



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA/865685/2022

Assessment report on the annual renewal of the conditional marketing authorisation

Procedure no.: EMEA/H/C/005675/R/0079

Invented name: Vaxzevria

Common name: COVID 19 Vaccine (ChAdOx1 S [recombinant])

Marketing authorisation holder (MAH): AstraZeneca AB

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



Status of this report and steps taken for the assessment

Current step	Description	Planned date	Actual Date
<input type="checkbox"/>	Start of procedure:	15 Aug 2022	15 Aug 2022
<input type="checkbox"/>	CHMP and PRAC Rapporteurs Joint Assessment Report	13 Sep 2022	13 Sep 2022
<input type="checkbox"/>	CHMP and PRAC members comments	19 Sep 2022	19 Sep 2022
<input type="checkbox"/>	Updated CHMP and PRAC Rapporteurs Joint Assessment Report	22 Sep 2022	26 Sep 2022
<input type="checkbox"/>	PRAC endorsed relevant sections of the assessment report	29 Sep 2022	29 Sep 2022
<input checked="" type="checkbox"/>	Opinion	13 Oct 2022	13 Oct 2022

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1. Background information on the annual renewal

The European Commission issued on 29 January 2021, a conditional marketing authorisation (MA) for Vaxzevria. This implied that, pursuant to Article 14-a of Regulation (EC) No 726/2004 and Article 5 of Commission Regulation (EC) No 507/2006, the marketing authorisation holder (MAH) has to complete ongoing studies, or to conduct new studies, as listed in Annex II.E of the MA, the so-called Specific Obligations (SOBs). These data form the basis of the renewal of the conditional MA.

A conditional MA is valid for one year and may be renewed annually upon request by the MAH. Therefore, pursuant to Article 14-a of Regulation (EC) No 726/2004 and Article 6(2) of Commission Regulation (EC) No 507/2006, the MAH AstraZeneca AB, submitted to the Agency on 22 July 2022 an application for renewal of the conditional MA for Vaxzevria. The expiry date of the MA is 29 January 2023.

The period covered by this annual renewal is 1 June 2021 to 31 May 2022.

2. Specific Obligations

2.1. Specific Obligations adopted with the initial marketing authorisation

The full list of SOBs as adopted with the initial marketing authorisation are shown in the next *Table 1*

Table 1 Chronological list of specific obligations to the MA submitted since the granting of the marketing authorisation

Description of the Commitment	Commitment Reference Number	Commitment Due Date	Date of submission	Procedure number within which commitment was submitted	Commitment Fulfilment Date	Commitment Status
In order to confirm the consistency of the active substance and finished product manufacturing process, the applicant should provide additional validation and comparability data and, introduce enhanced testing.	SOB 13 (MA CHMP AR SO1)	December 2021 with interim monthly updates beginning February 2021	04/06/2021 05/07/2021 05/08/2021 05/10/2021 05/11/2021	EMA/H/C/005675/SOB/013.4		Approved
In order to confirm the efficacy and safety of Vaxzevria, the MAH should submit the final Clinical Study Reports for the randomised, controlled, COV001, COV002, COV003 and COV005.	SOB/FSR015 SOB/FSR016 SOB/FSR017 SOB/FSR018	31/05/2022 Now 31/12/2022		EMA/H/C/005675/0000		
In order to confirm the efficacy and safety of Vaxzevria, the MAH should provide the primary analysis (based on the 7th of December data cut-off (post data-base lock) and final analysis from the pooled pivotal studies.	SOB 019	Primary analysis: 05/03/2021 Final pooled analysis: 31/05/2022	Primary analysis: 05/03/2021	EMA/H/C/005675/II/0002	24/06/2021	Positive CHMP Opinion for Primary Analysis, 24/06/2021

Description of the Commitment	Commitment Reference Number	Commitment Due Date	Date of submission	Procedure number within which commitment was submitted	Commitment Fulfilment Date	Commitment Status
In order to confirm the efficacy and safety of Vaxzevria in the elderly and subjects with underlying disease, the MAH should submit the overview and summaries of the primary analysis and final clinical study report for study D8110C00001.	SOB 020	Primary analysis 30/04/2021 Final CSR: 31/03/2024	Primary analysis: 04/06/2021	EMA/H/C/005675/II/0026	15/10/2021	Approval (EC decision) 15/10/2021 (primary analysis)
The stability data of three PPQ batches manufactured, should be provided as part of ongoing monthly PAM submissions.	EMA/H/C/005675/IB/0053 This SOB will be integrated in SOB 2 (SOB 014).					Approved
In order to ensure consistent product quality, the applicant should provide additional information on stability of the active substance and finished product and review the finished product specifications following further manufacturing experience.	Specific obligation (SOB 014)	The due date for SOB 014 has been amended from June 2022 to January 2023; see opinion of Type II variation EMA/H/C/005675/II/0074				Ongoing

2.2. Outstanding Specific Obligations – status report for period covered

At the time of this annual renewal, the list of pending SOBs is indicated in the following *Table 2*

Table 2 Summary table of the Specific obligations (SOBs) and other conditions

SOB Number	Description	Due Date	Date of submission and procedure number	Date when the obligation or condition has been resolved	Status
SOB 014	In order to ensure consistent product quality, the applicant should provide additional information on stability of the active substance and finished product and review the finished product specifications following further manufacturing experience.	January 2023 with interim monthly updates beginning February 2021	04 June 2021/ EMA/H/C/005675/SOB/014.4		Ongoing CHMP opinion for change of due date to January 2023 issued on 23 June 2022

