it decreased so that for periods ≥ 90 days to 30% (0-51%). For the three-dose regimen overall vaccine effectiveness was reported to be 39% (95% CI 13-57) increasing to 41% (95% CI 16-58) for the period of ≤ 90 days since the last dose and decreasing to 26% (95% -12-52) for the period ≥ 90 days since the last dose. However, when the ChAdOx1 nCoV-19 vaccine was given as part of a 4 dose regimen vaccination (CoronaVac-CoronaVac-ChAdOx1-BNT162b2) overall vaccine effectiveness was substantially augmented to 65%, remaining high at 67% (95%CI 51-78%) for the period ≥ 90 days since the last dose before decreasing to 49% (95% CI 15-70) for the period ≥ 90 days since the last dose. Moreover, vaccine effectiveness for preventing moderate to critical disease was reported as 56% (95% CI 25-75%) for the two dose ChAdOx1 nCoV-19 vaccine, 58% (95% CI 28-75) for the three-dose regimen and 82% (95%CI 59-92) for the 4 dose regimen (CoronaVac-CoronaVac-ChAdOx1-BNT162b2).

In another test-negative study design (Cerqueira-Silva et al 2023) national databases were utilised to estimate the vaccine effectiveness (VE) of a primary series (with ChAdOx1 or BNT162b2) plus an mRNA vaccine booster (with BNT162b2 or mRNA-1273) against symptomatic Syndrome Coronavirus 2 (SARS-CoV-2) infection and severe COVID-19 outcomes (hospitalization or death) during the period of Omicron dominance in Brazil and Scotland compared to unvaccinated individuals. In Brazil, a primary course of ChAdOx1 and a BNT162b2 booster (ChAdOx1-BNT162b2) dose led to an estimated VE against symptomatic infection of 51.6% (95% CI [51.0, 52.2], $p < 0.001$) after 14 to 29 days, waning to 4.2% (95% CI [0.7, 7.6], $p = 0.02$) at ≥ 4 months after the booster dose. In contrast, estimates of VE against severe outcomes of ChAdOx1-BNT162b2 peaked in Brazil at 93.5% (95% CI [93.0, 94.0], $p < 0.001$) at 14 to 29 days and 82.3% (95% CI [79.7, 84.7], $p < 0.001$) after ≥ 4 months. A similar pattern was observed in Scotland, where after the primary series of ChAdOx1, the VE peak at 98.3% (95% CI [87.3, 99.8], $p < 0.001$) 14 to 29 days past booster

dose for ChAdOx1-BNT162b2 and 94.4% (95% CI [87.7, 97.5], $p < 0.001$) for ChAdOx1-mRNA-1273 in the same period, declining to 77.8% (95% CI [51.4, 89.9], $p < 0.001$) and 76.0% (95% CI [59.3, 85.9], $p < 0.001$) at ≥ 4 months, respectively. The authors concluded that although modest short-lived protection against symptomatic infection by the omicron variant were observed, protection against hospitalization or death was substantial for at least 3 months.

A test-negative case-control study in adults from Bogota (Colombia) assessed the comparative vaccine effectiveness (VE) and the duration of protection with homologous primary series and homologous booster immunization using ChAdOx1, CoronaVac, BNT162b2, mRNA-1273, and Ad26.COV2.S vaccines Paternina-Caicedo et al 2023 During the Omicron predominant periods, the VE against symptomatic COVID-19 of primary series vaccination with ChAdOx1 was 36% (95% CI: 24 to 47), while varied between 34% (95% CI: 11 to 51) for Ad26.COV2.S and 65% (95% CI: 54 to 74) for mRNA-1273 during the first month after vaccination. The protection waned quickly and was not observed two months after ChAdOx1 primary series vaccination and lasted up to 3 to 4 months after BNT162b2, mRNA-1273 and Ad26.COV2.S vaccination. The VE of a booster dose of monovalent BNT162b2 against symptomatic COVID-19 was 45% (95% CI: 34 to 54). The booster doses of ChAdOx1, CoronaVac, and Ad26.COV2.S did not show protection against symptomatic COVID-19. The VE of booster vaccination was 69% (95% CI: -14 to 91) for ChAdOx1 and varied between 49% (95% CI: -126 to 88) for BNT162b2 and 68% (95% CI: 48 to 80) for CoronaVac for the prevention of COVID-19 hospitalization caused by Omicron variant.

REFORCO-Brazil test-negative case-control observational study evaluated the relative vaccine effectiveness (rVE) against COVID-19 hospitalization of four monovalent COVID-19 vaccines (AZD1222, Ad26.COV2.S, CoronaVac, and BNT162b2) as second boosters compared with any first boosters received ≥ 4 months previously, and as first boosters compared with primary-series vaccinations completed ≥ 4 months previously (Meeraus et al 2023). The interim analysis results showed that during a 7-month period of Omicron subvariant (BA.1, BA.2, BA.4, and BA.5) predominance, receiving a second booster dose of COVID-19 vaccine increased effectiveness against COVID-19 hospitalization by 24.7 % (95 % CI: 12.6 to 35.1) compared with eligible individuals who had received any first booster dose. The improved protection was similar with second booster doses of AZD1222 (rVE 29.4 %, 95 % CI: 8.6 to 45.5), Ad26.COV2.S (rVE 24.8 %; 95 % CI: 8.1 to 38.4), and BNT162b2 (rVE 25.5 %; 95 % CI: 4.2 to 42.2). The data did not show an improvement in protection against COVID-19 hospitalization with a second booster dose of CoronaVac relative to any first booster dose. During a 12-month period of Delta and Omicron subvariant predominance, the rVE of first booster doses against COVID-19 hospitalization was 46.8 % (95 % CI: 43.3 to 50.0) among individuals who had completed any primary series. The improvement in protection was similar for first booster doses of AZD1222 (rVE 42.5 %; 95 % CI: 28.0 to 54.0) and BNT162b2 (rVE 50.8 %; 95 % CI: 47.5 to 54.0) but was not seen with

Ad26.COV2.S or CoronaVac. In general, rVEs were higher in elderly (≥ 80 years) and immunocompromised/high-risk individuals.

A Brazil-based study (dos Santos et al 2023), linking national registries, estimated the VE of the primary series of vaccinations and the relative effectiveness of the booster against COVID-19-related severe cases and deaths. The VAXZEVRIA primary series provided increased protection against severe COVID-19 to diverse age groups of 20-59 years (VE: 88.3%; 95% CI: 80.2 to 94.3) and 60+ years (VE: 61.7%; 95% CI: 21.6 to 86.2) during the Omicron variant period. The study showed that the VAXZEVRIA 1st boosters were also effective in individuals who received the VAXZEVRIA primary series (VE: 49% in 20-59 years, and 79% in 60+ years). People who received CoronaVac (Sino) primary series plus VAXZEVRIA 1st booster (20-59 years) or BNT162b2 primary series plus VAXZEVRIA 1st booster (60+ years) showed VE of 97% and 93% respectively.

Another TNCC study covering six Latin American countries – Chile, Costa Rica, Ecuador, Guatemala, Paraguay and Uruguay Nogareda et al 2023 estimated the adjusted VE (aVE) of COVID-19 vaccines in preventing COVID-19-related hospitalisation during three different pandemic waves. Overall, during the Omicron variant period, the VAXZEVRIA primary series provided moderate protection against hospitalisation to individuals aged 18-64 years (21%) and ≥ 65 years (39%).

Another test-negative case control study (Kirsebom FMC et al 2022) was conducted to assess the real-world effectiveness of ChAdOx1-S COVID-19 booster vaccination against the Omicron and Delta variants in England. The study reported reassuring real-world evidence (RWE) that booster vaccination with ChAdOx1-S following a primary ChAdOx1-S course provides increased protection against mild and severe diseases with Omicron infection. Protection against the symptomatic disease was similar for both ChAdOx1-S (Spikevax) and BNT162b2 (Pfizer-BioNTech) vaccines among individuals 40–64-year-old but lower with ChAdOx1-S in older adults. Data extracted from NIMS (National Immunisation management System), as of 14 March 2022, on all adults aged 18 and older in England who received a ChAdOx1-S primary course followed by a ChAdOx1-S booster (43,171 individuals) or BNT162b2 booster (13,038,908 individuals) were analysed. The recipients of ChAdOx1-S booster were found to be predominantly female (adjusted odds ratio (OR) 1.67 (1.64–1.71)), from London (adjusted OR 2.84 (2.73–2.95)), health and social care workers (adjusted OR 1.58 (1.54–1.63)), in a clinical risk group (adjusted OR 1.58 (1.54–1.63)), in the clinically extremely vulnerable (CEV) group (adjusted OR 1.84 (1.79–1.89)), severely immunosuppressed (adjusted OR 2.05 (1.96–2.13)). For those aged 40-64 years, VE for symptomatic disease caused by the Omicron variant infection peaked at 61.2% (40.9–74.6%) one week after receiving a ChAdOx1-S booster as compared to 58.2% (57–59.4%) amongst those who received a BNT162b2 booster. However, there was a waning of protection observed after 15 or more weeks post booster vaccination. Similar levels of protection were

observed for those aged 65 years and older (66.1% (16.6–86.3%) and 68.5% (65.7–71.2%) for ChAdOx1-S and BNT162b2 booster vaccines, respectively), with waning of protection observed after 5-9 weeks post booster vaccination. The study also showed that the ChAdOx1-S booster provided over 80% protection against hospitalisation following Omicron infection in individuals aged 65 and older, one week after booster vaccination – though lower than that observed following BNT162b2 booster.

In a previously reported retrospective cohort study (Intawong et al 2022) conducted during an omicron predominant period, the duration of enhanced protection against severe Covid-19 with booster doses was investigated by utilizing a Hospital Information System for COVID-19 established in Chiang Mai, Thailand. Individuals aged 18 years or older, with a laboratory confirmed SARS-CoV-2 infection during 01 February to 31 July 2022 period were recruited into the study. Severe COVID-19 outcome was defined as requiring Invasive Mechanical Ventilation (IMV) during hospital admission or death within 30 days of positive SARS-CoV-2 test. Over half of the subjects with severe outcomes were not fully vaccinated, as compared to just 11% among those without severe outcomes. Subjects without severe outcomes were more likely to have received heterologous primary series with Sinovac/Sinopharm first dose followed by ChAdOx1 nCoV-19 second dose. No significant difference in the type of vaccine used for boosting as third, fourth and fifth dose was seen between the groups.

