EMA/622071/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report on the annual renewal of the conditional marketing authorisation

Vaxzevria

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

Procedure no.: EMEA/H/C/005675/R/0037

Note

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

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure:	16 Aug 2021	16 Aug 2021
☐	CHMP and PRAC Rapporteurs Joint Assessment Report	14 Sep 2021	14 Sep 2021
☐	CHMP and PRAC members comments	20 Sep 2021	20 Sep 2021
☐	Updated CHMP and PRAC Rapporteurs Joint Assessment Report	23 Sep 2021	23 Sep 2021
☐	PRAC endorsed relevant sections of the assessment report	30 Sep 2021	30 Sep 2021
☒	Opinion	14 Oct 2021	14 Oct 2021

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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 23 July 2021 an application for renewal of the conditional MA for Vaxzevria. The expiry date of the MA is 29 January 2022.

The period covered by this annual renewal is 29 January to 31 May 2021.

2. Specific Obligations

2.1. Specific Obligations adopted by the CHMP at the time of the initial marketing authorisation

Table 1: Specific Obligations adopted by the CHMP at the time of the initial marketing authorisation

Number	Description	Due date
SOB 013	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.	December 2021 with interim monthly updates beginning February 2021
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.	June 2022 with interim monthly updates beginning February 2021
SOB 015 SOB 016 SOB 017 SOB 018	In order to confirm the efficacy and safety of COVID-19 Vaccine AstraZeneca, the MAH should submit the final Clinical Study Reports for the randomised, controlled, COV001, COV002, COV003 and COV005.	31 May 2022
SOB 019	In order to confirm the efficacy and safety of COVID-19 Vaccine AstraZeneca, the MAH should provide the primary analysis (based on the 7th December data cut-off (post data-base lock) and final analysis from the pooled pivotal studies.	Primary analysis: 5 March 2021 Final pooled analysis: 31 May 2022
SOB 020	In order to confirm the efficacy and safety of COVID-19 Vaccine AstraZeneca 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

At the time of MA, further granularity was provided in the CHMP assessment report for each of the Quality SOBs adopted in Annex II. This granularity and the status of each of the SOB can be in section 2.2.

2.2. Outstanding Specific Obligations – status report for period covered

During the reporting period, the quality specific obligations were partially fulfilled. As a result of specific variations to introduce additional sites, these detailed SOBs were further updated. The table below gives the detailed SOBs at the time of renewal and describes where the SO has been partially completed.

Table 2: Full list of SOBs as adopted with the initial marketing authorisation

Number	Description	Status
SOB 13	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. **Active substance** a. 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. Responses to be provided no later than December 2021 with interim, monthly updates beginning February 2021. b. 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 Catalent Maryland, Inc.; Henogen S.A.; and Oxford Biomedica (UK) Ltd. 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. Responses to be provided no later than December 2021 with interim, monthly updates beginning February 2021. **Finished product** *c. The applicant should provide the final FP comparability data and analysis for CP Pharmaceuticals and Catalent Anagni-to demonstrate that the commercial product is representative of the product used in clinical trials. Responses to be provided no later than February 2021.* d. The applicant should provide the pending results and final PPQ reports of the three FP process performance qualification lots (including CPP; IPC and NCPP) manufactured at IDT Biologika ,CP Pharmaceuticals and Catalent Anagni and update section P.3.5.2.1 to confirm that the process is properly validated. Responses to be provided no later than March 2021. *e. The applicant should provide the final results for the additional FP in process testing performed as part of the process validation* specifically at Catalent Anagni and CP Pharmaceuticals, (AS post-shipping and thawing studies, mixing test studies, hold test studies and product homogeneity) to confirm *that the process is properly validated. Section P.3.5.2.1. should be updated. Responses to be provided no later than March 2021.* *f. The applicant should introduce an enhanced sampling strategy for the FP filing process at* all sites, at the beginning, at 25%, 50%, 75% and 100% of the filling process *no later than Feb 2021 in order to confirm*	Ongoing (December 2021 with interim monthly updates beginning February 2021.) SOB 13a-ongoing SOB 13b-ongoing SOB 13c-fulfilled SOB 13d-ongoing SOB 13e-fulfilled SOB 13f-fulfilled

Number	Description	Status
	batch to batch consistency. At least 2 vials per sample should be tested using a rapid test capable of providing sufficient assurance of batch homogeneity i.e. measured by absorbance. For this test the applicant should set justified acceptance criteria for homogeneity and the batch results should meet these.	
SOB 14	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. **Active substance** a. The applicant should provide additional AS stability data and analysis to confirm the storage period. This includes data following storage at -90 to -55°C, 2-8°C and 23-27°C/55-65% RH storage conditions for (Process 3 and 4) Pre-PPQ lots and for 3 PPQ lots manufactured at each AS commercial site. Updates should be provided upon availability of data for 3, 6 and 12 months and completion of the study. Responses to be provided no later than May 2022 with interim, monthly updates beginning February 2021. **Finished product** b. The applicant should provide additional finished product (FP) stability data to confirm the storage period with process 4 lots from all FP manufacturing sites and all requested FP configurations (FP presentations). Process 4 PPQ stability study updates should be provided post approval upon availability of data for 3, 6 and 12 months and completion of the study. Responses to be provided no later than June 2022 with interim, monthly updates beginning March 2021. c. The applicant should recalculate the rate of average loss of infectivity during FP storage at 2-8ºC when further stability data of three PPQ batches from each commercial site becomes available. If necessary, the release specification should be changed in order to ensure that batches will remain within shelf life specification during storage and handling. The applicant should report the recalculation periodically until sufficient data are available to fully justify the release specification. Responses to be provided no later than December 2021 with interim, 3-monthly updates beginning May 2021. **d.** The applicant should provide additional clinical justification for the end of shelf life FP infectivity specification. Additional immunogenicity data from clinical studies for participants primed and boosted with a Low Dose (LDLD), as well as a characterisation of breakthrough cases, i.e. the infectivity characteristics of the batches with which these individuals were immunised, should be evaluated as soon as available. Responses to be provided no later than September 2021.	Ongoing (June 2022 with interim monthly updates beginning February 2021) SOB 14a-ongoing SOB 14b-ongoing SOB 14c-ongoing SOB 14d-ongoing
SOB 015 SOB 016 SOB 017 SOB 018	In order to confirm the efficacy and safety of COVID-19 Vaccine AstraZeneca, the MAH should submit the final Clinical Study Reports for the randomised, controlled, COV001, COV002, COV003 and COV005.	31 May 2022
SOB 019	In order to confirm the efficacy and safety of COVID-19 Vaccine AstraZeneca, the MAH should provide the primary analysis (based on the 7th December data cut-off (post data-base lock) and final analysis from the pooled pivotal studies.	Primary analysis: 5 March 2021 *Fulfilled* Final pooled analysis: 31 May 2022 *Pending*
SOB 020	In order to confirm the efficacy and safety of COVID-19 Vaccine AstraZeneca in the elderly and subjects with underlying disease, the	Primary analysis: 30 April 2021