SOB Number	Description	Due Date	Date of submission and procedure number	Date when the obligation or condition has been resolved	Status
SOB 019	In order to confirm the efficacy and safety of VAXZEVRIA, the MAH should provide the primary analysis (based on the 7 th December 2020 data cut-off (post data-base lock) and final analysis from the pooled pivotal studies.	Primary analysis 05 March 2021 Final pooled analysis 31 December 2022	Primary analysis 05 March 2021/ EMA/H/C/005675 /II/0002	Primary analysis: 24 June 2021	Ongoing Favourable opinion for change of due date from 31 May 2022 to 31 December 2022 issued on 23 March 2022
SOB 020	In order to confirm the efficacy and safety of VAXZEVRIA in the elderly and subjects with underlying disease, the MAH should submit the overview and summaries of the primary analysis and final clinical study report for study D8110C00001.	Primary analysis 30 April 2021 Final CSR 31 March 2024	Primary analysis 04 June 2021/ EMA/H/C/005675 /II/0026	Primary analysis 15 October 2021	Ongoing
SOB 013	In order to confirm the consistency of the active substance and the finished product manufacturing process, the applicant should provide additional validation and comparability data and, introduce enhanced testing.	March 2022 with interim monthly updates beginning February 2021	17 December 2021 / EMA/H/C/005675 /IB/0059	CHMP opinion for completion of SOB issued 23 June 2022	Completed Favourable opinion for change of due date to March 2022 issued on 26 January 2022
SOB 015 / SOB 016 / SOB 017 / SOB 018	In order to confirm the efficacy and safety of VAXZEVRIA, the MAH should submit the final Clinical Study Reports for the randomised, controlled, COV001, COV002, COV003 and COV005.	31 December 2022			Ongoing Favourable opinion for change of due date from 31 May 2022 to 31 December 2022 issued on 23 March 2022

Quality

Two Specific Obligations were raised at the time of the conditional authorization. The due date established for Specific Obligations at the time of the conditional authorization was December 2021 with interim monthly updates beginning February 2021, for SO1 (SO13), and June 2022 with interim monthly updates beginning February 2021, for SO2 (SO14). Some points of these SO have been updated after the assessment of Type IB variations in the context of approved PAMCs to include additional manufacturing sites.

During the period covered from the conditional authorization to the first annual renewal, SOB 1 c, e and f and RECs 1, 5, 6, 8, 9, 10, 11, 15, 20, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 35 and 53 and legally binding LEG002 were fulfilled.

During the period covered by this annual renewal, data on Quality Specific Obligations (SOB) and Recommendations (REC) have been monthly provided. Specific Obligation SO13 and quality related recommendations 1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 35, 36, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 66, 67, 68, 69 and 71 are fulfilled. SO14 is still ongoing.

By variation II-74 (June 2022), Annex IIE was updated to remove the specific obligation relating to provision of process validation data for the active substance and finished product (SO13-1a and SO13-1b) which has been fulfilled, and to change the date of the specific obligation relating to the provision of additional information on stability of the active substance and finished product (and review the finished product specifications following further manufacturing experience) from June 2022 to January 2023 (SO14). The change in date was agreed as stability studies were ongoing and further data from these studies are expected to be submitted in due course. This remaining quality SOB (SOB 014) may

be reclassified as a REC. This specific obligation regarding stability data was raised because, at the time of the conditional authorisation, in order to ensure consistent product quality, there was a need for additional stability data from all manufacturing sites to support the shelf life granted, both for the active substance and for the finished product. The Company has been providing stability data in monthly updates indicating that product stability is guaranteed for the approved shelf life.

The remaining quality SOB (SOB 014) may be reclassified as a REC.

Non-clinical

There were no non-clinical SOBs to be addressed for this annual renewal.

Clinical

During the period covered by this renewal the primary analysis for SOB 019 and SOB 020 were submitted in procedures EMA/H/C/005675/II/0002 and EMA/H/C/005675/II/0026, respectively. Both aspects of the respective SOBs are considered fulfilled. It is noted that neither these two SOBs nor the rest of clinical SOBs (SOB15, SOB16, SOB17, and SOB18) have been fully fulfilled during the time period covered by this annual renewal.

SOBs 015, SOB 016, SOB 017 and SOB 018 are currently ongoing, where final CSR submission is due on 31 December 2022. It is noted that in the list of SOBs adopted at the time of the MA, final clinical study reports for SOB 015, SOB 016, SOB 017, SOB 018 and for the final analysis from the pooled pivotal studies were due for 31 December 2022. However, following the request from the MAH (EMA/H/C/005675/IB/0069), the due dates were amended to 31 December 2022.

Overall, it is agreed with the MAH that the data collected as part of the specific obligations for Vaxzevria during the period covered by this renewal support its positive benefit-risk balance for the approved indication.

Currently the only outstanding information in relation to the original SOBs is the final CSR from individual studies COV001, COV002, COV003, COV005, and D8110C00001, as well as the final analysis from the pooled pivotal studies (efficacy analysis from trials COV002 and COV003, and a pooled safety analysis based on all four trials COV001, COV002, COV003, and COV005).

It is not expected that the remaining outstanding data in the final CSRs will bring substantial additional confirmatory evidence impacting the benefit-risk profile of Vaxzevria in its current indication. Even though the MAH has requested a renewal of the current conditional marketing authorization, it is considered that the current conditional marketing authorization could be converted into a standard marketing authorization. The remaining clinical SOBs may therefore be reclassified as Category 3 studies in the RMP, with the final CSRs to be submitted at the agreed due date as supportive data.

As part of this annual renewal, the CHMP is of the opinion that the SOBs 015, 016, 017, 018, 019 and 029 can therefore be deleted from Annex II. The RMP will be updated accordingly at the next regulatory opportunity.

2.3. Overall conclusion on Specific Obligations

Quality:

During the period covered by this annual renewal, new data regarding the quality SOB 013 and SOB 014 have been submitted which were submitted in compliance with the deadlines. SOB 013 was considered fulfilled and SOB 014 had a deadline which was accepted to be postponed to January 2023,

however, it may be reclassified as a REC. The SOBs can therefore be deleted from Annex II.

Non-clinical:

There were no non-clinical SOBs to be addressed for this annual renewal.

Legally Binding measures (LEG) and Recommendations (REC) concerning the non-clinical assessment have been all adequately resolved.