A couple of studies indirectly elucidated the comparative effectiveness of VAXZEVRIA; a Colombia-based study explored the effectiveness of vaccination schedules on the probability of infection

Marcela Gálvez et al 2023, and another study (Liu et al 2023) compared rates of Omicron BA.1/2 infection in Australian adults who had received COVID-19 vaccines as either a primary course or a booster dose. Marcela Gálvez et al 2023 found a higher infection rate in participants who received CoronaVac (Odds Ratio (OR) = 1.49, CI 1.06–2.10) and Ad26.COV2.S (OR = 1.63, CI 1.10–2.43) than who received VAXZEVRIA (OR = 1.17, CI 0.79–1.71). On the other hand, Liu et al 2023 showed that compared to recipients of BNT162b2 primary vaccine course, adjusted hazard ratios (aHR) for COVID-19 infection were 1.03 (95% CI 0.82–1.30), 1.19 (0.95–1.49), 1.70 (1.46–1.97) respectively for mRNA-1273 (Moderna), VAXZEVRIA and NVX-CoV2373 (Novavax). Similarly, for booster dose, the respective aHR compared to BNT162b2 were 1.02 (95% CI 1.00–1.04), 1.20 (1.10–1.32), and 1.39 (1.20–1.60).

In summary, despite in vitro evidence of failing neutralising titres against more recent VOC RWE studies in multiple geographical regions continue to support the benefit of vaccination with VAXZEVRIA, suggesting the immune response and protection provided is more complex than humoral responses taken in isolation.

17.4 Characterisation of benefits

The original clinical development program allowed AstraZeneca to demonstrate robust efficacy of VAXZEVRIA against SARS-COV-2 variants circulating early in the COVID-19 pandemic.

Worldwide, more than 771 million confirmed cases of COVID-19 were recorded and over 13 and a half billion doses of COVID-19 vaccines of different platform technologies were administered (WHO 2023). In this context, it has been widely demonstrated that vaccines that are able to booster immunity in previously immunized individuals are beneficial in the control of COVID-19.

An estimate derived from a mathematical modelling study has recently estimated that VAXZEVRIA was responsible for saving 6 million lives in the first year of use (Watson et al 2022 and Airfinity 2023) since its origination in November 2021 in SA, including various sublineages, had become the predominant SARS-COV-2 circulant variant worldwide. While 2-dose primary series immunisation with VAXZEVRIA may provide limited neutralising potency against the Omicron variant, a booster dose of VAXZEVRIA has been reported to increase nAb titers against this multiple sublineages of this variant (including BA.1, BA.2, BA.4/5, BQ.1, and BQ.1.1). While no neutralising activity against the contemporary XBB.1.5 was observed with third dose boosters (in a study conducted well before the evolution of this VOC), some neutralising activity partly driven by hybrid immunity was observed with a fourth dose booster (not part of approved indication) in a small sample of study participants conducted more recently. It is unknown how the level of immune response against different variants correlates with clinical outcome. Importantly, VAXZEVRIA has shown to induce polyfunctional CD4+ and CD8+ T cells with breadth across the entire Spike protein. Real-world effectiveness data indicate booster doses of VAXZEVRIA can substantially increase protection against variants of concern due, in part, to the contribution of T cell mediated immunogenicity as T cell responses are somewhat conserved against the emerging variants of concern while these variants are mostly able to evade humoral responses.

While correlation between humoral responses and degree of protection against symptomatic disease have been described at a population level, T-cell responses likely play a more central role in the pathogenesis of severe disease. Recovery from an episode of severe disease is likely a combination of viral clearance and the downregulation of host driven non-infectious inflammatory responses, where T-cell responses are known to be important Shrotri et al 2021. This may explain the protection against severe disease still afforded by the original vaccine, despite the significantly lower humoral immune responses against these most distant variants (ICMRA 2023, Choi et al 2022 and Meyer et al 2023).

In addition to robust efficacy data demonstrated through Clinical Development programme, further studies found that VAXZEVRIA continues to protect against hospitalization and

severe disease in the real-world setting even in the Omicron era. More specifically, as outlined above RWE studies have recently confirmed that, although Omicron is able to escape vaccine immunity, VAXZEVRIA offers protection against Omicron when administered as booster dose similarly to vaccines using different vaccine platforms, including RNA vaccines. This was additionally demonstrated in a large meta-analysis of 20 observational studies, consisting of 4 cohorts and 16 test-negative case-control studies from seven different Countries in North America, Europe and Middle East (Pratama et al 2022). In this study, the effectiveness of different types of vaccine (including VAXZEVRIA) against Omicron was shown to be protective when administered as booster even though the protection of primary series was confirmed to be low for the same types of vaccines investigated. Furthermore, data on effectiveness of third and fourth booster of VAXZEVRIA continue to emerge from Thailand (Intawong et al 2022; Sritipsukho et al 2023), Brazil and Scotland (Cerqueira-Silva et al 2023). These studies show that VAXZEVRIA along with other vaccines when given in the context of a heterologous booster vaccination program, continue to protect from hospitalisation and severe COVID-19, however protection against symptomatic infection is not durable (ICMRA 2023).

18 INTEGRATED BENEFIT-RISK ANALYSIS FOR APPROVED INDICATIONS

The analysis of the benefit-risk balance incorporates an evaluation of the safety and efficacy/effectiveness information that became available during the reporting period, in the context of what was known previously. This evaluation involves the following:

- Critically examining information that has emerged during the reporting period to determine whether it has generated new signals, led to the identification of new potential or identified risks, or contributed to knowledge of previously identified risks.
- Critically summarising relevant new safety and efficacy/effectiveness information that could have an impact on the benefit-risk balance.
- Conducting an integrated benefit-risk analysis for all approved indication(s) based on the cumulative information available since the DIBD (where the DIBD is unknown or AstraZeneca does not have access to data from the clinical development period, the earliest possible applicable date is used as the starting point for inclusion and evaluation of the cumulative information).
- Summarising any risk minimisation actions that may have been taken or implemented during the reporting period, as well as risk minimisation actions that are planned to be implemented.
- Outlining plans for signal or risk evaluations, including timelines and/or proposals for additional pharmacovigilance activities.

18.1 Benefit-risk context - medical need and important alternatives

A description of the medical need for VAXZEVRIA and important alternatives available is provided below in active immunisation of individuals ≥ 18 years old for the prevention of COVID-19.

18.1.1 Medical need for the product

Soon after the 2019 report of the then unknown pneumonia occurring in clusters of patients in Hubei province of Wuhan (Gov.cn 2023), the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the causative agent of COVID-19 in January 2020 (Zhou 2020). Following the WHO declaration of the COVID-19 pandemic on 11 March 2020, COVID-19 has been reported worldwide, devastating lives and causing economic chaos across the Globe.

As of 08 November 2023, over 771 million confirmed cases of COVID-19 have been diagnosed globally with more than 6.9 million deaths (WHO 2023).

There is a medical need to maintain and/or increase protection in vaccinated individuals in the face of waning immunity and emerging variants of SARS-CoV-2. For many infectious diseases, multiple or additional 'booster' doses beyond those prescribed by the original vaccination protocol are a standard part of the vaccination schedule. For example, booster vaccines are given for tetanus, diphtheria, and polio (NHS 2023). Boosters can help to elevate the level of antibodies and memory immune cells, and in some instances, strengthen their potency (Callaway 2021).

Later in the COVID-19 pandemic, viral mutations led to the emergence of more efficiently transmissible versions of SARS-CoV-2, actively monitored by WHO and categorized as variants of interest or variants of concern, depending on their epidemiological characteristics and pathogenesis. Earlier AstraZeneca reported AZD1222 VE against COVID-19 caused by the variants of concerns Alpha (B.1.1.7); Beta (B.1.351); Gamma (P.1) and Delta (B.1.617.2). The epidemiological landscaped has changed and more recently, further mutations in SARS-CoV-2 led to the identification of more transmissible Omicron variant of concern, that dominating transmission within communities worldwide in 2022 and early 2023 (Nyberg et al 2022). AstraZeneca further characterized neutralizing antibody responses induced by a primary series vaccination and following 3rd and 4th dose booster immunizations with AZD1222 against Omicron subvariants, including BA.1, BA.2, BA.4/5, BQ.1, BQ.1.1., and XBB.1.5. As SARS-CoV-2 continues to evolve, new immunologically evasive Omicron subvariants such as BA.2.86, FL.1.5.1, EG.5, and HV.1 emerge and cause the disease among both vaccinated and unvaccinated people (CDC 2023).

It has been noticed that hybrid immunity conferred by a mix of natural infection and ancestral strain immunization is not as effective against Omicron variants in comparison with the earlier

strains of SARS-CoV-2. Once infected with SARS-CoV-2, the majority of individuals may remain asymptomatic or will experience light to mild symptoms. When severely affected, patients may still need hospitalization to primarily treat pneumonia and acute respiratory distress syndrome (ARDS). Systemic failure of multiple organs may ensue, leading to death. Certain comorbidities and older age are known to increase the risk for severe COVID-19 and death (Coopersmith et al 2021). Apart from VAXZEVRIA, the contribution of the available therapeutic armamentarium towards the treatment of COVID-19 or prophylaxis from infection is significant and growing as new therapeutics are being developed, vaccines to prevent severe COVID-19 and death remaining the primary agents of choice to control the COVID-19 pandemic.

18.1.2 Important alternatives available

Following the WHO declaration of the COVID-19 pandemic on 11 March 2020, accelerated vaccine development began worldwide to prevent infection with the causative agent, SARS-CoV-2. As reported by WHO, on 30 March 2023 there were 183 vaccines in clinical development and 199 in pre-clinical development.