Number	Description	Status
	MAH should submit the overview and summaries of the primary analysis and final clinical study report for study D8110C00001.	*Fulfilled* Final CSR: 31 March 2024 *Pending*

Quality

Two specific obligations (SOB) were established at the time of the conditional marketing authorisation. After that, some points in SOB 013 and 014 were updated as a consequence of variations, some of them to add new manufacturing sites. The MAH is sending monthly updates. SOB 013 c, e and f are considered solved.

Clinical

Since the granting of the conditional MA, the MAH has submitted the following primary analyses regarding SOBs 019 and 020:

SOB 019: Pooled data from the four trials (COV001, COV002, COV003, and COV005) at data cut-off date of 07 December 2020

Within this type II variation, the MAH provided the pooled efficacy analysis of the four trials, since trials COV001 and COV005 had reached the predefined criterion (having at least 5 cases of COVID-19 lab confirmed disease) for being included in the pooled efficacy analysis. Regarding safety data, the MAH submitted the pooled data from the four trials but at data cut-off date of 07 December 2020 (DCO2). The results from DCO2 resulted in an update of the safety profile of Vaxzevria in section 4.8 of the SmPC. The following adverse drug reactions (ADR) were added with their respective frequency: abdominal pain (uncommon), urticaria (uncommon), pain in extremity (common), influenza-like illness (common), asthenia (common) and lethargy (uncommon). Based on the data reviewed at the DCO02, the benefit-risk profile of Vaxzevria has been shown to be consistently favourable, over two data cut-offs, for the proposed indication in adults from age 18 years and older, including adults from age 65 years and above, as well as those with comorbidities. CHMP issued a positive opinion on 24 June 2021 in procedure EMEA/H/C/005675/II/0002.

CHMP assessment comment

It follows a summary of the assessment of this variation for which CHMP issued a positive opinion on 24 June 2021 in procedure EMEA/H/C/005675/II/0002.

The clinical data on which the CMA for Vaxzevria was granted came from 4 studies: COV001 (Phase I/II); COV002 (Phase II/III); COV003 (Phase II/III) and COV005 (Phase I/II). The CMA was granted based on a pooled efficacy analysis from trials COV002 and COV003, and a pooled safety analysis based on all four trials. Efficacy data from the interim pooled efficacy analysis (DCO1, 04 November 2020) have previously been submitted in the initial marketing authorisation application (MAA). During assessment of that MAA, pooled efficacy data from trials COV002 (UK) and COV003 (Brazil) (at data cut-off date of 07 December 2020 -DCO2) were also submitted by the MAH and these data were the basis on which the CHMP granted a positive opinion for a CMA. These data were also the main data stated in the SmPC. Regarding safety, at the time of granting a CMA, the data analysed were from a pooled analysis of the 4 University of Oxford-sponsored studies COV001 (UK), COV002, COV003, and COV005 (South Africa) at DCO1.

The MAH provided under variation II/0002 the pooled efficacy analysis of the four trials, since trials COV001 and COV005 reached the predefined criterion for being included in the pooled efficacy

analysis. Regarding safety data, the MAH submits the pooled data from the four trials but at data cut-off date of 07 December 2020 (DCO2).

The efficacy analysis described in that variation incorporated data from trials COV001 and COV005. It is noted that trials COV001 and COV005 contributed each with only five COVID-19 cases (2 and 8 cases in the AZD1222 (Vaxzevria) and in the control group, respectively). As expected from the few new cases incorporated, the estimates of vaccine efficacy (VE) determined (for primary and secondary endpoints) when using the pooled data from the four trials are very similar to those obtained when considering only the trials COV002 and COV003.

The immunogenicity analysis submitted included 841 additional subjects that are added to the data from 2,871 subjects submitted at DC01. These new data from more than 800 subjects did not modify the conclusion reached at the time of the CMA was granted.

In conclusion, in relation to the vaccine efficacy analysis the data submitted in variation II/0002 corresponding to the pooled efficacy analysis of four clinical trials (COV001; COV002; COV003 and COV005) do not change the conclusions reached at the time the CMA was granted.

The safety update presented (as of the data cut-off date of 7th December 2020) modestly extends both the size and long term follow up of the safety database (initial cut-off 4th November 2020). It included 12,282 subjects in the AZD1222 group (+261 subjects) and 11,962 in the control group. The proportion of subjects who had received both vaccine doses increased from approximately 55% of the pooled data set population up to 85.1% and 85.3% in AZD1222 and control group, respectively. In addition, in this DCO2 allowed for a median follow-up of > 2 months after the second dose. As it can be expected, demographics and baseline characteristics do not differ substantially from those of the initially submitted set of data and were well balanced among treatment groups. Most of the participants were adults aged 18 to 64 (90.6%), only 9.4% of participants age 65 or older.