Clinical:

During the period covered by this annual renewal, new data regarding SOBs have emerged. The new data emerged are compliant in terms of adherence to deadlines and are compliant in terms of acceptability of data submitted. Moreover, these new data do not modify the current benefit-risk balance of the vaccine in the approved indication.

Currently the only pending information in relation to the original SOBs is the final CSR from individual studies COV001, COV002, COV003, COV005, and D8110C00001, as well as the final analysis from the pooled pivotal studies (efficacy analysis from trials COV002 and COV003, and a pooled safety analysis based on all four trials COV001, COV002, COV003, and COV005). However, it is not expected that the remaining outstanding data in the final CSRs will bring substantial additional confirmatory evidence impacting the benefit-risk profile of Vaxzevria in its current indication. It is considered that the current conditional approval should be converted into a standard marketing authorization. The remaining clinical SOBs may therefore be reclassified as Category 3 studies in the RMP, with the final CSRs to be submitted at the agreed due date as supportive data.

As part of this annual renewal, the CHMP is of the opinion that the SOBs 015, 016, 017, 018, 019 and 029 can therefore be deleted from Annex II. The RMP will be updated accordingly at the next regulatory opportunity.

3. Additional scientific data provided relevant for the assessment of the benefit/risk balance

3.1. Quality

Please see above rationale for pending Quality REC.

3.2. Non-clinical

Non-clinical ANX-044, LEG-004 and RECS 060, 061, 062 and 063 have been fulfilled during the period covered by this annual renewal (EMA/H/C/005675/II/17/G). Updated information was included in sections 4.6 and 5.3 of SmPC following assessment and the ANX-044 study was recommended to be deleted from Annex II.

As part of the type II variation EMA/H/C/005675/II/31, the MAH submitted the final report for study MS1222-0002 which fulfils the Annex II obligation (ANX-045) as well as the post-authorisation measure (PAM- MEA-082) "In Vitro expression of Spike protein" as detailed under additional pharmacovigilance activities in the EU Risk Management Plan (RMP) for Vaxzevria. As a result, Annex II of the product information was updated to remove ANX-045.

Moreover, the MAH provided two additional studies linked to support the investigation on the platelet activation: the final study report for MS1222-0001 "Computational Prediction of Spike Protein

Interaction with Platelet Factor 4 (PF4)" and the study report for 520447 "Investigative Vaccine Study in the Mouse" to evaluate spike protein levels and haematology parameters.

There are no outstanding issues regarding the non-clinical assessment.

3.3. Clinical efficacy

The new information regarding clinical efficacy that emerged during the period covered by this annual renewal is as follows:

a) One clinical trial (D8111C00002) was completed. This trial is a Phase I/II Randomised, Double-blind, Placebo-controlled Multicentre Study in Participants Aged 18 Years or Older to Determine the Safety and Immunogenicity of Vaxzevria, a Non-replicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19: Phase I/II. This clinical trial was carried out in Japan and recruited in total 256 participants and it is noted that detailed report on this study has not been submitted to CHMP. Nonetheless, the MAH indicates that AZD1222 administered in 2 intramuscular (IM) injections was generally well-tolerated and had an acceptable safety profile in Japanese adult participants across all age groups (18 to 55 years, 56 to 69 years, and ≥ 70 years), and the number of serious adverse events (SAEs) reported between Day 58 and Day 365, in addition to the unsolicited adverse events (AEs) collected up to Day 57, was low. The MAH also indicates that the immunogenicity data collected from this trial suggest that AZD1222 elicits strong early immune responses against SARS-CoV-2 in the Japanese adult population across all the age groups; however, waning of immune responses, with neutralizing antibodies below the lower limit of quantification, was observed in a large proportion of participants by Day 365.

b) Additional information (safety and efficacy data) from study D8110C00001 was under evaluation in procedure EMA/H/C/005675/II/0075 at the time of the submission of this renewal. Primary analysis results for study D8110C00001 were provided in a previous submission (EMA/H/C/005675/II/0026) based on a data cut off (DCO) date of 05 March 2021. The new submitted data in this application are the results of the 6-month follow-up analysis and are based on a DCO date of 30 July 2021. The new efficacy data supports maintenance of efficacy for at least 6-months: whereas the primary efficacy analysis showed a vaccine efficacy (VE) of 74.0%, with a lower bound of the 95% CI of 65.3%, the new data provide an estimate of VE of 66.98%. with a lower bound of the 95% CI of 58.87%. The same immunogenicity conclusions reached at the time primary analysis are made upon assessing the new data. From the safety point of view, the data reported from the 6-months follow-up did not show new safety concerns for AZD1222. This variation concluded positively on 15 September 2022.

c) Clinical trial D7220C00001 is an ongoing Phase II/III, partially double-blinded, randomised, multinational, active controlled study to evaluate the safety and immunogenicity of AZD2816 (a modified AZD1222 vaccine targeted against the Beta variant of SARS-CoV-2) and AZD1222 (original vaccine expressing the Wuhan strain) as a 1-dose booster vaccination in previously vaccinated adult participants (either with AZD1222 or an mRNA vaccine) and also as a 2-dose primary vaccination schemes in previously unvaccinated adult participants. Based on the results from Clinical trial, the SmPC was updated to incorporate the use of AZD1222 as a homologous or heterologous (on subjects that received a primary's series of an mRNA vaccine) booster (EMA/H/C/005675/II/0052).

The new data from these studies demonstrated that the benefit risk balance of Vaxzevria remains unchanged.

3.4. Clinical safety

The MAH submitted the Addendum to the Clinical Overview (ACO), covering the period between 29 January 2021 and 31 May 2022.

3.4.1. Actions taken for safety reason

In April 2021, a contraindication for patients who have experienced major venous and/or arterial thrombosis in combination with thrombocytopenia following vaccination with any COVID-19 vaccine was added to the Company Core Data Sheet (CDS). Information was also added to Section 4.4 (Special warnings and special precautions for use) to inform health care professionals on this condition.