Different types of vaccines against COVID-19 have been developed, including:

- inactivated or weakened virus vaccines (ie, Sinovac-Coronavac, Sinopharm, Bharat, Valneva), which use a form of the virus that has been inactivated or weakened so that it doesn't cause disease but still generates an immune response;
- protein-based vaccines (ie, Novavax / SII), which use harmless fragments of proteins or protein shells that mimic the COVID-19 virus to safely generate an immune response;
- viral vector vaccines (ie, Vaxzervria (AstraZeneca/Oxford), Janssen, CanSino), which use a safe virus that cannot cause disease but serves as a platform to produce coronavirus proteins to generate an immune response; and
- RNA and Deoxyribonucleic Acid (DNA) vaccines (ie, Pfizer/ BioNTech, Moderna), which use genetically engineered RNA or DNA to generate a protein that itself safely prompts an immune response (WHO 2023a).

18.2 Benefit-risk analysis evaluation

An evaluation of the benefit-risk profile for the use of VAXZEVRIA in authorised indications cited in Section 17.1 (Important baseline efficacy/effectiveness information) is provided below.

18.2.1 Active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older

18.2.1.1 Context of use of the medicinal product

The VAXZEVRIA vaccination course consists of two separate doses of 0.5 ml each for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The second dose should be administered between 4 and 12 weeks after the first dose. It is recommended that individuals who receive a first dose of VAXZEVRIA complete the vaccination course with the same vaccine. A booster dose (third dose) of 0.5 ml may be given to individuals who completed the primary vaccination course with VAXZEVRIA at least 3-months after completing the primary 2-dose vaccination course (homologous boosting). VAXZEVRIA may be given as a booster dose after completion of a primary vaccination course with any other COVID-19 vaccine (heterologous boosting).

Since its identification in SA in November 2021, the SARS-COV-2 Omicron variant spread rapidly across continents. More recently, evolution of Omicron variant led to the emergence of several subvariants designated XBB, XBD, XBF, etc. Currently circulating variants under monitoring (as of 23 October 2023) could be found on WHO activities tracking page (WHO 2023). Active primary immunizations against SARS-COV-2 failed to demonstrate efficacy against Omicron variant, regardless the brand of COVID-19 vaccine investigated in clinical trials [WHO 2023a]. Nonetheless, it has been demonstrated that VAXZEVRIA continues to protect against hospitalization, severe disease and death as described in section 17.1.

Currently, over 13 and a half billion of doses of vaccines of any technology were administered to the world population (WHO 2023a). A mathematical modelling study performed to estimate the number of deaths avoided by vaccination before the Omicron era, estimated that nearly 20 million of deaths were averted following the introduction of a handful of COVID-19 vaccination programmes around the world up to the end of 2021 (Watson et al 2022). As part of COVID-19 Vaccines Global Access (COVAX) vaccination programme to distribute COVID-19 vaccines to Low- And Middle-Income Countries (LMIC), VAXZEVRIA has contributed to avert millions of deaths worldwide. In Brazil alone, a country that utilized Coronavac and VAXZEVRIA vaccine in their first year at the start of the immunization campaign, a significant number of deaths due to COVID-19 were averted in the first year of national vaccination campaign (Santos et al. 2023).

18.2.1.2 Considerations relating to key benefit(s)

VAXZEVRIA vaccine was developed to address an urgent public health need early in the COVID pandemic. As the pandemic evolves, world-wide efforts to develop effective vaccines against the Omicron SARS-COV-2 variant and subsequent likely VOC are ongoing. However, VAXZEVRIA has not been updated to reflect newer advice from EMA/FDA/WHO and other agencies on strain recommendations.

The emergence of Omicron variants posed a challenge to the control of SARS-COV-2 infection worldwide regardless the type of COVID-19 vaccine. VAXZEVRIA Induced neutralizing responses against the Omicron XBB.1.5 were not observed with primary series or third dose boosters in samples pre-emergence of XBB, however detectable nAbs were detected in approximately half of evaluated study participants who had received a fourth dose booster of VAXZEVRIA in study COV003, where hybrid immunity was likely. Real World Evidence on the effectiveness of VAXZEVRIA against different later variants of Omicron is limited.

However, since VAXZEVRIA has shown to induce polyfunctional CD4 and CD8 T cells with breadth across the entire Spike protein Swanson et al 2021 and these T cell epitopes are conserved across variants including XBB descendants, this could explain the protection against severe disease still afforded by the vaccines using the ancestral strain ICMRA 2023

18.2.1.3 Considerations relating to risk

The important identified risks associated with VAXZEVRIA are characterised in detail in Section 16.4.

Considerations regarding the key important identified and potential risks are summarized below:

- **Thrombosis in combination with thrombocytopenia:** A very rare and serious combination of thrombosis and thrombocytopenia, including TTS, in some cases accompanied by bleeding, has been observed following vaccination with VAXZEVRIA during Post-authorisation use. The majority of the events occurred within the first 21 days following vaccination and some events had a fatal outcome. The reporting rates after the second dose are lower compared to the first dose. No new or emerging concern regarding TTS has been identified with booster doses of AZD1222. Based on the available data, thrombosis in combination with thrombocytopenia is considered a very rare adverse reaction of VAXZEVRIA. The CDS reflects AstraZeneca's position on this risk.
- **Immune-mediated neurological conditions:** There is a theoretical concern that vaccination could be associated with immune-mediated neurological conditions. Very rare events of demyelinating disorders were reported in the VAXZEVRIA clinical development programme and in the post-marketing use, however, there is no evidence suggesting a causal relationship between VAXZEVRIA and demyelinating disorders. Severe neurological conditions may result in persistent or significant disability or incapacity and require early detection, careful monitoring, and timely medical intervention. CDS reflects AstraZeneca's position on this risk.
- **CVST without thrombocytopenia:** Events of cerebrovascular venous and sinus thrombosis (CVST) without thrombocytopenia have been reported very rarely in the post-authorisation setting following vaccination with VAXZEVRIA. The exact mechanism of CVST without thrombocytopenia following administration with VAXZEVRIA is unknown. There are no known risk factors for the development of CVST without thrombocytopenia following vaccination. Events of CVST without thrombocytopenia

may require different treatment approaches than thrombosis in combination with thrombocytopenia (eg, use of heparin or warfarin). Based on the available data, a causal association has not been established between VAXZEVRIA and CVST without thrombocytopenia. However, such events are considered an important potential risk and CDS reflects AstraZeneca's position on this risk.

The significance of the limited information that became available during the reporting period has been evaluated in the context of what was known previously. An integrated evaluation of the key benefits and risks continue to suggest an overall positive benefit-risk profile for the use of VAXZEVRIA.

18.2.1.4 Strengths, weaknesses, and uncertainties of the evidence

VAXZEVRIA confers a strong immune response when administered as a booster both in the homologous or heterologous primary series settings and is considered safe for use. The accumulating evidence of the effectiveness of VAXZEVRIA against the landscape of constantly mutating Omicron variants indicates that booster doses continue to provide protection against progression to severe disease, hospitalization and associated mortality but that protection against symptomatic disease may be decreasing. This evidence is derived primarily from RWE studies (see section 17.4) coming from different geographical locations.

18.2.1.5 Methodology and reasoning used to develop the benefit-risk evaluation

The basis for efficacy of VAXZEVRIA given as a primary series has already been provided in previous PBRERs. Evidence primarily from RWE studies indicates that booster doses of VAXZEVRIA (3rd and/or 4th doses) continue to safeguard and provide a considerable degree of protection against critical outcomes such as progression to severe disease, hospitalization and death.

AstraZeneca's pharmacovigilance system provides the framework for the identification of any risks associated with the use of VAXZEVRIA in the approved indication. All information that has emerged during the reporting period has been reviewed and evaluated by AstraZeneca, irrespective of reporting source, seriousness, or causality. This has included an analysis of clinical trials, literature studies, safety topics that are kept under close surveillance, as well as an assessment of any new safety issues.

The significance of the information that became available during the reporting period has been evaluated in the context of what was known previously. An integrated evaluation of the key benefits (including changes in the epidemiological context) and risks give an overall positive benefit-risk profile for the use of VAXZEVRIA.

Based on AstraZeneca's evaluation, the benefits of VAXZEVRIA continues to outweigh the risks and the CDS accurately reflect the known benefit-risk profile.

19 CONCLUSIONS AND ACTIONS

VAXZEVRIA is indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals > 18 years of age, as described in previous sections.

During the reporting period, use of VAXZEVRIA is less comparable to the previous intervals as the context of treatment and prevention of the disease have evolved during the last year.

VAXZEVRIA was developed from the ancestral SARS-CoV 2, and the clinical efficacy studies with VAXZEVRIA were conducted when the ancestral SARS-CoV 2, Alpha, Beta and Delta were the predominant circulating variants.

Emergence of new variants (eg Omicron XBB) has led to significant reduction in protection against symptomatic infection and mild disease; however, there is more durable protection against severe disease and death. Evidence on the vaccine effectiveness of VAXZEVRIA against recent variants of Omicron is limited.

Real world effectiveness data indicate booster doses of VAXZEVRIA provide some protection against variants of concern potentially due, in part, to the contribution of T-cell mediated immunogenicity.

Thus, during the reporting period, the CDS has been updated to include information about circulating variants at the time clinical efficacy studies were conducted and for healthcare providers to consider the characteristics of circulating variants including regional or geographical differences for the use of VAXZEVRIA.

In addition, during the reporting period, CDS Section 4.8 (undesirable effects) was updated to include ADR Decrease appetite with a frequency of 'uncommon'.

The benefit of VAXZEVRIA has been weighed against the safety experience in the clinical program as well from post-marketing use.

Based on AstraZeneca's evaluation, the benefits of VAXZEVRIA continues to outweigh the risks and the CDS accurately reflect the known benefit-risk profile.

20 APPENDICES TO THE PBRER

A full list of Appendices and Regional Appendices is provided in the List of Appendices presented in the Table of Contents.