As a consequence of the small increase of the database, overall frequencies of either solicited local and systemic adverse events (AEs), unsolicited AEs, serious AEs and adverse events of special interest (AESI) presented remained barely unchanged compared to those initially provided. No new unexpected safety findings have been identified based on the data cut-off date as of 7th December 2020, however new ADR were added to the SmPC: abdominal pain (uncommon), urticaria (uncommon), pain in extremity (common), influenza-like illness (common), asthenia (common) and lethargy (uncommon).

In relation to this SOB 019, it is still pending the submission of the final analysis from the pooled pivotal studies and the final clinical study reports, which are due by 31 May 2022.

SOB 020 Study D8110C00001 - Phase III randomised, double-blind, placebo-controlled, multicentre study assessing the safety, efficacy, and immunogenicity of AZD1222 compared to saline placebo for the prevention of COVID-19 conducted in the USA, Chile, and Peru.

This study report on the primary efficacy analysis was submitted on 31 May 2021 and it has been assessed within procedure II/0026.

Study D8110C0001 is a 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 in adults ≥ 18 years of age who are healthy or have medically stable chronic diseases and are at increased risk for SARS-CoV-2 acquisition and COVID-19. All participants will remain on study for 2 years following administration of first dose of study intervention (Day 730).

The primary efficacy analysis for study D8110C0001 was submitted on 31 May 2021. These results confirm the efficacy, immunogenicity and safety of Vaxzevria in 32,379 participants 18 years of age or older, of whom 19,179 (59.2%) had one or more pre-existing comorbidities and 7,238 (22.4%) were

≥65 years of age at enrolment.

CHMP assessment comment

It follows a summary of the assessment of this variation.

The EMEA/H/C/005675/II/0026 variation focused on assessing the data from trial D8110C00001. The trial was carried out in the US, Chile and Peru. In this trial, a time interval of 4 weeks between doses was selected whereas this period varied between 4 and 12 weeks according to the pooled efficacy data on which the CMA was granted.

The applicant has assessed the humoral immunogenicity in a subset of 3,000 participants. The submitted data are enough to conclude that Vaxzevria induces a strong immune response against the S protein, which response is in line with the data reflected in the EPAR. This is also in line with data observed in the phase I/II study in Japan (D8111C00002) (assessed in variation EMEA/H/C/005675/II/0019).

The Vaccine efficacy determined against COVID-19 symptomatic illness that occur ≥15 days post second dose of study intervention was 74.0% (95%CI: 65.3 – 80.5). Importantly high VE estimate was determined both in participants ≥18 to <65 years of age [VE: 72.8% (95% CI: 63.4 – 79.9)] and in participants ≥65 years of age [VE: 83.5% (95%CI: 54.2 – 94.1)]. This result is relevant in the clinical data did not allow an estimate of vaccine efficacy in subjects over 55 years of age at the time of the CMA.

The cumulative incidence curve of the time to first case of SARS-CoV-2 Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) positive symptomatic COVID-19 occurring ≥15 days post second dose of study showed separation of the curve for the Vaxzevria group from the placebo group at around 15 days post second dose that continues to diverge over time. This result was in line with that from the pooled efficacy analysis that was the basis for granting the CMA.

Robust efficacy was observed regardless of age, gender, and ethnicity. With respect to comorbidities, the VE estimates were similar to the overall population for participants with 1, 2 or ≥3 comorbidities, and no differences were observed among the comorbidity by age category subgroups.

A total of 8 severe COVID-19 cases were observed in the placebo group and none in Vaxzevria group, a result which indicates VE against severe disease.

In conclusion, the results from study D8110C00001 are robust and show a significant VE of Vaxzevria against symptomatic COVID-19 disease (regardless of severity) and also against severe disease.

The safety evaluation of Vaxzevria vaccine in study D8110C00001 (data cut-off 5th March 2021) was performed on 32,379 participants (21,587 participants in the Vaxzevria group and 10,792 in the placebo group). The majority of participants received a two-dose regimen.

Overall, the observed safety profile in study D8110C00001 is in line with the results of the pooled University of Oxford studies submitted in the CMA (data cut-off 4th Nov 2020) and in the variation EMEA/H/C/005675/II/0002 (data cut-off 7th Dec 2020 [SOB 019]) and remain as favorable. Less frequently solicited AEs were reported after the second dose than after first dose of Vaxzevria. However, no difference in the incidences of unsolicited AEs after first and second dose was observed. In addition, solicited and unsolicited AEs were reported less frequently in adults aged ≥65 than in adults aged 18-64 and higher incidences of solicited and unsolicited AEs were observed in females than males.

No related deaths were reported during the study. The incidence of SAEs and AESIs was low and no clinically meaningful imbalances were observed except for facial paralysis and muscle spasms, no other

safety concern was identified. No thrombosis with thrombocytopenia syndrome (TTS) events were reported during the study.

Overall, the observed safety profile in study D8110C00001 is in line with the results of the pooled University of Oxford studies submitted in the CMA (data cut-off 4th Nov 2020) and in the variation EMEA/H/C/005675/II/0002 (data cut-off 7th Dec 2020 [SOB019]) and remain as favorable . This study has been assessed within variation EMEA/H/C/005675/II/0026 (SOB).

2.3. Overall conclusion on Specific Obligation

In relation to quality SOBs, SOB 013 c, e and f have been fulfilled but the rest of the SOBs are still ongoing. The MAH is sending updates according to the agreed plan. Since SOBs 013 and 014 have not been completely fulfilled the SOBs as described in Annex II remains.