In November 2021, AstraZeneca updated the Vaxzevria CDS Section 4.4 (Warnings and precautions) to add new text regarding very rare events of cerebrovascular sinus thrombosis (CVST) to inform healthcare professionals that CVST and thrombosis with thrombocytopenia syndrome (TTS) require a different treatment approach and recommend that applicable guidance be consulted. Subsequently, AstraZeneca added CVST without thrombocytopenia as an Important potential risk in the Core risk management plan (RMP).

In response to impositions received from European Medicines Agency (EMA), Medicines and Healthcare Products Regulatory Agency (MHRA) and other health authorities, local market product information documents have been updated with:

- A contraindication for individuals with a known history of **Capillary Leak Syndrome (CLS)** and information that patients with an acute episode of CLS following vaccination require prompt recognition and treatment (June 2021) (EMA/H/C/005675/IAIN/0029)
- Information stating that if an individual has a history of a 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 (EMA/H/C/005675/IAIN/0048- October 2021). Also, Thrombocytopenia, including immune thrombocytopenia was added as an Important identified risk in the EU RMP for VAXZEVRIA as imposition.
- Information for healthcare professionals to be alert of Guillain-Barré Syndrome (GBS) (EMA/H/C/005675/IB/034-July 2021) and transverse myelitis (TM) (EMA/H/C/005675/IB0067- February 2022) signs and symptoms to ensure correct diagnosis, in order to initiate adequate supportive care and treatment, and to rule out other causes. In addition, GBS was added as an Important identified Risk in the EU RMP for Vaxzevria as imposition.

Following Health Authority Impositions Direct Healthcare Professional Communication (DHPC) letters were disseminated providing information on

- Risk of thrombocytopenia and coagulation disorders (March 2021)
- Thrombosis in combination with thrombocytopenia (April and June 2021)
- Contraindication in individuals with previous capillary leak syndrome (June 2021)
- Risk of thrombocytopenia (including immune thrombocytopenia) with or without associated bleeding (October 2021)

In the context of the recent PSUSA (EMA/H/C/PSUSA/00010912/202112) tinnitus, hypoaesthesia and paraesthesia have been added in section 4.8 of the SmPC.

3.4.2. Completed, ongoing and planned Clinical Studies

During the reporting period, 11 AstraZeneca or Oxford sponsored clinical trials were ongoing and 1 was completed. However, no additional efficacy or safety issues were identified to affect Benefit-Risk assessment till DLP 31 May 2022.

3.4.3. Non-interventional studies

No relevant safety information or information with potential impact on the benefit-risk or risk evaluations arose from AstraZeneca-sponsored non-interventional studies of Vaxzevria during the reporting period. Ongoing non-interventional studies did not yet collect sufficient data for concluding on an impact on the benefit risk of Vaxzevria.

Post authorisation safety studies (PASS) are currently ongoing including a pregnancy registry (C-VIPER consortium) and a study to evaluate the association between Vaxzevria and safety concerns of interest using secondary health data sources. Data made available are still preliminary.

Of note that the study on Enhanced active surveillance of adults in the UK was removed from the EU-RMP due to problems of recruitment. Preliminary results did not raise safety signal but the number of enrollees was limited.

Several other studies categories in the pharmacovigilance plan as category 1, category 2 and category 3 studies are ongoing as detailed in the RMP.

3.5. Safety signals

The MAH did not discuss safety signals issued during the reporting period. These signals were discussed through periodic safety update reports, summary safety reports (SSRs) or dedicated procedures.

3.5.1. Literature

Although a number of literature articles reviewed during the reporting period, no literature articles with new and significant safety findings relevant to Vaxzevria were identified. This is based on review of literature data as available during the reporting period as available from PBRER for periods 29 December 2020 to 28 June 2021 and 29 June 2021 to 28 December 2021 with additional literature review conducted post-Data Lock Point (DLP) of the last PSUR from 29 December 2021 till the DLP of this ACO (31 May 2022).

Publications of interest were discussed in the PSURs and in the SSRs. No new safety information from the literature was identified during the reporting period that could affect the benefit risk assessment.

Overall, literature supported increased risks of thrombotic events after vaccination, thrombocytopenia which are recognised adverse drug reactions in the product information. Literature findings were also helpful for the assessment of safety signals such as, most recently, Guillain-Barré Syndrome (recognised ADR in product information) or Corneal Graft Rejection (EPITT no: 19791, assessment ongoing at the time of the submission of this renewal). On 1st September 2022, PRAC agreed that a causal association between Vaxzevria and Corneal Graft rejection could not be established at this stage.

An epidemiological study based on data from French national databases (Epi-Phare; Botton et al 2022) suggested a slightly increased risk of pulmonary embolism and myocardial infarction following

vaccination with Vaxzevria. A cumulative review of the cases was under assessment at the end of the reporting period (May 2022) through a dedicated procedure (LEG 103). The assessment concluded that these safety endpoints should continue to be monitored but did not impact the benefit-risk balance of the vaccine.

3.5.2. Late breaking information

The evaluation of the validated signal of Tinnitus and based on the evaluation of currently available information from various sources, AstraZeneca considers that there is a reasonable possibility of a causal association between Vaxzevria and tinnitus, CDS (Version 19, dated 01 July 2022) Section 4.8 was updated to include 'tinnitus' as ADR. Tinnitus was included in Section 4.8 of the EU SmPC with the frequency of 'Uncommon' via procedure PSUSA/00010912/202112.

3.6. Pharmacovigilance inspections

The MAH did not provide any information on Pharmacovigilance inspections during the reporting period.

In October 2021, the Swedish Medical Product Agency (MPA) supervised a pharmacovigilance inspection (EMA/INS/PhV/312755/2021 – INS/PHV/2021/006). The inspection revealed no critical findings, 5 major and 2 minor findings. The major findings were related to the Safety Summary Reports, the handling of Individual Case Safety Reports (ICSRs) and adverse reactions, signal management, the Business Continuity Plan (BCP) testing and the pharmacovigilance training. The minor findings were related to the content of the Pharmacovigilance System Master File (PSMF) and the reconciliation between the complaint database and the safety database.