Where submitted, Regional Appendices provide information meeting local requirements.

21 REFERENCES

Abu-Raddad et al 2021

Abu-Raddad LJ, Chemaitelly H, Butt AA. Effectiveness of the BNT162b2 Covid-19 vaccine against the B.1.1.7 and B.1.351 variants. *N Engl J Med* 2021; 385:187-89.

Agrawal et al 2023

Agrawal N, Kaushiki Hajra, Uddalak Chakraborty, Saswati Halder. Adverse cutaneous reactions post Covid-19 vaccination- Case series from a tertiary care centre in Eastern India. *J Pak Assoc Dermatol* [Internet]. 2023Mar.5 [cited 2024Feb.8];33(1):116-22. Available from: <https://www.jpapd.com.pk/index.php/jpapd/article/view/2067>

Aimo et al 2022

Aimo C, Mariotti EB, Corrà A, Cipollini E, Le Rose O, Serravalle C, et al. Stevens-Johnson syndrome induced by Vaxvetria (AZD1222) COVID-19 vaccine. *J Eur Acad Dermatol Venereol*. 2022 Jun;36(6):e417-e419. doi: 10.1111/jdv.17988. Epub 2022 Feb 21.

Airfinity 2023

Airfinity [Internet]. Airfinity. [cited 2023]. Available from: <https://www.airfinity.com/articles/astrazeneca-and-pfizer-biontech-saved-over-12-million-lives-in-the-first>.

Ajdinaj et al 2022

P. Ajdinajl, M. Rispolil, L. Ferril, G. Polito1, M. De Rosal, D. Angelucci2, et al. CO-OCCURRENCE OF DERMATOMYOSITIS AND MYASTHENIA GRAVIS AFTER COVID-19 VACCINE: A CASE REPORT.

Ajlan et al 2022

Ajlan AA, Ali T, Aleid H, Almeshari K, DeVol E, Alkaff MA, et al. Comparison of the safety and immunogenicity of the BNT-162b2 vaccine and the ChAdOx1 vaccine for solid organ transplant recipients: a prospective study. *BMC Infectious Diseases*. 2022;22(1) Acute generalised exanthematous pustulosis 2008.

Almasi-Nasrabadi et al 2023

Almasi-Nasrabadi M, Ayyalaraju RS, Sharma A, Elsheikh S, Ayob S. New onset pemphigus foliaceus following AstraZeneca COVID-19 vaccination. *J Eur Acad Dermatol Venereol*. 2023 Jan;37(1):e1-e3. doi: 10.1111/jdv.18484. Epub 2022 Aug 29. PMID: 35964302; PMCID: PMC9539208.

Andrews et al 2022a

Andrews N, Tessier E, Stowe J, et al. Duration of protection against mild and severe disease by Covid-19 vaccines. *N Engl J Med* 2022;386:340-350.

Awokoya et al 2022

Awokoya, O.;Ah-Weng, A.;Srikanth, S.;Kaur, C.;Vyas, A. Erythema multiforme related to AstraZeneca SARS-CoV-2 vaccine British Journal of Dermatology ; 186(6):e252, 2022.

Baker et al 2021

Baker AT, Boyd RJ, Sarkar D, Teijeira-Crespo A, Chan CK, Bates E et al. ChAdOx1 interacts with CAR and PF4 with implications for thrombosis with thrombocytopenia syndrome. Sci Adv. 2021;7(49):eabl8213.

Banwell et al 2023

Banwell B, Bennett JL, Marignier R,. Diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease: International MOGAD Panel proposed criteria. The Lancet Neurology. 2023 Mar 1;22(3):268-82.

Ben Salem et al 2022

Ben Salem C, Khelif A, Sahnoun D, Ghariani N, Sriha B, Denguezli M. Another case of generalized bullous fixed drug eruption following an adenoviral vector-based COVID-19 vaccine (ChAdOx1 nCov-19). J Eur Acad Dermatol Venereol. 2022 Jul;36(7):e516-e517. doi: 10.1111/jdv.18059.

Butler et al 2021

Butler M, Tamborska A, Wood GK, Ellul M, Thomas RH, Galea I, et al. Considerations for causality assessment of neurological and neuropsychiatric complications of SARS-CoV-2 vaccines: from cerebral venous sinus thrombosis to functional neurological disorder. J Neurol Neurosurg Psychiatry 2021;92(11): 1144–51.

Callaway 2021

Callaway E. COVID vaccine boosters: the most important questions. Nature. 2021 Aug;596(7871):178-180. doi: 10.1038/d41586-021-02158-6. PMID: 34354274.

CDC 2023

Centers for Disease Control and Prevention. COVID Data Tracker. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2023, November 10. <https://covid.cdc.gov/covid-data-tracker>

Cerqueira-Silva et al 2023

Cerqueira-Silva T, Shah SA, Robertson C, Sanchez M, Katikireddi SV, de Araujo Oliveira V et al. Effectiveness of mRNA boosters after homologous primary series with BNT162b2 or ChAdOx1 against symptomatic infection and severe COVID-19 in Brazil and Scotland: A test-negative design case-control study. PLOS Medicine 2023;20(1):e1004156. doi: 10.1371/journal.pmed.1004156.

Chen et al 2022

Chen CC, Huang YJ, Lai MJ, Lin MH, Lin WC, Lin HY, et al. Immunogenicity and safety of two-dose SARS-CoV-2 vaccination via different platforms in kidney transplantation recipients. *Front Immunol.* 2022;13:951576.

Chanprapaph et al 2022

Chanprapaph K, Seree-Aphinan C, Rattanakaemakorn P, Pomsoong C, Ratanapokasatit Y, Setthaudom C, et al. A real-world prospective cohort study of immunogenicity and reactogenicity of ChAdOx1-S[recombinant] among patients with immune-mediated dermatological diseases. *Br J Dermatol.* 2022.

Chao et al 2022

Chao, Yin-Cheng; Liu, Kwei-Lan,* . New-onset bullous pemphigoid triggered by AstraZeneca COVID-19 vaccine. *Dermatologica Sinica* 40(4): p 245-246, Oct–Dec 2022. | DOI: 10.4103/1027-8117.358000

Charfi et al 2022

Charfi O.; Zaiem A, Khouloud B.; Sarrah K.; Riadh D.; Centre National De Pharmacovigilance, Service de Recueil et D'analyse des Effets Indésirables Drug Safety

Chiang et al 2023

Chiang, Jenny I.; Lin, Ruey-Yil; Lee, Meng-Suil, 2.*. Two cases with dermatomyositis-like skin rash and myopathy following COVID-19 vaccination. *Dermatologica Sinica* 41(1):p 48-49, Jan–Mar 2023. | DOI: 10.4103/ds.DS-D-22-00118

Choi et al 2022

Choi SF, Kim DU, Noh JY, Kim S, Park SH, Jeong HW, et al. T cell epitopes in SARS-CoV-2 proteins are substantially conserved in the Omicron variant. *Cell Mol Immunol.* 2022;19(3):447-8. Doi:10.1038/s41423-022-00838-5. Epub 2022 Jan 18.

Conceptions in England and Wales 2018

Conceptions in England and Wales Dataset. Available from <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/conceptionandfertilityrates/datasets/conceptionstatisticsenglandandwalesreferencetables>.

Coopersmith et al 2021

Coopersmith CM, Antonelli M, Bauer SR, Deutschman CS, Evans LE, Ferrer R, et al, The Surviving Sepsis Campaign: Research Priorities for Coronavirus Disease 2019 in Critical Illness. *Crit Care Med.* 2021;49(4):598-622.

Corra et al 2023

Corrá A, Barei F, Genovese G, Zussino M, Spigariolo CB, Mariotti EB, et al. Five cases of new-onset pemphigus following vaccinations against coronavirus disease 2019. *J Dermatol.*

2023 Feb;50(2):229-233. doi: 10.1111/1346-8138.16554. Epub 2022 Aug 17. PMID: 35975548; PMCID: PMC9538601.

Cowan et al 2023

Cowan TL, Huang C, Murrell DF. Autoimmune blistering skin diseases triggered by COVID-19 vaccinations: An Australian case series. *Front Med (Lausanne)*. 2023 Jan 10;9:1117176. doi: 10.3389/fmed.2022.1117176.

Czarnowska et al 2022

Czarnowska A, Tarasiuk J, Zajkowska O, Wnuk M, Marona M, Nowak K, et al. Safety of Vaccines against SARS-CoV-2 among Polish Patients with Multiple Sclerosis Treated with Disease-Modifying Therapies. *Vaccines*. 2022;10(5).

Da Cruz et al 2022

da Cruz Gouveia PA, Cavalcanti LNF, Alves LCF, Almeida DM, Barretto LWA. Stevens-Johnson syndrome after ChAdOx1 nCoV-19 vaccine. *Indian J Dermatol Venereol Leprol*. 2022 Sep-Oct;88(5):702. doi: 10.25259/IJDVL_941_2021

Dash et al 2021

Dash S, Sirka CS, Mishra S, Viswan P. COVID-19 vaccine-induced Stevens-Johnson syndrome. *Clin Exp Dermatol*. 2021 Dec;46(8):1615-1617. doi: 10.1111/ced.14784.

Deng et al 2022

Deng L, Glover C, Dymock M, Pillsbury A, Marsh JA, Quinn HE, et al. The short term safety of COVID-19 vaccines in Australia: AusVaxSafety active surveillance, February - August 2021. *Med J Aust*. 2022;217(4):195-202

dos Santos et al 2023

Santos CVBD, Noronha TG, Werneck GL, Struchiner CJ, Villela DAM. Estimated COVID-19 severe cases and deaths averted in the first year of the vaccination campaign in Brazil: A retrospective observational study. *Lancet Reg Health Am*. 2023;17:100418. doi: 10.1016/j.lana.2022.100418. Epub 2022 Dec 22.