In relation to clinical SOBs, SOB 19 and SOB 20, the interim reports (primary analysis) stated in the corresponding SOBs have been submitted. Interim data regarding SOB 019 was submitted as expected (March 2021) and assessed in variation EMEA/H/C/005675/II/0002, for which a positive CHMP opinion was granted on 24 June 2021. The SOB is still not fulfilled, the final pooled analysis and clinical study reports (CSRs) are due on 31 May 2022. Regarding SOB 020, the original commitment date for the interim data was 30 April 2021, but upon request from the MAH, EMA agreed to revise the commitment date to 04 June 2021, when the data was submitted. The data regarding SOB 020 has been assessed in variation EMEA/H/C/005675/II/0026, for which a positive CHMP opinion was granted on 14 October 2021. The SOB is still not fulfilled, the final clinical study report is due on 31 March 2024.

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

3.1. Quality

No additional information has been submitted in support of this renewal application. An ongoing variation in parallel is noted for which there are issues still being addressed. An addendum to the Quality Overall Summary (QOS) and expert statement to include editorial updates in line with recent post-approval change submissions, is provided.

3.2. Clinical efficacy

Since approval of Vaxzevria, the following additional efficacy data have become available outside of the SOBs.

- Immunogenicity from study D8111C00002 (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 COVID-19 VACCINE ASTRAZENECA, a non-replicating ChAdOx1 vector vaccine, for the prevention of COVID-19). In Japanese participants from study D8111C00002, antibody titers for the Spike and receptor binding domains (RBD) antigens and for the neutralising antibodies (pseudoneutralization) to SARS-CoV-2 increased substantially after the first vaccination with AZD1222 and increased further after the second vaccination. The seroconversion rates for both the Spike and the RBD antigens at 28 days (Day 57) after the second vaccination with AZD1222 were 100%. This study was assessed under procedure EMEA/H/C/005675/II/0019, which has been finalised.
- Procedure under Article 5(3) of Regulation EC (No) 726/2004. The European Medicines Agency

was requested to provide, if possible, a recommendation on the administration of the second dose of Vaxzevria on the basis of the available data. On 9 April 2021 the European Commission (EC) triggered the above-mentioned procedure (EMEA/H/A-5(3)/1507), which has now concluded.

- Post-authorisation measure MEA/010.1. The MAH provided the protocol for "Brand-specific COVID-19 vaccine effectiveness against severe COVID-19 disease in Europe". This protocol is developed in the context of the COVIDRIVE study platform. This protocol has already been assessed.

CHMP assessment comment:

Regarding Japanese study D8111C00002, the data indicate that AZD1222 elicits strong immune responses against SARS-CoV-2 in the Japanese adult population across all the age groups (see procedure EMEA/H/C/005675/II/0019). The immunogenicity results obtained in this study are in line with those that served as the basis for granting the CMA and that are reported in the EPAR. The study reports had no regulatory consequences and did not necessitate any changes to the product information.

Regarding Procedure under Article 5(3) for the second dose of Vaxzevria, it was recommended adherence to the recommended vaccination posology of two doses as stipulated in the product information is vital to benefit from the highest level of protection against the virus. Regarding the possibility of administering an mRNA vaccine as a second dose, preliminary results from non-commercial studies in Spain, Germany and the UK suggested a satisfactory immune response and no safety concerns, however further data was awaited and no definitive recommendation could be made at that stage.

It is welcomed that a study to measure the effectiveness of Vaxzevria vaccine is ongoing under the umbrella of the COVIDRIVE consortium.

3.3. Clinical safety

Within the current application for CMA renewal, the MAH has not provided any new safety data. The MAH submitted the Addendum to the Clinical Overview (ACO), covering the period from 29 January 2021 and until 31 May 2021.

Table 3: Summary of significant safety-related changes to Vaxzevria Core data sheet (CDS) during the reporting period.

CDS version date	CDS Section Number – CDS Section Title - Detail of the safety-related change
01 March 2021	CDS Section - 4.4– Special warnings and special precautions for use Hypersensitivity including anaphylaxis Hypersensitivity reactions including anaphylaxis and angioedema have occurred following administration of COVID-19 Vaccine AstraZeneca. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine. A second dose of the vaccine should not be given to those who have experienced a severe hypersensitivity reaction to the first dose of COVID-19 Vaccine AstraZeneca.

CDS version date	CDS Section Number – CDS Section Title - Detail of the safety-related change
	CDS Section 4.8– Undesirable effects <u>Overall summary of the safety profile</u> The overall safety of COVID-19 Vaccine AstraZeneca is based on an analysis of pooled data from four clinical trials conducted in the United Kingdom, Brazil, and South Africa. At the time of analysis, 24,244 participants ≥18 years old had been randomised and received either COVID-19 Vaccine AstraZeneca or control. Out of these, 12,282 received at least one dose of COVID-19 Vaccine AstraZeneca, with a median duration of follow-up of 4.5 months. Demographic characteristics were generally similar among participants who received COVID-19 Vaccine AstraZeneca and those who received control. Overall, among the participants who received COVID-19 Vaccine AstraZeneca, 89.8% were aged 18 to 64 years and 10.2% were 65 years of age or older. The majority of recipients were White (75.5%), 9.8% were Black and 3.7% were Asian; 55.8% were female and 44.2% male.
02 April 2021	CDS Section - 4.4 – Special warnings and special precautions for use Addition of text to alert healthcare providers and vaccine recipients to the very rare events of serious thrombosis with thrombocytopenia
06 April 2021	CDS Section - 4.4 - Special warnings and special precautions for use Further revisions to text relating to very rare events of serious thrombosis with thrombocytopenia
19 April 2021	CDS Section - 4.3 - Contraindications – addition of a contraindication: Patients who have experienced major venous and/or arterial thrombosis in combination with thrombocytopenia following vaccination with any COVID-19 vaccine. CDS Section - 4.4 - Special warnings and special precautions for use – revisions to text related to events of thrombosis occurring with thrombocytopenia CDS Section 4.8 – Undesirable effects – addition of the following under Postauthorization experience: Vascular disorders: A very rare and serious combination of thrombosis and thrombocytopenia
26 April 2021	CDS Section 4.6 – Pregnancy and lactation – addition of results from COVID-19 VACCINE ASTRAZENECA non-clinical studies CDS Section 5.3 – Pre-clinical safety data – revisions to include most recent COVID-19 VACCINE ASTRAZENECA non-clinical studies.
27 May 2021	CDS Section 4.8 – Undesirable effects – addition to add a short summary of safety data from Study D8110C00001

Since the initial marketing authorisation, the PRAC has initiated the below mentioned signal assessments

Table 4: Summary of the validated signals that were ongoing or closed during the reporting period.