The MAH was recommended to evaluate their ability to process ICSRs in due time and with an appropriate assessment. The MAH was also strongly recommended to follow up the quality related to the pharmacovigilance processes and procedures. Regarding case reports in clinical studies, the MAH was recommended to use multiple categories for cases causality assessment (such as WHO-UCM system for standardized case causality assessment).

In response to this inspection, the MAH proposed corrective and preventative actions, that appear to adequately address the issues identified. MPA will further review the implementation and effectiveness of these actions.

The Inspectors concluded that special attention should be given to the quality of the handling of ICSRs considering the possible impact on the signal detection activities and safety summary reports. Other Inspections conducted in 2021 were discussed in the former renewal assessment. No inspection was conducted in 2022.

3.7. Discussion

The safety information collected since the previous renewal procedure (covering the period 29 January to 31 May 2021) does not modify the benefit risk profile of the vaccine. However, the risks of SARS-COV-2 infection and the context of treatment and prevention of the disease have evolved.

TTS and CVST, the key risks identified for Vaxzevria, are greater risks in young adults who benefit less from vaccination. This observation led to question the benefit risk balance in the younger population and for several EU Member States to restrict the use of the vaccine, especially after more alternative

vaccines were made available. Review of ongoing clinical trial data and post-marketing experience did not alter the overall positive benefit-risk profile of Vaxzevria that supported the last approval.

4. Risk management plan

No updated version of the RMP was submitted within this renewal procedure. The RMP version 5 has been submitted within procedure EMEA/H/C/005675/II/075 in order to:

- Update the table of safety concern: Reclassify 'anaphylaxis' as non-important safety concern;
- Update information on important identified, potential risks and missing information;
- Update the list of AESI;
- Update the pharmacovigilance plan (milestone, completed studies, etc.)

The assessment of procedure EMEA/H/C/005675/II/075 was ongoing at the time of the submission of this renewal application.

4.1. Risk evaluation

Table 3 - Summary of safety concerns – Vaxzevria RMP version 1.5 (Approval date 29-01-2021)

Risk category	Safety concern
Important identified risks	None
Important potential risks	<ul style="list-style-type: none"> • Nervous system disorder, including immune-mediated neurological conditions • Vaccine associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) • Anaphylaxis
Missing information	<ul style="list-style-type: none"> • Use during pregnancy and breastfeeding • Use in immunocompromised patients • Use in frail patients with co-morbidities (eg, 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

During the reporting period, the list of safety concerns in the EU-RMP was updated as follows:

- EU RMP Version 2: No update to safety concerns, Version 2 was created in order to update the characterisation of AZD1222 safety concerns with the key data from the primary analysis (data cut-off [DCO] date of 07 December 2020) of the pivotal clinical studies in the ongoing AZD1222 clinical development programme
- EU RMP Version 3: The list of safety concerns was updated to add a new important identified risk of 'Thrombosis with thrombocytopenia syndrome' and a new important potential risk of 'Thrombosis'. The existing important potential risk of 'Anaphylaxis' was re-categorised as an important identified risk
- EU RMP Version 4: The list of safety concerns was updated to add a new important identified risk of 'Thrombocytopenia, including immune thrombocytopenia' and 'Guillain-Barré syndrome'

- EU RMP Version 5: The important identified risk "Anaphylaxis" was reclassified as non-important and removed from the list of safety concerns at the request of EMA

Table 4 - Summary of safety concerns – Vaxzevria RMP version 5.1 (EU submission 31-03-2022, procedure EMEA/H/C/005675/II/075)

Risk category	Safety concern
Important identified risks	<ul style="list-style-type: none"> • Thrombosis with thrombocytopenia syndrome • Thrombocytopenia, including immune thrombocytopenia • Guillain-Barré syndrome
Important potential risks	<ul style="list-style-type: none"> • Thrombosis • Nervous system disorder, including immune-mediated neurological conditions • Vaccine associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)
Missing information	<ul style="list-style-type: none"> • Use during pregnancy and breastfeeding • Use in immunocompromised patients • Use in frail patients with co-morbidities (eg, 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

Safety information on risks and new information from the clinical trials and post-marketing experience will be described in detail in the upcoming PBRER (DLP 28 June 2022).

5. Changes to the Product Information

The Annexes I, II and III were amended to reflect the granting of a marketing authorisation not subject to Specific Obligations for Vaxzevria. The MAH took the opportunity to implement other minor administrative updates (see Attachment 1).

6. Overall conclusions and benefit-risk balance

6.1. Specific Obligations (SOBs)

Compliance of SOB data submitted

During the period covered by this annual renewal data on the SOBs have been submitted that overall are compliant in terms of adherence to deadlines and are compliant in terms of acceptability of data submitted.

Quality

Two Specific Obligations were raised at the time of the conditional authorization. The due date established for Specific Obligations at the time of the conditional authorization was December 2021

with interim monthly updates beginning February 2021, for SO1 (SO13), and June 2022 with interim monthly updates beginning February 2021, for SO2 (SO14). Some points of these SO have been updated after the assessment of Type IB variations in the context of approved PAMCs to include additional manufacturing sites.

During the period covered from the conditional authorization to the first annual renewal, SO1 c, e and f and RECs 1, 5, 6, 8, 9, 10, 11, 15, 20, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 35 and 53 and legally binding LEG002 were fulfilled.

During the period covered by this annual renewal, data on Quality Specific Obligations (SO) and Recommendations (REC) have been monthly provided. Specific Obligation SO13 and quality related recommendations 1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 35, 36, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 66, 67, 68, 69 and 71 are fulfilled. SO14 is still ongoing.