Duijster et al 2023

Duijster JW, Schoep ME, Nieboer TE, Jajou R, Kant A, van Hunsel F. Menstrual abnormalities after COVID-19 vaccination in the Netherlands: A description of spontaneous and longitudinal patient-reported data. *Br J Clin Pharmacol*. 2023 Oct;89(10):3126-3138. doi: 10.1111/bcp.15799. Epub 2023 Jun 25. PMID: 37222170

ECDC 2023

European Centre for Disease Prevention and Control. SARS-CoV-2 variants of concern as of 20 October 2023. Available from: <https://www.ecdc.europa.eu/en/covid-19/variants-concern>. Accessed 13 November 2023.systematic review. *Ann Med Surg (Lond)*. 2022;76:103486.

Etemadifar et al 2022

Etemadifar M, Mansouri AR, Nouri H, Sedaghat N, Salari M, Maghsoudi M, et al. Post-COVID-19 acute disseminated encephalomyelitis: Case report and review of the literature. *Neuroimmunology Reports*. 2022;2:100066.

FDA Guideline

<https://www.fda.gov/media/159007/download>

Francis et al 2023

Francis AG, Elhadd K, Camera V Acute inflammatory diseases of the central nervous system after SARS-CoV-2 vaccination. *Neurology-Neuroimmunology Neuroinflammation*. 2023 Jan 1;10(1).

Gasparotto M et al 2023

Gasparotto M, Bindoli S, Padoan R, Cozzi G, Depascale R, Zanatta E, et al, New onset and flare of rheumatic diseases following COVID-19 vaccination are mild and respond well to treatment: 9-month follow-up data from a single centre cohort. *Clin Exp Rheumatol*. 2023 Mar;41(3):642-648. doi: 10.55563/clinexprheumatol/vx44zn. Epub 2022 Aug 5.

Gasparotto et al 2022

Gasparotto M, Bindoli S, Padoan R, Cozzi G, Depascale R, Zanatta E, et al. New onset and flare of rheumatic diseases following COVID-19 vaccination are mild and respond well to treatment: 9-month follow-up data from a single centre cohort. *Clin Exp Rheumatol*. 2022.

Gov.cn 2023

Gov.cn. [cited 2023]. Available from: <http://wjw.wuhan.gov.cn/front/web/>

Goodarzi et al 2021

Hatami, P., Aryanian, Z., Nicknam Asl, H., Goodarzi, A. Mucocutaneous adverse effects following COVID-19 vaccination: a case series with a comprehensive review of the literature. *Iranian Journal of Dermatology*, 2021; 24(4): 331-338. doi: 10.22034/ijd.2021.311094.1451

Greinacher et al 2021 (a)

Greinacher, A. Anti-platelet factor 4 antibodies causing VITT do not cross react with SARS-CoV-2 spike protein. *Blood* 138, 1269–1277 (2021).

Greinacher et al 2021 (b)

Greinacher, A. Insights in ChAdOx1 nCoV-19 vaccine-induced immune thrombotic thrombocytopenia. *Blood* 138, 2256–2268 (2021)

Greinacher et al 2021 (NEJM)

Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S (2021). Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. The new england journal of medicine (NEJM), 384 (22): 2092-101. DOI: 10.1056/NEJMoa2104840.

Gubernot et al 2021

Gubernot D, Jazwa A, Niu M, Baumblatt J, Gee J, Moro P et al. U.S. Population-Based background incidence rates of medical conditions for use in safety assessment of COVID-19 vaccines. Vaccine. 2021 Jun 23;39(28):3666-3677. doi: 10.1016/j.vaccine.2021.05.016. Epub 2021 May 14.

Guégan et al 2021

Annabi E, Dupin N, Sohier P, Garel B, Franck N, Aractingi S, et al. Rare cutaneous adverse effects of COVID-19 vaccines: a case series and review of the literature. J Eur Acad Dermatol Venereol. 2021 Dec;35(12):e847-e850. doi: 10.1111/jdv.17578. Epub 2021 Sep 2

Guevarra et al 2023

Guevarra E, Navarra S. New onset clinically amyopathic dermatomyositis following SARS-CoV-2 vaccine: A case report. International Journal of Rheumatic Diseases. 2023:159-0.

Gupta et al 2022

Kothari RS, Subramani D, Asnani DR, Raman A, Deora MS, Gupta A Erythema multiforme after Covishield/ChAdOx1 vaccination First published: 27 December 2021
<https://doi.org/10.1111/dth.15289>

Haase et al 2022

Haase M, Lesny P, Anderson M, Cloherty G, Stec M, Haase-Fielitz A, et al. Humoral immunogenicity and tolerability of heterologous ChAd/BNT compared with homologous BNT/BNT and ChAd/ChAd SARS-CoV-2 vaccination in hemodialysis patients : A multicenter prospective observational study. J Nephrol. 2022;35(5):1467-78.

Hali et al 2022

Hali F Sr, Araqi L Jr, Marnissi F, Meftah A, Chiheb S. Autoimmune Bullous Dermatitis Following COVID-19 Vaccination: A Series of Five Cases. Cureus. 2022 Mar 13;14(3):e23127. doi: 10.7759/cureus.23127. PMID: 35425676; PMCID: PMC9004698.

Hamaluba M et al 2023

Hamaluba M, Sang S, Orindi B, Njau I, Karanja HK, Kamau N, et al. Safety and immunogenicity of ChAdOx1 nCoV-19 (AZD1222) vaccine in adults in Kenya: a phase 1/2 single-blind, randomized controlled trial. 2023. Unpublished Manuscript.

Happaerts et al 2022

Happaerts M, Vanassche T. Acquired hemophilia following COVID-19 vaccination: Case report and review of literature. *Res Pract Thromb Haemost*. 2022 Sep 9;6(6):e12785. doi: 10.1002/rth2.12785. PMID: 36176309

Hemachudha et al 1987 [A]

Hemachudha T, Griffin DE, Giffels JJ, Johnson RT, Moser AB, Phanuphak P. Myelin basic protein as an encephalitogen in encephalomyelitis and polyneuritis following rabies vaccination. *N Engl J Med*. 1987;316:369-374.

Hemachudha et al 1987 [B]

Hemachudha T, Phanuphak P, Johnson RT, Griffin DE, Ratanavongsiri J, Siriprasomsup W. Neurologic complications of Semple-type rabies vaccine: Clinical and immunologic studies. *Neurology*. 1987;37(4):550.

Hemminki and Forssas 1999

Hemminki E, Forssas E. Epidemiology of miscarriage and its relation to other reproductive events in Finland. *Am J Obstet Gynecol*. 1999;181(2):396-401

Heo et al 2023

Heo YW, Lee SH, Hong SP. A Case of Acute Localized Exanthematous Pustulosis Induced by AZD1222 COVID-19 Vaccine. *Korean J Dermatol*. 2023;61(1):66-67.

Hibbs et al 2015

Hibbs BF, Moro PL, Lewis P, Miller ER, Shimabukuro TT. Vaccination errors reported to the Vaccine Adverse Event Reporting System, (VAERS) United States, 2000-2013. *Vaccine*. 2015 Jun 22;33(28):3171-8. doi: 10.1016/j.vaccine.2015.05.006.

Hou et al 2022

Hou PC, Huang HY, Lee JY, Hsu CK. Pyostomatitis vegetans following coronavirus disease 2019 vaccination in a patient with ulcerative colitis. *J Dermatol*. 2022 Aug;49(8):e285-e286. doi: 10.1111/1346-8138.16409. Epub 2022 May 2. PMID: 35491619; PMCID: PMC9347529.

Hozumi et al 1999

HOZUMI A, YUKI N, YAMAZAKI K, HIRATA K. Facial diplegia with paraesthesias: facial nerve enhancement in three dimensional MRI. *Journal of Neurology, Neurosurgery & Psychiatry*. 1999 May 1;66(5):688

Huff et al 1983

Huff JC, Weston WL, Tonnesen MG. Erythema multiforme: a critical review of characteristics, diagnostic criteria, and causes. *J Am Acad Dermatol*. 1983 Jun;8(6):763-75. doi: 10.1016/s0190-9622(83)80003-6. PMID: 6345608

Huiberts AJ et al 2023

Huiberts AJ, de Gier B, Hoeve CE, de Melker HE, Hahné SJM, den Hartog G, et al. Vaccine effectiveness of primary and booster COVID-19 vaccinations against SARS-CoV-2 infection in the Netherlands from July 12, 2021 to June 6, 2022: A prospective cohort study. *Int J Infect Dis.* 2023 Aug;133:36-42. doi: 10.1016/j.ijid.2023.04.401. Epub 2023 Apr 20.

ICMRA 2023

ICMRA COVID-19 Omicron variant workshop, 08 May 2023 <https://icmra.info/drupal/covid-19/8may2023>

Intawong et al 2022

Intawong K, Chariyalertsak S, Chalom K, Wonghirundecha T, Kowatcharakul W, Thongprachum A, et al. Effectiveness of heterologous third and fourth dose COVID-19 vaccine schedules for SARS-CoV-2 infection during delta and omicron predominance in Thailand: A test-negative, case-control study. *The Lancet Regional Health - Southeast Asia.* 2022;100121.

Jaiswal et al 2023

Jaiswal V, Mukherjee D, Peng Ang S, Kainth T, Naz S, Babu Shrestha A, et al. COVID-19 vaccine-associated myocarditis: Analysis of the suspected cases reported to the EudraVigilance and a systematic review of the published literature. *Int J Cardiol Heart Vasc.* 2023 Dec 3;49:101280. doi: 10.1016/j.ijcha.2023.101280. PMID: 38143781; PMCID: PMC10746454.

Jia et al 2023

Jia Y, Fu B, Dong L, Zhao M. Sweet syndrome induced by SARS-CoV-2 vaccines: A systematic review of patient-report studies. *Hum Vaccin Immunother.* 2023 Aug 1;19(2):2217076. doi: 10.1080/21645515.2023.2217076.

Jmor et al 2022

Shilan Jmor, Vincent Yip, First published: 20 September 2023
<https://doi.org/10.1002/psb.2085>

Jurynczyk et al 2017

Jurynczyk M, Messina S, Woodhall MR. Clinical presentation and prognosis in MOG-antibody disease: a UK study. *Brain.* 2017 Dec 1;140(12):3128-38.