Validated signal	Ongoing or Closed at the DLP of the Addendum to the Clinical Overview
Hypersensitivity including Anaphylaxis	Closed
Thrombotic events with Thrombocytopenia	Closed
Thrombocytopenia	Ongoing*
Guillain-Barré Syndrome	Ongoing*
Acute Macular Outer retinopathy (AMOR)	Ongoing*
Capillary leak syndrome	Ongoing*
Immune thrombocytopenia	Ongoing*

* These validated signals of thrombocytopenia were closed after the DLP of this review/renewal procedure.

During the reporting period, assessments of Monthly Summary Safety update Reports (MSSRs) associated with EPITT notifications permitted EMA to identify safety signals and safety topics of interest/concern. Those were:

- Anaphylactic reactions (EPITT 19668; 17.02.2021)
- Capillary Leak Syndrome (CLS) (EPITT 19672, 24.02.2021)
- Embolic and thrombotic events SMQ (EPITT 19683; 11.03.21) which involved the thrombosis with thrombocytopenia (TTS), as well as thrombosis (with and without thrombocytopenia) issues
- Immune Thrombocytopenia (EPITT 19678; 05.03.21)
- Acute Macular Outer retinopathy (AMOR) (EPITT 19703; 07.05.21)

Data related to those topics were carefully reviewed through Monthly Summary Safety Reports (MSSRs) or relevant signal procedures leading to several requests to update the product information and RMP.

Changes to the SmPC made for safety reasons:

The assessment of those safety signals and safety topics led to updated to the SmPC. Some additions were requested or implemented after the DLP of this review (*in italic in the text*).

Additions to Section 4.3, contra-indication

- Individuals how have experienced thrombosis with thrombocytopenia (TTS) following vaccination with Vaxzevria
- *Individuals who have previously experienced episodes of capillary leak syndrome (CLS) (implemented within procedure IAIN/0029)*

Addition to Section 4.4, Warning

- Hypersensitivity including anaphylaxis: warning for the recognition of the associated conditions and recommendations for (not giving) second dose with Vaxzevria to those who have experienced anaphylaxis to the first dose with Vaxzevria. In contrast to the CDS, no recommendation is included in the EU-SmPC in case of severe hypersensitivity (other than anaphylaxis) after the first dose

- Thrombosis with thrombocytopenia syndrome: warning on the occurrence, precaution for use
- *Capillary Leak Syndrome: warning for the recognition of this rare condition (implemented within procedure IB/0044)*
- *Immune thrombocytopenia: a variation add a warning on ITP (implemented within procedure IAIN/0048)*

Addition to Section 4.8

- Thrombosis with thrombocytopenia syndrome: very rare (Vascular disorders); Thrombocytopenia: common (Blood and lymphatic system disorders)
- *Capillary Leak Syndrome*: *frequency unknown (Vascular disorders) (implemented within procedure IAIN/0029)*
- *Guillain-Barré syndrome: A variation to add GBS in 4.8 (implemented within procedure IB/0044)*
- *Immune thrombocytopenia: a variation add ITP in 4.8 (implemented within procedure IAIN/0048)*

It should be noted that changes to the MAH CDS and to the EU product information may differ slightly.

	CDS	**SmPC**
Section 4.4	A second dose of the vaccine should not be given to those who have experienced a severe hypersensitivity reaction to the first dose of COVID-19 Vaccine AstraZeneca	A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of Vaxzevria
Section 4.8 Undesirable effects	/	Decreased appetite, Lethargy, Asthenia, Injection site bruising

Updates to the RMP are discussed in Section 4.

PRAC conclusion: The close monitoring of notification reports permitted the early identification of safety signals. These were assessed and SmPC were updated quite rapidly.

The PRAC considers that the new safety topics identified during the reporting period do not modify the balance benefit-risk of the product. However, safety data should continue to be closely monitored.

3.4. Pharmacovigilance inspections

There were PhV inspections carried out to AZ Saudi Arabia (January 2021), AZ Czech Republic & Slovakia (April/May 2021) and AZ Canada (May/June 2021) by the inspecting authorities National Pharmacovigilance Centre (Saudi Arabia), HA-SUKL (Slovak Local) and Health Canada, respectively.

PRAC assessment comment:

The outcome of three pharmacovigilance inspections were presented. Those inspections were not specific to Vaxzevria and did not permit to identify a major problem in relation with the vaccine.

4. Risk management plan

The core RMP was created during the reporting period (Version 1.0, dated 15 February 2021).

No updated version of the RMP was submitted within this renewal procedure. The approved RMP at the end of the reporting period was 3.0. Since the DLP of this annual renewal, the RMP version 4.1 is currently under assessment within procedure EMEA/H/C/005675/II/0040.

The below table summarises safety concerns identified in RMP for Vaxzevria at the beginning of the reporting period (RMP v1) and at the end of the reporting period (RMP v3).