By variation II-74 (June 2022), Annex IIE was updated to remove the specific obligation relating to provision of process validation data for the active substance and finished product (SO13-1a and SO13-1b) which has been fulfilled, and to change the date of the specific obligation relating to the provision of additional information on stability of the active substance and finished product (and review the finished product specifications following further manufacturing experience) from June 2022 to January 2023 (SO14). The change in date was agreed as stability studies were ongoing and further data from these studies are expected to be submitted in due course. This remaining quality SOB (SOB 014) may be reclassified as a REC. This specific obligation regarding stability data was raised because, at the time of the conditional authorisation, in order to ensure consistent product quality, there was a need for additional stability data from all manufacturing sites to support the shelf life granted, both for the active substance and for the finished product. The Company has been providing stability data in monthly updates indicating that product stability is guaranteed for the approved shelf life.

SO13-1a: The applicant should provide specific dates for data completion for each site as follows: for current pre-process performance qualification (PPQ) and PPQ active substance (AS) batches, additional test release and characterisation data as well as new results for the degradation stability studies should be completed for Catalent Maryland, MD, US; Oxford Biomedica, Oxford, UK and Henogen S.A., Seneffe, BE to confirm that the process is properly validated.

SO13-1b: The applicant should provide specific dates for data completion for each site as follows, including for PPQ batches to be manufactured: complete final PPQ validation reports and comparability analysis (for three AS batches) must be performed for Henogen, Rue de la Marlette, Seneffe, BE; Catalent, 7555 Harmans Road, Maryland, USA; Oxford Biomedica, Alec Issigonis Way, Oxford, UK; Halix, Tinbergenweg 1 2333 BB, Leiden, NL; SK Bioscience Co Limited, 150, Saneopdanji-gil, Pungsan-eup, Andong-si, Gyeongsangbuk-do, Republic of Korea; and WuXi Biologics Co., Ltd, 108 Meiliang Road, Mashan, Binhu District, WuXi, Jiangsu 214092, China active substance manufacturing sites. Complete batch release and analytical comparability data (including degradation trend comparison) for PPQ batches should be presented to confirm that the process is properly validated and to demonstrate that the commercial AS is representative of the material used in clinical trials.

SO13 a and b were already removed from Annex II by variation II-74 (June 2022).

Non-clinical

There were no non-clinical SOBs to be addressed for this annual renewal. Non-clinical ANX, LEGs and RECs have been fulfilled during the period covered by this annual renewal (assessed in variation EMEA/H/C/005675/II/17/G and EMEA/H/C/005675/II/31). There are no outstanding issues regarding the non-clinical assessment.

Clinical

During the period covered by this renewal the primary analysis for SOB 019 and SOB 020 were submitted in procedures EMA/H/C/005675/II/0002 and EMA/H/C/005675/II/0026, respectively. Both aspects of the respective SOBs are considered fulfilled. It is noted that neither these two SOBs nor the rest of clinical SOBs (SOB15, SOB16, SOB17, and SOB18) have been fully fulfilled during the time period covered by this annual renewal.

SOBs 015, SOB 016, SOB 017 and SOB 018 are currently ongoing, where final CSR submission is due on 31 December 2022. It is noted that in the list of SOBs adopted at the time of the MA, final clinical study reports for SOB 015, SOB 016, SOB 017, SOB 018 and for the final analysis from the pooled pivotal studies were due for 31 December 2022. However, following the request from the MAH (EMA/H/C/005675/IB/0069), the due dates were amended to 31 December 2022.

Overall, it is agreed with the MAH that the data collected as part of the specific obligations for Vaxzevria during the period covered by this renewal support its positive benefit-risk balance for the approved indication.

Currently the only outstanding information in relation to the original SOBs is the final CSR from individual studies COV001, COV002, COV003, COV005, and D8110C00001, as well as the final analysis from the pooled pivotal studies (efficacy analysis from trials COV002 and COV003, and a pooled safety analysis based on all four trials COV001, COV002, COV003, and COV005). The MAH has asked for renewal of the current CMA.

It is not expected that the remaining outstanding data in the final CSRs will bring substantial additional confirmatory evidence impacting the benefit-risk profile of Vaxzevria in its current indication. It is considered that the current conditional marketing authorization could be converted into a standard marketing authorization. The remaining clinical SOBs may therefore be reclassified as Category 3 studies in the RMP, with the final CSRs to be submitted at the agreed due date as supportive data.

As part of this annual renewal, the CHMP is of the opinion that the SOBs 015, 016, 017, 018, 019 and 029 can therefore be deleted from Annex II. The RMP will be updated accordingly at the next regulatory opportunity.

Updated list of specific obligations (SOBs)

The CHMP is of the opinion that the comprehensive existing data package for this vaccine warrants conversion of the current conditional approval into a full marketing authorisation. Nevertheless, as depicted in the below table, the final study reports for ongoing clinical trials shall be submitted by the MAH according to the agreed due dates.

Number	Description	Due date
SOB 019	In order to confirm the efficacy and safety of VAXZEVRIA, the MAH should provide the primary analysis (based on the 7th December 2020 data cut-off (post data-base lock) and final analysis from the pooled pivotal studies.	Final pooled analysis 31 December 2022
SOB 020	In order to confirm the efficacy and safety of VAXZEVRIA in the elderly and subjects with underlying disease, the MAH should submit the overview and summaries of the primary analysis and final clinical study report for study D8110C00001.	Final CSR 31 March 2024

Number	Description	Due date
SOB 015 / SOB 016 / SOB 017 / SOB 018	In order to confirm the efficacy and safety of VAXZEVRIA, the MAH should submit the final Clinical Study Reports for the randomised, controlled, COV001, COV002, COV003 and COV005.	Final CSRs 31 December 2022
SOB 014	In order to ensure consistent product quality, the applicant should provide additional information on stability of the active substance and finished product and review the finished product specifications following further manufacturing experience.	January 2023 with interim monthly updates beginning February 2021

The data available concerning Vaxzevria is considered comprehensive; therefore, the CHMP is of the view that the six remaining clinical Specific Obligations may be reclassified as category 3 studies in the RMP at the next regulatory opportunity and final CSRs should be submitted as supportive data. It is proposed to re-classify quality SOB 014 from a specific obligation to a recommendation. In addition, it is considered that it is not necessary to receive interim monthly updates, a single report on the due date being sufficient.