Kang et al 2021

Kang SY, Park SY, Kim JH, Lee SM, Lee SP. COVID-19 vaccine-induced acute generalized exanthematous pustulosis. *Korean J Intern Med.* 2021 Nov;36(6):1537-1538. doi: 10.3904/kjim.2021.198. Epub 2021 Jun 16. PMID: 34130372; PMCID: PMC8588970.

Keane 1994

Keane JR. Bilateral seventh nerve palsy: analysis of 43 cases and review of the literature. *Neurology*. 1994 Jul 1;44(7):1198-202. doi: 10.1212/wnl.44.7.1198.

Kherlopian et al 2022

Kherlopian A, Zhao C, Ge L, Forward E, Fischer G. A case of toxic epidermal necrolysis after ChAdOx1 nCov-19 (AZD1222) vaccination. *Australas J Dermatol*. 2022 Feb;63(1):e93-e95. doi: 10.1111/ajd.13742.

Khoury et al 2021

Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, et al. Davenport MP. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med*. 2021 Jul;27(7):1205-1211. doi: 10.1038/s41591-021-01377-8.

Kirsebom FMC et al 2022

Kirsebom, F.C.M., Andrews, N., Sachdeva, R. et al. Effectiveness of ChAdOx1-S COVID-19 booster vaccination against the Omicron and Delta variants in England. *Nat Commun* 13, 7688 (2022).

Kirsebom et al 2022

Kirsebom, F.C.M., Andrews, N., Sachdeva, R. et al. Effectiveness of ChAdOx1-S COVID-19 booster vaccination against the Omicron and Delta variants in England. *Nat Commun* 13, 7688 (2022). <https://doi.org/10.1038/s41467-022-35168-7>

Kobyashi et al 2022

Kobyashi Y, Adachi T, Arakawa H, Takeuchi M, Inazumi T. Erythema multiforme following vaccination for SARS-CoV-2: Report of a case and review of the literature - Secondary Publication. *Australas J Dermatol*. 2022 Nov;63(4):e381-e385. doi: 10.1111/ajd.13917.

Kuntz et al 2018

Kuntz J, Crane B, Weinmann S, Naleway AL; Vaccine Safety Datalink Investigator Team. Myocarditis and pericarditis are rare following live viral vaccinations in adults. *Vaccine*. 2018 Mar 14;36(12):1524-1527. doi: 10.1016/j.vaccine.2018.02.030. Epub 2018 Feb 15.

Ladapo et al 2022

Ladapo J. Exploring the relationship between all-cause and cardiac-related mortality following covid-19 vaccination or infection in Florida residents: a self-controlled case series study. Florida Dept of Health. 7 October 2022. <https://floridahealthcovid19.gov/wp-content/uploads/2022/10/20221007-guidance-mrna-covid19-vaccines-analysis.pdf> Li et al 2022

Lai et al 2022

Lai, Po-Ta; Tseng, Han-Chi¹, Refractory bullous pemphigoid with prurigo nodularis successfully treated with dupilumab monotherapy. *Dermatologica Sinica* 40(4): p 237-238, Oct–Dec 2022. | DOI: 10.4103/1027-8117.357999

Lansang et al 2023

Lansang RP, Amdemichael E, Sajic D. IgA pemphigus following COVID-19 vaccination: A case report. *SAGE Open Med Case Rep.* 2023 Jun 14;11:2050313X231181022. doi: 10.1177/2050313X231181022. PMID: 37337523; PMCID: PMC10271809.

Law B 2021

Law B. Safety Platform for Emergency vaccines. SO2- D2.5.2.1 - AESI Case Definition Companion. Guide for 1st Tier AESI. Acute Encephalitis. Accessed on 29 June 2022. Available from: https://brightoncollaboration.us/wp-content/uploads/2021/03/SPEAC_D2.5.2.1_Encephalitis-Case-Definition-Companion-Guide_V1.0_format12064-1.pdf.

Law B 2021 [A]

Law B. Safety Platform for Emergency vaccines. SO2- D2.5.2.1 - AESI Case Definition Companion. Guide for 1st Tier AESI. Guillain Barré and Miller Fisher Syndromes. Accessed on 05 December 2021. Available from: https://brightoncollaboration.us/wp-content/uploads/2021/03/SPEAC_D2.5.2.1-GBS-Case-Definition-Companion-Guide_V1.0_format12062-1.pdf.

Law B 2021 [B]

Law B. Safety Platform for Emergency vaccines. SO2- D2.5.2.1 - AESI Case Definition Companion. Guide for 1st Tier AESI. Acute Disseminated Encephalomyelitis. 2021; Available from: https://brightoncollaboration.us/wp-content/uploads/2021/03/SPEAC_D2.5.2.1_ADEM-Case-Definition-Companion-Guide_V1.0_format12063-1.pdf.

Law B 2021 [C]

Law B. Safety Platform for Emergency vaccines. SO2- D2.5.2.1 - AESI Case Definition Companion. Guide for 1st Tier AESI. Acute Myelitis. 2021; Available from: https://brightoncollaboration.us/wp-content/uploads/2021/03/SPEAC_D2.5.2.1_Myelitis-Case-Definition-Companion-Guide_V3.0_13Feb2021_format12066-1.pdf.

Le Vu et al 2023

Le Vu S, Bertrand M, Botton J, Jabagi MJ, Drouin J, Semenzato L, et al. Risk of Guillain-Barré Syndrome Following COVID-19 Vaccines: A Nationwide Self-Controlled Case Series Study. *Neurology*. 2023 Nov 21;101(21):e2094-e2102. doi: 10.1212/WNL.0000000000207847. Epub 2023 Oct 3. PMID: 37788935; PMCID: PMC10663040.

Leake et al 2004

Leake JA, Albani S, Kao AS, Senac MO, Billman GF, Nespeca MP, et al. Acute disseminated encephalomyelitis in childhood: epidemiologic, clinical and laboratory features. *Pediatr Infect Dis J*. 2004;23:756-64.

Leclerc et al 2021

Leclerc S, Royal V, Lamarche C, Laurin LP. Minimal change disease with severe acute kidney injury following the Oxford-AstraZeneca COVID-19 vaccine: a case report. *American Journal of Kidney Diseases*. 2021 Oct 1;78(4):607-10.

Lee et al 2023

Lee YK, Kwon Y, Heo Y, Kim EK, Kim SY, Cho H, et al. Safety monitoring of COVID-19 vaccines: February 26, 2021, To June 4, 2022, Republic of Korea. *Clin Exp Pediatr*. 2023 Oct;66(10):415-423. doi: 10.3345/cep.2022.00815. Epub 2023 Jun 13. PMID: 37309116; PMCID: PMC10556797.

Lee HJ et al 2023

Lee HJ, Yun SY, Choi JY, Lee YB. Stevens-Johnson Syndrome Following ChAdOx1 nCoV-19 Vaccination (AstraZeneca). *Ann Dermatol*. 2023 May;35(Suppl 1):S170-S172. <https://doi.org/10.5021/ad.21.138>

Lehmann et al (2023)

Lehmann HC, Oberle D, Keller-Stanislawski B, Rieck T, Streit R. Rare cases of Guillain-Barré syndrome after COVID-19 vaccination, Germany, December 2020 to August 2021. *Euro Surveill*. 2023 Jun;28(24):2200744. doi: 10.2807/1560-7917.ES.2023.28.24.2200744.

Levison et al 2019

Levison LS, Thomsen RW, Christensen DH, Møllekjær T, Sindrup SH, Andersen H. Guillain-Barré syndrome in Denmark: validation of diagnostic codes and a population-based nationwide study of the incidence in a 30-year period. *Clin Epidemiol*. 2019 Apr 18;11:275-283. doi: 10.2147/CLEP.S199839.

Li et al 2022

Li G, Cappuccini F, Marchevsky NG, Aley PK, Aley R, Anslow R, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 (AZD1222) vaccine in children aged 6-17 years: a preliminary report of COV006, a phase 2 single-blind, randomised, controlled trial. *Lancet*. 2022 Jun 11;399(10342):2212-2225. doi: 10.1016/S0140-6736(22)00770-X. Erratum in: *Lancet*. 2022 Jul 2;400(10345):24. PMID: 35691324; PMCID: PMC9183219.

Liu et al 2023

Bette Liu, Sandrine Stepien, Jiahui Qian, Heather Gidding, Katrina Nicolopoulos, Janaki Amin, et al. Comparative effectiveness of four COVID-19 vaccines, BNT162b2 mRNA, mRNA-1273, ChAdOx1 nCov-19 and NVX-CoV2373 against SARS-CoV-2 B.1.1.529

(Omicron) infection. Vaccine, Volume 41, Issue 38, 2023, Pages 5587-5591, ISSN 0264-410X, <https://doi.org/10.1016/j.vaccine.2023.07.050>.

Ljung et al 2023

Ljung R, Xu Y, Sundström A, Leach S, Hallberg E, Bygdell M, et al. Association between SARS-CoV-2 vaccination and healthcare contacts for menstrual disturbance and bleeding in women before and after menopause: nationwide, register based cohort study. BMJ. 2023 May 3;381:e074778. doi: 10.1136/bmj-2023-074778. PMID: 37137493; PMCID: PMC10543813.

Lundberg et al 2017

Lundberg IE, Tjärnlund A, Bottai M, Werth VP, Pilkington C, Visser M, et al. International Myositis Classification Criteria Project consortium, The Euromyositis register and The Juvenile Dermatomyositis Cohort Biomarker Study and Repository (JDRG) (UK and Ireland). 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile IIM and their major subgroups. Ann Rheum Dis. 2017 Dec;76(12):1955-1964. doi: 10.1136/annrheumdis-2017-211468.