Table 5: Summary of safety concerns – EU RMP for VAXZEVRIA (version 1, Succession 5, Approval date 29 January 2021 & Version 3.0, Succession 2; Internal Approval data: 27 May, 2021)

Risk category	**Safety concern** RMP version 1, succession 5	**Safety concern** RMP version 3.0, succession 2
Important identified risk	None	• **Thrombosis with thrombocytopenia syndrome** • **Anaphylaxis**
Important potential risk	• Anaphylaxis • Nervous system disorders, including Immune-mediated neurological conditions • Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)	• Nervous system disorders, including Immune-mediated neurological conditions • Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) • **Thrombosis**
Missing information	• Use during pregnancy and while breastfeeding • Use in immunocompromised patients • Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders) • Interactions with other vaccines • Use in patients with autoimmune or inflammatory disorders • Long-term safety	• Use during pregnancy and while breastfeeding • Use in immunocompromised patients • Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders) • Interactions with other vaccines • Use in patients with autoimmune or inflammatory disorders • Long-term safety

PRAC assessment comment:

During the reporting period, and according to PRAC requests, the following changes to the safety specifications were made:

- 'Anaphylaxis' was upgraded from Important potential risk to Important identified risk;
- 'Thrombosis with thrombocytopenia syndrome' was included as Important identified risk;

- 'Thrombosis' was included as Important potential risk.

After the DLP of this renewal, the MAH was requested to include:

- 'Guillain-Barré syndrome' as an important identified risk (*PRAC outcome on assessment of the 6th MSSR of Vaxzevria – Procedure EMEA/H/C/005675/MEA/027.5*)
- 'Thrombocytopenia with or without associated bleeding' as an important potential risk (3rd *PRAC recommendation on signal assessment report on ITP with Vaxzevria – Procedure SD 034 / EPITT 19678*)

5. Changes to the Product Information

Minor editorial updates were included during the assessment of this renewal (see attachment 1).

Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Vaxzevria (COVID 19 Vaccine (ChAdOx1 S [recombinant])) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU and it is approved under a conditional marketing authorisation.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

6. Overall conclusions and benefit-risk balance

6.1. Specific Obligations (SOBs)

Compliance of SOB data submitted

The table below gives the detailed SOBs at the time of renewal and describes where the SOB has been partially completed.

Number	Description	Due date	Status
SOB 013 a-f	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. a) 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. Responses to be provided no later than December 2021 with interim, monthly updates beginning February 2021. b) The applicant should provide specific dates for data completion for each site as follows, including for	December 2021 with interim monthly updates beginning February 2021	SO13a- ongoing

Number	Description	Due date	Status
	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. Responses to be provided no later than December 2021 with interim, monthly updates beginning February 2021. *c) The applicant should provide the final FP comparability data and analysis for CP Pharmaceuticals and Catalent Anagni to demonstrate that the commercial product is representative of the product used in clinical trials. Responses to be provided no later than February 2021.* d) The applicant should provide the pending results and final PPQ reports of the three FP process performance qualification lots (including CPP; IPC and NCPP) manufactured at IDT Biologika, CP Pharmaceuticals, Catalent Anagni, SK Bio and Universal Farma S.L. and update section P.3.5.2.1 to confirm that the process is properly validated. Responses to be provided no later than March 2021. *e) The applicant should provide the final results for the additional FP in process testing performed as part of the process validation specifically at Catalent Anagni and CP Pharmaceuticals, (AS post-shipping and thawing studies, mixing test studies, hold test studies and product homogeneity) to confirm that the process is properly validated. Section P.3.5.2.1. should be updated. Responses to be provided no later than March 2021.* *f) The applicant should introduce an enhanced sampling strategy for the FP filing process at all sites, at the beginning, at 25%, 50%, 75% and 100% of the filling process no later than February 2021 in order to confirm batch to batch consistency. At least 2 vials per sample should be tested using a rapid test capable of providing sufficient assurance of batch homogeneity i.e. measured by absorbance. For this test the applicant should set justified acceptance criteria for homogeneity and the batch results should meet these.*		SO13b- ongoing SO13c- fulfilled SO13d- ongoing SO13e- fulfilled SO13f- fulfilled
	In order to ensure consistent product quality, the applicant should provide additional information on	June 2022 with interim monthly	

Number	Description	Due date	Status
SOB 014 a-d	stability of the active substance and finished product and review the finished product specifications following further manufacturing experience. a) The applicant should provide additional AS stability data and analysis to confirm the storage period. This includes data following storage at -90 to -55°C, 2-8°C and 23-27°C/55-65% RH storage conditions for (Process 3 and 4) Pre-PPQ lots and for 3 PPQ lots manufactured at each AS commercial site (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). Updates should be provided upon availability of data for 3, 6 and 12 months and completion of the study. Responses to be provided no later than May 2022 with interim, monthly updates beginning February 2021. b) The applicant should provide additional finished product (FP) stability data to confirm the storage period with process 4 lots from all FP manufacturing sites and all requested FP configurations (FP presentations). Process 4 PPQ stability study updates should be provided post approval upon availability of data for 3, 6 and 12 months and completion of the study. Responses to be provided no later than June 2022 with interim, monthly updates beginning March 2021. c) The applicant should recalculate the rate of average loss of infectivity during FP storage at 2-8 °C when further stability data of three PPQ batches from each commercial site becomes available. If necessary, the release specification should be changed in order to ensure that batches will remain within shelf life specification during storage and handling. The applicant should report the recalculation periodically until sufficient data are available to fully justify the release specification. Responses to be provided no later than December 2021 with interim, 3-monthly updates beginning May 2021. d) The applicant should provide additional clinical justification for the end of shelf life FP infectivity specification. Additional immunogenicity data from clinical studies for participants primed and boosted with a Low Dose (LDLD), as well as a characterisation of breakthrough cases, i.e. the infectivity characteristics of the batches with which these individuals were immunised, should be evaluated as soon as available. Responses to be provided no later than September 2021.	updates beginning February 2021	SO14a- ongoing SO14b- ongoing SO14c- ongoing SO14d- ongoing

During the period covered by this annual renewal, data on Quality Specific Obligations (SOB), have been provided. So far, SOB 013 c, e and f have been fulfilled. The rest of the SOBs are still ongoing. Therefore, the quality SOBs in Annex II remain outstanding.