6.2. Benefit-risk Balance

During the period covered by this annual renewal, new data have emerged. However, these data do not have an impact on the benefit-risk of Vaxzevria in the approved indication.

The data collected as part of the specific obligation(s) for Vaxzevria during the period covered by this annual renewal supported its positive benefit-risk balance in the approved indication(s).

Favourable effects

The favourable effects were demonstrated in the initial marketing authorisation for individuals 18 years of age and older.

Since the last renewal, the following type II variations have been submitted and assessed by CHMP:

-The primary analysis for SOB 019 (study to confirm the efficacy and safety of Vaxzevria from the pooled pivotal studies COV001, COV002, COV003 and COV005) was submitted (EMA/H/C/005675/II/0002) with resolution of the primary analysis obligation on 24 June 2021. The new data included additional immunogenicity data and a small number of additional COVID-19 cases as compared to the analysis made at the time of the MA. The new data did not modify the efficacy and the safety conclusions, nor the original positive benefit risk as determined at the time of the conditional MA.

- The primary analysis for SOB 020 (to confirm the efficacy and safety of Vaxzevria in the elderly and subjects with underlying disease from clinical trial D8110C00001) was submitted (EMA/H/C/005675/II/0026) with obligation resolution on 15 October 2021. Study D8110C00001 is a Phase III randomized, double-blind, placebo-controlled multicenter study in adults to determine the safety, efficacy, and immunogenicity of two doses of AZD1222 given with a 4-week time interval for the prevention of COVID-19. The trial was carried out in the US, Chile and Peru. The Vaccine efficacy determined against COVID-19 symptomatic illness that occurred ≥ 15 days post second dose of study intervention was 73.9% (95%CI: 65.3 - 80.4), a VE which was in line with that described when MA

was granted. High VE estimate was also determined in participants ≥ 65 years of age [VE: 83.5% (95%CI: 54.1 - 94.0)], and these results provided evidence of VE in this old population, an important result that was lacking at the time CMA was granted, since the pivotal trials included a small number of subjects ≥ 65 yoa. Moreover, participants with one or more comorbidities who received Vaxzevria (≥ 15 days post dose 2) had an efficacy of 75.2% (95% CI: 64.2; 82.9) and participants without comorbidities had a vaccine efficacy of 71.8% (95% CI: 55.5, 82.1). Changes in the SmPc were incorporated to describe the results from the clinical trial D8110C00001.

-The results from clinical trial D7220C00001, which evaluated the safety and immunogenicity of a 1-dose booster vaccination of Vaxzevria in previously vaccinated adult participants (either with AZD1222 or an mRNA vaccine), was assessed in procedure EMEA/H/C/005675/II/0052; May 2022. The efficacy of an homologous and heterologous booster (participants who had previously received primary vaccination with an mRNA vaccine) was demonstrated in terms of immunogenicity. Based on the results from this Clinical trial, the SmPC was updated to incorporate the use of AZD1222 as a homologous or heterologous (on subjects that received a primary series of an mRNA vaccine) booster.

Thus, the vaccine efficacy has been confirmed and updated with the results of clinical studies that were not available at the time of the initial marketing authorisation.

Uncertainties and limitations about favourable effects

Remaining uncertainties are the same raised at the time the conditional MA was granted. On the one hand, protection conferred to certain risk groups (such as immunocompromised subjects and pregnant women) is unknown, and on the other hand, comprehensive data on protection (and duration of protection) achieved against new variants of SARS-CoV-2 is lacking.

Unfavourable effects

The safety profile for the primary vaccination series were defined in the initial marketing authorization based on the pooled safety data for the studies COV001, COV002, COV003 and COV005 (data cut-off 4th Nov 2020) and in the procedure EMEA/H/C/005675/II/0002 that updates the primary analysis of the pooled studies to cut-off date 7th Dec 2020. In addition, the safety profile for the primary vaccination was evaluated in the procedure EMEA/H/C/005675/II/0026 with the primary analysis of the study D8110C00001 conducted in United States, Peru and Chile.

Overall, most of the local and systemic AEs following AZD1222 were mild or moderate and self-limiting. The most frequently reported adverse events (within 7 days after any vaccination) are injection site tenderness, injection site pain, headache, fatigue, myalgia, malaise, chills, arthralgia and nausea. The incidences of reported adverse events were less frequent after the second dose than after the first dose of AZD1222. In addition, the adverse events were reported in adults aged ≥ 65 less frequently than in adults aged 18-64 and higher incidences were observed in females than in males.

Moreover, some AEs such as Transverse Myelitis, Thrombosis with thrombocytopenia Syndrome, Cerebrovascular venous and sinus thrombosis without thrombocytopenia, Guillain-Barre syndrome, Capillary leak syndrome and anaphylaxis were included as ADR in the SmPC with frequencies not known or very rare as a consequence of the post marketing use of Vaxzevria for primary vaccination.

The safety profile of the booster dose of AZD1222 (homologous and heterologous) was evaluated in the procedure EMEA/H/C/005675/II/0052 based on interim analysis from the study D7220C00001. The reactogenicity profile of the booster dose was similar and not different to the known reactogenicity described for AZD1222. However, higher frequencies of adverse events were observed after the booster dose in the heterologous regimen than in the homologous one. In line with what was observed

with the primary vaccination series, the incidences of the adverse events were lower in adults aged \geq 65 years than younger adults and higher in females than in males.

In summary, the safety of the vaccine has been confirmed and updated with the results of clinical studies and post marketing experience generated since the the initial marketing authorisation.

Uncertainties and limitations about unfavourable effects

The uncertainties and limitations of unfavourable effects have been discussed in other procedures. The principal uncertainties are related to long-term effects, interactions with other vaccines and effects in specific risk groups.