Lunn et al 2021

Lunn MP, Carr AC, Keddle S, Pakpoor J, Pipis M, Willison HJ. Guillain-Barré syndrome, SARS-CoV-2 and molecular mimicry and Ongoing challenges in unravelling the association between COVID-19 and Guillain-Barre syndrome and Unclear association between COVID-19 and Guillain-Barre syndrome and Currently available data regarding the potential association between COVID-19 and Guillain-Barre' syndrome. Brain, 2021 doi:10.1093/brain/awab070

Macías et al 2023

Macías Saint-Gerons D, Ibarz MT, Castro JL, Forés-Martos J, Tabarés-Seisdedos R. Myopericarditis Associated with the Novavax COVID-19 Vaccine (NVX-CoV2373): A Retrospective Analysis of Individual Case Safety Reports from VigiBase. Drugs Real World Outcomes. 2023 Jun;10(2):263-270. doi: 10.1007/s40801-023-00355-5. Epub 2023 Feb 14. PMID: 36788170; PMCID: PMC9928497.

Madhavan M et al 2022

Madhavan M, Ritchie AJ, Aboagye J, Jenkin D, Provstgaard-Morys S, Tarbet I, et al. Tolerability and immunogenicity of an intranasally-administered adenovirus-vectored COVID-19 vaccine: An open-label partially-randomised ascending dose phase I trial. EBioMedicine. 2022 Nov;85:104298. doi: 10.1016/j.ebiom.2022.104298

Mahaux et al 2016

Mahaux O, Bauchau V, Van Holle L. Pharmacoepidemiological considerations in observed-to-expected analyses for vaccines. Pharmacoepidemiol Drug Saf. 2016 Feb;25(2):215-22. doi: 10.1002/pds.3918

Marcela Gálvez et al 2023

Gálvez JM, Pinzón-Rondón AM, Chaparro-Solano HM, Tovar-Romero HV, Ramírez-Prieto J, Ortigoza-Espitia SA, et al. Effectiveness of the Booster Dose in Protecting against COVID-19, Colombia 2022. *Vaccines* (Basel). 2023 Sep 7;11(9):1461. doi: 10.3390/vaccines11091461. PMID: 37766137; PMCID: PMC10538081.

Maronese et al 2022

Maronese CA, Caproni M, Moltrasio C, Genovese G, Vezzoli P, Sena P, Previtali G, et al. Bullous Pemphigoid Associated With COVID-19 Vaccines: An Italian Multicentre Study. *Front Med* (Lausanne). 2022 Feb 28;9:841506. doi: 10.3389/fmed.2022.841506

Massari et al 2023

Massari M, Spila Alegiani S, Morciano C, Menniti Ippoliti F, Belleudi V, Trifirò G, et al. Post-marketing active surveillance of Barrè Syndrome following vaccination with COVID-19 mRNA vaccines in persons aged > 12 years in Italy: A multi-database, self-controlled case series study. *medRxiv preprint* doi: <https://doi.org/10.1101/2023.01.17.23284585>; this version posted January 19, 2023.

Meeraus et al 2023

Meeraus W, Stuurman AL, Durukal I, Conde-Sousa E, Lee A, Maria AS, et al. COVID-19 vaccine booster doses provide increased protection against COVID-19 hospitalization compared with previously vaccinated individuals: Interim findings from the REFORCO-Brazil real-world effectiveness study during Delta and Omicron. *Vaccine*. 2023;41(42):6366-6378.

Mehta et al 2022

Mehta N, Gaurav V, Agarwal S, Bhari N. ChAdOx1 COVID-19 Vaccine-Associated Erythema Multiforme Major and Erythema Multiforme-Like Vasculitis: A Tale of Two Cases. *Indian J Dermatol*. 2022 Nov-Dec;67(6):810-812. doi: 10.4103/ijd.ijd_849_22

Meyer et al 2023

Meyer S, Blaas I, Bollineni RC, Delic-Sarac M, Tran TT, Knetter C et al. Prevalent and immunodominant CD8 T cell epitopes are conserved in SARS-CoV-2 variants. *Cell Rep*. 2023 Jan 31;42(1):111995. doi: 10.1016/j.celrep.2023.111995. Epub 2023 Jan 9.

Nabizadeh et al 2023

Nabizadeh F, Noori M, Rahmani S, Hosseini H. Acute disseminated encephalomyelitis (ADEM) following COVID-19 vaccination: A systematic review. *Journal of Clinical Neuroscience*. 2023 May 1;111:57-70.

Nafilyan et al 2023

Nafilyan V, Bermingham CR, Ward IL, Morgan J, Zaccardi F, Khunti K et al. Risk of death following COVID-19 vaccination or positive SARS-CoV-2 test in young people in England. *Nat Commun.* 2023 14, 1541. <https://doi.org/10.1038/s41467-023-36494-0>.

NHS 2023

National Health Service. 3-in-1 teenage booster overview. [Cited November 2023]. Available from: <https://www.nhs.uk/conditions/vaccinations/3-in-1-teenage-booster/>. Accessed 11 November 2023.

Nagdevet al 2022

Nagdev G, Chavan G, Sahu G, Devasilpa Raju PD. COVID-19 Vaccination a Cause of Guillain-Barré Syndrome? A Case Series. *Cureus.* 2022 Oct 30;14(10):e30888. doi: 10.7759/cureus.30888.

Netravathi et al 2022

Netravathi M, Dhamija K, Gupta M, et al. COVID-19 vaccine associated demyelination & its association with MOG antibody. *Mult Scler Relat Disord.* 2022 Apr;60:103739. doi: 10.1016/j.msard.2022.103739. Epub 2022 Mar 13.

Nogareda et al 2023

Nogareda F, Regan AK, Couto P, Fowlkes AL, Gharpure R, Loayza S, et al. REVELAC-i Working Group. Effectiveness of COVID-19 vaccines against hospitalisation in Latin America during three pandemic waves, 2021-2022: a test-negative case-control design. *Lancet Reg Health Am.* 2023 Nov 10;27:100626. doi: 10.1016/j.lana.2023.100626. PMID: 38035125; PMCID: PMC10682274.

Nyberg et al 2022

Nyberg T, Ferguson NM, Nash SG, Webster HH, Flaxman S, Andrews N, et al, Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B. 1.1. 529) and delta (B. 1.617. 2) variants in England: a cohort study. *The Lancet.* 2022 Apr 2;399(10332):1303-12.

O'Connell et al 2020

O'Connell K, Hamilton-Shield A, Woodhall M. Prevalence and incidence of neuromyelitis optica spectrum disorder, aquaporin-4 antibody-positive NMOSD and MOG antibody-positive disease in Oxfordshire, UK. *Journal of Neurology, Neurosurgery & Psychiatry.* 2020 Oct 1;91(10):1126-8.

O'Connor et al 2022

O'Connor T, O'Callaghan-Maher M, Ryan P, Gibson G. Drug reaction with eosinophilia and systemic symptoms syndrome following vaccination with the AstraZeneca COVID-19 vaccine. *JAAD Case Rep.* 2022 Feb;20:14-16. doi: 10.1016/j.jdcr.2021.11.028

Pakvisal et al 2022

Pakvisal N, Sainamthip P, Teeyapun N, Luangdilok S, Wanlapakorn N, Yorsaeng R, et al. Vaccine-Related adverse events following AZD1222 (ChAdOx1-nCoV-19) Covid-19 vaccine in solid malignancy patients receiving cancer treatment, as compared to age-matched healthy controls. Hum Vaccin Immunother. 2022;18(6):2094149.

Paternina-Caicedo et al 2023

Paternina-Caicedo A, Quevedo DS, Ríos DS, Moyano D, Alvis-Guzmán N, Alviz-Zakzuk NR, et al. Comparative effectiveness and duration of protection of ChAdOx1, CoronaVac, BNT162b2, mRNA-1273, and Ad26.COV2.S COVID-19 vaccines for symptomatic and hospitalized Mu, Delta, and Omicron: A test-negative case-control study. Vaccine. 2023;41(42):6291-6299.

Patone et al 2021

Patone M, Handunnetthi L, Saatci D, Pan J, Katikireddi SV, Razvi S et al. Neurological complications after first dose of COVID-19 vaccines and SARS-CoV-2 infection. Nat Med. 2021;27(12):2144-53 doi: 10.1038/s41591-021-01556-7. Epub 2021 Oct 25.

Pham et al 2023

Pham NN, Nguyen TTP, Vu TTP, Nguyen HT. Pemphigus Foliaceus after COVID-19 Vaccination: A Report of Two Cases. Case Rep Dermatol Med. 2023 Oct 19;2023:1218388. doi: 10.1155/2023/1218388. PMID: 37900286; PMCID: PMC10602704

Richard et al 2024

Buka Richard J, Montague SJ, Moran LA, Martin EM, Slater A, Watson SP, Nicolson PLR. PF4 activates the c-Mpl-Jak2 pathway in platelets. Blood. 2024 Jan 4;143(1):64-69. doi: 10.1182/blood.2023020872. PMID: 37883794; PMCID: PMC10862235.

Pollozhani et al 2023

Cutaneous lupus erythematosus after COVID-19 vaccine: Report of four cases, 32nd Annual Congress of the European Academy of Dermatology and Venereology (EADV)

Pratama et al 2022

Pratama NR, Wafa IA, Budi DS, Sutanto H, Asmarawati TP, Barlian Effendi G, et al. Effectiveness of COVID-19 Vaccines against SARS-CoV-2 Omicron Variant (B.1.1.529): A Systematic Review with Meta-Analysis and Meta-Regression. Vaccines. 2022 Dec 19;10(12):2180.

Ramessur et al 2021

Ramessur R, Saffar N, Czako B, Agarwal A, Batta K. Cutaneous thrombosis associated with skin necrosis following Oxford-AstraZeneca COVID-19 vaccination. Clin Exp Dermatol. 2021 Dec;46(8):1610-1612. doi: 10.1111/ced.14819.

Roujeau et al 2012

Roujeau J. Chapter 39. Erythema Multiforme. In: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K. eds. Fitzpatrick's Dermatology in General Medicine, 8e. McGraw Hill; 2012. Accessed December 26, 2022.