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 SOB 013, and June 2022 with interim monthly updates beginning February 2021, for SOB 014.

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

In relation to clinical SOBs, SOB 19 and SOB 20, the interim reports (primary analysis) stated in the corresponding SOBs have been submitted. Interim data regarding SOB 019 was submitted as expected (March 2021) and assessed in variation EMEA/H/C/005675/II/0002, for which a positive CHMP opinion was granted on 24 June 2021. The SOB is still not fulfilled, the final pooled analysis and clinical study reports (CSRs) are due on 31 May 2022. Regarding SOB 020, the original commitment date for the interim data was 30 April 2021, but upon request from the MAH, EMA agreed to revise the commitment date to 04 June 2021, when the data was finally submitted. The data regarding SOB 020 has been assessed in variation EMEA/H/C/005675/II/0026, for which a positive CHMP opinion was granted on 14 October 2021. The SOB is still not fulfilled, the final clinical study report is due on 31 March 2024.

Updated list of specific obligations (SOBs)

In the framework of a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Number	Description	Due date
SOB 013	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.	30/12/2021
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.	30/06/2022
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 studies COV001, COV002, COV003 and COV005.	31 May 2022
SOB 019	In order to confirm the efficacy and safety of Vaxzevria, the MAH should provide the final analysis from the pooled pivotal studies.	Final pooled analysis: 31 May 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 final clinical study report for study D8110C00001.	Final CSR: 31 March 2024

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.

Furthermore, the data collected as part of the specific obligations for Vaxzevria during the period covered by this annual renewal continue to support its positive benefit-risk balance in the approved indication.

Favourable effects

As stated in the EPAR of the conditional marketing authorisation (CMA) for Vaxzevria, vaccine efficacy determined from pooled analysis of trials COV002 and COV003 for seronegative subjects who received two standard doses of $5x10^{10}$ vp per dose with a 4-12 week dose interval (i.e. 28 to 84 days) was 59.5% (95% CI: 45.8, 69.7).

The data submitted regarding SOB 019 (variation EMEA/H/C/005675/II/0002) provided the pooled efficacy analysis of the four trials (COV001; COV002; COV003 and COV005) at data cut-off date of 07 December 2020. The estimate of vaccine efficacy (VE) determined from this pooled analysis (VE=58.8%; 95%CI: 44.6, 69.6) was very similar to that determined from the pooled analysis from trials COV002 and COV003. In relation to safety, due to the modest extend of both the size and long-term exposure of the safety database, the overall frequencies of either solicited local and systemic adverse events (AEs), unsolicited AEs, serious adverse events (SAEs) and adverse events of special interest (AESI) presented remain barely unchanged to those approved at the time of the CMA opinion.

In addition, SOB 020 (variation EMEA/H/C/005675/II/0026) that focused on the assessment of the data from trial D8110C00001, provided further reassurance on VE. The primary efficacy analysis determined a VE against COVID-19 symptomatic illness that occur ≥15 days post second dose of study intervention of 74.0% (95%CI: 65.3 – 80.5). Importantly high VE estimates were determined both in participants ≥18 to <65 years of age (yoa) [VE: 72.8% (95% CI: 63.4 – 79.9)] and in participants ≥65 years of age [VE: 83.5% (95%CI: 54.2 – 94.1)]. This result is relevant in that VE in subjects older than 55 yoa could not be demonstrated in the pooled efficacy analysis that served as the basis for the CMA.

At the time of the CMA, the VE regarding prevention of severe COVID-19 could not be estimated since the number of cases were low. Data from study D8110C00001 (SOB 020) showed a clear indication of vaccine efficacy against severe diseases since there were 0 cases in the AZD1222 group and 8 COVID-19 cases in the placebo group.

At the time the CMA was granted, an immune response in terms of both the humoral response against S protein (binding antibodies) and SARS-CoV-2 virus (neutralization assays) and the cellular response have been shown in vaccinated subjects. This has also been confirmed during the assessment of the data from studies submitted after the granting of the CMA such as D8110C00001 (assessed in procedure EMEA/H/C/005675/II/0026) and D8111C00002 (clinical trial in Japan; assessed in procedure EMEA/H/C/005675/II/0019).

Uncertainties and limitations about favourable effects

The uncertainties and limitations of favourable effects are similar to those at the time of the initial assessment. The principal uncertainties remain on the duration of protection and efficacy in risk groups, e.g. pregnant women and immunocompromised subjects. Another uncertainty relates to vaccine efficacy against upcoming virus variants of concern. Results described in the EPAR (initial CMA) and from SOB 020 indicate that VE against symptomatic COVID-19 starts 2-3 weeks from first dose. However, precise VE after receiving one dose has not been properly determined, and it would be

expected to be impacted according to the infecting strain (whether it is the original Wuhan strain or a variant). As stated in the SmPC, it is therefore important that a second dose is given after 4 and within 12 weeks after the first dose to achieve the protection suggested by the main study outcomes.

In relation to pregnancy, the protocol on the Pregnancy Registry of Women Exposed to AZD1222 Immediately Before or During Pregnancy as part of the C-VIPER Registry Consortium (D8110C00003; Pregistry-sponsored) was agreed by PRAC (EMEA/H/C/0005675/MEA/006.1)

In relation to immunocompromised subjects a study protocol has been agreed at CHMP (Procedure No. EMEA/H/C/0005675/MEA/009.1).

Moreover, in order to comply with the planned additional Pharmacovigilance activity milestone included in the Risk Management Plan for Vaxzevria to evaluate effectiveness in real-world setting, a study protocol has been agreed by CHMP (EMEA/H/C/0005675/MEA/010.1)

Data on concomitant administration of Vaxzevria with other vaccines has not been submitted by the MAH.