Regarding the booster dose, there were no data from participants aged <30 years in the study D7220C00001. However, it is to be expected that the reactogenicity pattern after a booster dose will be similar between subjects aged 18-29 years and subjects ≥ 30 years, with the exception of the frequencies profile, since it is known that the reactogenicity decreases with the age. In addition, it is not possible to determine the risk of several rare severe adverse reactions associated with the use of AZD1222, such as capillary leak syndrome, cerebrovascular venous and sinus thrombosis, myelitis transverse and thrombosis with thrombocytopenia syndrome after AZD1222 booster dose, especially in previously mRNA-vaccinated subjects who will receive AZD1222 vaccine for the first time.

Benefit-risk assessment and discussion

The benefits of Vaxzevria in terms of protection against COVID-19 outweigh the risks associated with vaccination. Although new data has emerged during this last year, these new data does not change the positive B/R balance in the approved indication.

Balance of benefits and risks

Based on the cumulative evidence in terms of favourable and unfavourable effects, the benefit-risk profile of Vaxzevria remains positive.

Scientific grounds for recommending the granting of a marketing authorisation not subject to specific obligations

Quality

The remaining quality SOB (SOB 014) may be reclassified as a REC.

This specific obligation regarding stability data was raised because, at the time of the conditional authorisation, in order to ensure consistent product quality, there was a need for additional stability data from all manufacturing sites to support the shelf life granted, both for the active substance and for the finished product. The Company has been providing stability data in monthly updates indicating that product stability is guaranteed for the approved shelf life. Concurrently, there is a variation (IB 81) under evaluation to extend the shelf-life of the finished product, Vaxzevria Suspension for Injection, as packaged for sale, from 6 months to 9 months when stored at 2-8°C. This variation concluded positively on 7th October 2022.

Non-clinical

There are no non-clinical SOBs to be addressed.

Clinical

During the reporting period, there were 11 ongoing clinical trials and 1 was completed. As of 31 May 2022 approximately 60518 study participants enrolled in AZD1222 Clinical Development program had received at least one dose of VAXZEVRIA.

Vaxzevria has been approved in 93 countries. Cumulatively, a total of 2.08 billion doses of Vaxzevria have been delivered to the EU and other 24 countries and, as of 31 May 2022, more than 2.828 billion vaccine doses have been administered globally.

The overall benefits of VAXZEVRIA in the prevention of COVID-19 with robust efficacy overall, in a wide array of subgroups, including adults ≥ 65 years of age and persons with at least one comorbidity at enrolment, and in the prevention of severe/critical COVID-19 illness and COVID-19 related emergency department visits and deaths continue to outweigh risks from adverse drug reactions, including the very rare risk of thrombosis in combination with thrombocytopenia identified through post-marketing safety reports.

The current analysis of the benefit-risk profile incorporates an evaluation of the information that became available during the reporting period. The benefits of vaccination with VAXZEVRIA as 2-dose primary series and a booster dose is demonstrated in clinical studies and real world evidence. The safety profile of VAXZEVRIA continued to evolve during the reporting period with availability of safety information in the post-marketing setting.

In conclusion, the initial MA established the positive benefit-risk profile of Vaxzevria in adults 18 years of age and older, and additional CT data as well as Pharmacovigilance information together with post-authorization effectiveness studies corroborate the positive B/R for this vaccine. The VAXZEVRIA product information is up to date with current scientific knowledge, taking into account any proposed updates to the SmPC, package leaflet, labelling and RMP.

According to the Guideline on the conditional MA (EMA/CHMP/509951/2006, Rev.1), section 6. MA not subject to SOB: "When the specific obligations have been fulfilled, the CHMP may, in accordance with Article 7 of Commission Regulation (EC) No 507/2006, adopt an opinion recommending the granting of a marketing authorisation in accordance with Article 14(1) of Regulation (EC) No 726/2004 ('marketing authorisation not subject to specific obligations'). This can be done at the time of renewal of the conditional marketing authorisation or at the time of assessment of the data submitted to fulfil the last remaining specific obligation."

Therefore, the efficacy and safety of Vaxzevria has been comprehensively characterized, both with data from CT and from Real World Evidence, and the currently pending information in relation to the original SOBs is the final CSR from individual studies COV001, COV002, COV003, COV005, and D8110C00001, as well as the final analysis from the pooled pivotal studies (efficacy analysis from trials COV002 and COV003, and a pooled safety analysis based on all four trials COV001, COV002, COV003, and COV005). The MAH has asked for renewal of the current CMA. However, the final CSRs still pending are not expected to change the positive benefit/risk of this vaccine and therefore, it is considered that the current conditional approval could be converted into a full marketing authorization. Due to the transformation into a full MA, these previous SOBs should be reclassified as category 3 studies in the RMP and the final study reports for the ongoing clinical trials shall be submitted by the applicant according to the given due dates.

Overall, taking into account that the quality and clinical data submitted by the MAH during the period covered by this annual renewal do not change the benefit/risk balance of the vaccine in the approved indication all SOBs can be removed from Annex II. The remaining quality SOB can be re-classified as a REC and the remaining clinical SOBs can be reclassified as category 3 studies in the RMP. Therefore, the current CMA can be converted to a full marketing authorization.

7. Recommendations

Based on the review of the available information on the status of the fulfilment of Specific Obligations, the benefit-risk balance for Vaxzevria in its approved indication(s) (please refer to the Summary of Product Characteristics) continues to be favourable and all specific obligations have been fulfilled or re-classified as RMP category 3 or REC, and therefore the granting of a marketing authorisation no longer subject to specific obligations is recommended, subject to the conditions and obligations as detailed in this assessment report.

Amendments to the marketing authorisation

The Annexes I, II and III to the current marketing authorisation for the above-mentioned medicinal product were amended to reflect the granting of a marketing authorisation no longer subject to Specific Obligations for Vaxzevria and to implement other minor administrative updates.

The renewal requires no amendments to the terms of the marketing authorisation.

Conditions of the marketing authorisation

The marketing authorisation is subject to the following conditions:

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
In order to ensure that all reported thrombotic events with thrombocytopenia and/or bleeding events are investigated by performing an in-depth exploration of platelet function in the interventional study in immunocompromised subjects, the MAH should submit the clinical study report, in accordance with a revised and agreed study protocol.	30 November 2023

PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.