<https://accessmedicine.mhmedical.com/content.aspx?bookid=392§ionid=41138736>

Rowhani-Rahbara et al 2012

Rowhani-Rahbara A, Kleina NP, Dekker CL, Edward KM, Marchant CD, Vellozzi C, et al. Biologically plausible and evidence-based risk intervals in immunization safety research. *Vaccine*. 2012;31;271-7.

Saleem et al 2022

Saleem U, Goh ES. A Case Report of Exfoliative Bullous Rash Following AstraZeneca Vaccine. *Cureus*. 2022 Nov 16;14(11).

Samim et al 2023

Samim M.M., Dhar Debjyoti, Arshad Faheem, et al. Co-VAN study: COVID-19 vaccine associated neurological diseases- an experience from an apex neurosciences centre and review of the literature, *Journal of Clinical Neuroscience*. Volume 108, 2023. Pages 37-75.

<https://doi.org/10.1016/j.jocn.2022.12.015>

Santos et al. 2023

Santos CVBD, Valiati NCM, Noronha TG, Porto VBG, Pacheco AG, Freitas LP, et al. The effectiveness of COVID-19 vaccines against severe cases and deaths in Brazil from 2021 to 2022: a registry-based study. *Lancet Reg Health Am*. 2023 Apr;20:100465. doi: 10.1016/j.lana.2023.100465. Epub 2023 Mar 13. PMID: 36936517; PMCID: PMC10010656.

Sejvar et al 2007

Sejvar JJ, Kohl KS, Bilynsky R, Blumberg D, Cvetkovich T, Galama J, et al. Encephalitis, myelitis and acute disseminated encephalomyelitis (ADEM): Case definitions and guidelines for collection, analysis and presentation of immunization safety data. *Vaccine*. 2007;25:57715792.

Seque et al 2022-1

Seque CA, Enokihara MMSS, Nascimento MM, Porro AM, Tomimori J. Rare cutaneous reactions after ChAdOx1 (Oxford-AstraZeneca) vaccine: 12 case series from Brazil. *J Eur Acad Dermatol Venereol*. 2022 Aug;36(8):e601-e603. doi: 10.1111/jdv.18112

Seque et al 2022-2

Seque CA, Enokihara MMSS, Nascimento MM, Porro AM, Tomimori J. Rare cutaneous reactions after ChAdOx1 (Oxford-AstraZeneca) vaccine: 12 case series from Brazil. *J Eur Acad Dermatol Venereol*. 2022 Aug;36(8):e601-e603. doi: 10.1111/jdv.18112

Shrotri et al 2021

Shrotri M, van Schalkwyk MCI, Post N, Eddy D, Huntley C, Leeman D, et al. T cell response to SARS-CoV-2 infection in humans: A systematic review. PLoS ONE. 2021 Jan 25;16(1):e0245532. doi: 10.1371/journal.pone.0245532.

Singh et al 2022

Singh, Shweta MS; Gupta, Nidhi DNB; Sangwan, Virender MS. COVISHIELD Vaccine--Induced Ocular Stevens-Johnson Syndrome: A Case Report. Cornea Open 1(1):p e0002, December 2022. | DOI: 10.1097/coa.0000000000000002

Sritipsukho et al 2023

Sritipsukho P, Khawcharoenporn T, Siribumrungwong B, Damronglerd P, Suwantarat N, Satdhabudha A, et al. Real-life effectiveness of COVID-19 vaccine during the Omicron variant-dominant pandemic: how many booster doses do we need?. Emerging Microbes & Infections. 2023 Dec 31;12(1):2174779.

Stratton et al 1994

Stratton KR, Howe CJ, Johnston RB Jr., editors. Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality. Washington (DC): National Academies Press (US); 1994. 3, Neurologic Disorders. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK236298/>

Suparna et al 2023

Suparna MY, Patil D, Shivaswamy KN, Sumathy TK. Dermatomyositis: severe acute respiratory syndrome coronavirus 2, an initiator or a trigger?. Journal of the Egyptian Women's Dermatologic Society. 2023 Jan 1;20(1):52-6.

Swanson et al 2021

Swanson PA, Padilla M, Hoyland W, McGlinchey K, Fields PA, Bibi S, et al. AZD1222/ChAdOx1 nCoV-19 vaccination induces a polyfunctional spike protein-specific TH1 response with a diverse TCR repertoire. Sci Transl Med. 2021;13(620). Available online at: <https://www.science.org/doi/10.1126/scitranslmed.abj7211>.

Szebeni et al 2022

Szebeni GJ, Gémes N, Honfi D, Szabó E, Neuperger P, Balog JÁ, et al. Humoral and Cellular Immunogenicity and Safety of Five Different SARS-CoV-2 Vaccines in Patients With Autoimmune Rheumatic and Musculoskeletal Diseases in Remission or With Low Disease Activity and in Healthy Controls: A Single Center Study. Frontiers in Immunology. 2022;13

Walle et al 2022

Walle T, Bajaj S, Kraske JA, Rösner T, Cussigh CS, Kälber KA, et al. Cytokine release syndrome-like serum responses after COVID-19 vaccination are frequent and clinically inapparent under cancer immunotherapy. Nature Cancer. 2022;3(9):1039-51.

Walid et al 2023

Walid N. Amyopathic dermatomyositis induced by the COVID-19 vaccination. *J Clin Images Med Case Rep.* 2023; 4(6): 2480.

Warkentin et al 2023

Warkentin TE, Baskin-Miller J, Raybould AL, Sheppard JA, Daka M, Nazy I, Moll S. Adenovirus-associated thrombocytopenia, thrombosis, and VITT-like antibodies. *New England Journal of Medicine.* 2023 Aug 10;389(6):574-7.

Watson et al 2022

Watson OJ, Barnsley G, Toor J, Hogan AB, Winskill P, Ghani AC. Global impact of the first year of COVID-19 vaccination: a mathematical modelling study. *Lancet Infect Dis.* 2022;22(9):1293-1302. doi: 10.1016/S1473-3099(22)00320-6. Epub 2022 Jun 23. PMID: 35753318; PMCID: PMC9225255

Wang et al 2022 [A]

Wang H, Zhao S, Wang S, Zheng Y, Wang S, Chen H, et al. Global magnitude of encephalitis burden and its evolving pattern over the past 30 years. *Journal of Infection.* 2022 Jun 1;84(6):777-87.

Wantavornprasert et al 2021-1

Wantavornprasert K, Noppakun N, Klaewsongkram J, Rerknimitr P. Generalized bullous fixed drug eruption after Oxford-AstraZeneca (ChAdOx1 nCoV-19) vaccination. *Clin Exp Dermatol.* 2022 Feb;47(2):428-432. doi: 10.1111/ced.14926.

Wantavornprasert et al 2021-2

Wantavornprasert K, Noppakun N, Klaewsongkram J, Rerknimitr P. Generalized bullous fixed drug eruption after Oxford-AstraZeneca (ChAdOx1 nCoV-19) vaccination. *Clin Exp Dermatol.* 2022 Feb;47(2):428-432. doi: 10.1111/ced.14926.

Watcharananan et al 2022

Watcharananan SP, Jaru-Ampornpan P, Sahawongcharoen S, Naitook N, Himananto O, Jongkaewwattana A, et al. Comparison of the immunogenicity of ChAdOx1 nCoV-19 vaccine against the wild-type and delta variants in kidney transplant recipients and healthy volunteers. *Am J Transplant.* 2022;22(5):1459-66.

WHO

https://www.ema.europa.eu/en/documents/other/ecdc-ema-statement-updating-covid-19-vaccines-composition-new-sars-cov-2-virus-variants_en.pdf

WHO 2023

WHO Coronavirus (COVID-19) Dashboard. Geneva: World Health Organization, 2023. Available online: <https://covid19.who.int/>, accessed on 13 November 2023.

WHO 2023a

COVID-19 vaccines. Geneva: World Health Organization, 2023. Available online: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines>, accessed on 13 November 2023.

WHO interim guidance 2021

Interim recommendations for an extended primary series with an additional vaccine dose for COVID-19 vaccination in immunocompromised persons (https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-immunocompromised-persons; accessed 3 January 2023)

WHO COVID-19 dashboard

WHO COVID-19 Dashboard. Geneva: World Health Organization, 2020. Available online: <https://covid19.who.int/>, accessed on 02 August 2023.

Willame et al 2021 (A)

Willame C, Dodd C, Gini R, Duran CE, Ehrenstein V, Thomsen RM et al. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccines, an ACCESS study. D3-Draft Final Report. 2021;(2.0). DOI: 10.5281/zenodo.5255870.

Willame et al 2021 (B)

Willame C, Dodd C, van der Aa L, Picelli G, Emborg HD, Kahlert J et al. Incidence Rates of Autoimmune Diseases in European Healthcare Databases: A Contribution of the ADVANCE Project. Drug Saf. 2021;44(3):383-395.

Wu CF et al 2023

Wu CF, Chen WT, Chen YL, Liu FC. Therapeutic Effects of Treating COVID-19 Vaccine-Induced Anti-TIF1- γ -Positive Dermatomyositis. Medicina. 2023 Sep 20;59(9):1688. <https://doi.org/10.3390/medicina59091688>

Yang et al 2022

Yan g IN, Lu CL, Tang HJ, Kuo YC, Tsai LH, Tu KC, et al. Safety of ChAdOx1 nCoV-19 vaccination in patients with end-stage renal disease on hemodialysis. PLoS One. 2022;17(9):e0273676.

Zhou et al 2020

Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020 Mar;579(7798):270-273. doi: 10.1038/s41586-020-2012-7. Epub 2020 Feb 3. Erratum in: Nature. 2020 Dec;588(7836):E6. PMID: 32015507; PMCID: PMC7095418.

Zhou et al 2022

Zou H, Daveluy S. Pemphigus vulgaris after COVID-19 infection and vaccination. J Am Acad Dermatol. 2022 Sep;87(3):709-710. doi: 10.1016/j.jaad.2022.05.013. Epub 2022 May 13. PMID: 35569594; PMCID: PMC9123945.