Unfavourable effects

The safety database includes over 33,000 participants aged ≥18 years who received AZD1222 (12,000 approx. from pooled safety dataset and 21,000 approx. from study D8110C00001). Reactogenicity data was collected in a subset of 4,762 participants receiving AZD1222. Additionally, cumulatively, from the 29 December 2020 (international birth date, IBD) to the 31 May 2021 DLP, patient exposure by ADZ1222 doses distributed was estimated at over 500 million doses in over 70 countries.

Data from clinical studies

Data reported by clinical trial, showed that the frequencies of any solicited local and systemic AEs were reported more frequently in AZD1222 than in the control or placebo group. Most of the local and systemic AEs following AZD1222 were mild or moderate and self-limiting. The most frequently reported solicited adverse events (within 7 day after any vaccination) are injection site tenderness (68%), injection site pain (58%), headache (53%), fatigue (53%), myalgia (44%), malaise (44%), pyrexia (includes feverishness (33%) and fever ≥38°C (8%), chills (32%), arthralgia (27%) and nausea (22%).

Unsolicited AEs reported (within 28 days after any vaccination) were largely consistent with AEs observed following vaccination and the majority was mild to moderate in severity. A reduction of the percentages of AEs was shown after the second dose in both the study vaccine and the comparator.

Overall incidence of AESIs was low in the University of Oxford (COV) studies and in study D8110C00001. Noticeably, AESI were reported more frequently in study D8110C00001 (2.4% in AD1222) than in the University of Oxford pooled trials (0.9% in AZD1222 group). This increase in frequency of AESI is mainly due to the fact that in D8110C00001 trial vaccine-associated enhanced respiratory disease (VAERD) cases, that were the most frequently reported AESI, were included in the AESI category. In this study all COVID-19 cases were categorized under VAERD and included as AESIs.

Overall, the incidence of SAEs in pooled studies (SOB 019) and in study D8110C00001 (SOB020) was low and similar in the AZD1222 and control or placebo groups. Fewer than 1% of participants reported a SAE overall (any dose). Both in the University of Oxford studies and in study D8110C00001, the most frequently reported SAEs by system organic class (SOC) in the AZD1222 and groups were Infections and Infestations, and the most frequently reported preferred term (PT) was Appendicitis.

Only ≤0,1% participants reported a SAE considered treatment-related by the investigator, 2 in the AZD1222 group (pyrexia, myelitis transverse) and 2 in the control group (autoimmune haemolytic

anaemia and myelitis) in the Oxford pooled studies and 1 subject in the AZD1222 (hypoaesthesia and chronic inflammatory demyelinating polyradiculoneuropathy) group and 2 in the placebo group in study D8110C00001 (optic ischaemic neuropathy and neurosensory hypoacusia). Except pyrexia all other SAEs were AESIs.

In the D8110C00001 study 5 events of facial paralysis (AESI) were reported in the AZD1222 group versus 0 in the placebo group (the imbalance was also seen in the pooled studies, although it was less pronounced).

No anaphylactic reactions were reported in the clinical trial. Nonetheless, anaphylaxis and angioedema were included as adverse reactions from post-marketing data based on a safety signal of serious hypersensitivity/ anaphylactic reaction (see section on post-marketing data).

Post-marketing data

During the reporting period, PRAC regularly assessed monthly safety information through monthly summary safety repots (MSSRs). Those assessments, along with EPITT (European Pharmacovigilance Issues Tracking Tool) notifications, led to the identification of several safety signals which themselves led to updates of Vaxzevria Product Information and RMP. The PRAC considers that the Benefit-risks balance of Vaxzevria remains positive. This recommendation is issued before the first PSUR for Vaxzevria is assessed and following conclusion of the article 5.3 review which was under assessment at the time of the DLP. Vaxzevria should continue to be closely monitored for safety.

a) Safety signals identified during the reporting period:

- *Hypersensitivity including anaphylaxis*
- *Thrombotic events with thrombocytopenia*
- *Thrombocytopenia*
- *Guillain-Barré Syndrome*
- *Capillary leak syndrome*
- *Immune thrombocytopenia*

In addition:

- *Thrombosis* has been included in RMP as important potential risk.
- *Acute Macular Outer Retinopathy* was identified as a safety signal in May and confirmed in June (after the DLP)

b) Analysis of data under Article 5(3) of Regulation (EC) 726/2004:

On 9 April 2021, the European Commission Health and Food Safety requested to EMA further analysis on thrombosis with thrombocytopenia (TTS) and Vaxzevria in order to better characterise risk factors and "*in order to provide more specific recommendations to the Member States to guide their vaccination programme".* The Agency was also requested "*to provide, if possible, a recommendation on the administration of the second dose of the AstraZeneca vaccine".*

On 14th September 2021, the CHMP concluded that "*With regards to a possible recommendation on the administration of the second dose, the CHMP considered available data on the occurrence of TTS following the second dose as well as safety and efficacy aspects of different scenarios surrounding the second dose.*

The CHMP concluded that two separate doses of Vaxzevria should be administered 4 to 12 weeks apart, in line with the current product information. The mechanism behind the observed cases of TTS remains unclear, and whilst spontaneous reporting suggests that the risk following the second dose may be lower than the risk observed following the first dose, no firm conclusion should be drawn."

Uncertainties and limitations about unfavourable effects

Long-term safety data is not yet available. Participants in the pooled clinical trials have had a median follow-up of >2 months after the second dose and the participants in study D8110C00001 had a median number of follow-up days of 92 days after first dose and 61 days after second dose.

Some serious adverse events with a neuro-inflammatory aetiology have been observed in the safety database for which relatedness to the study treatment cannot be excluded at this stage (see section 3.5). Regular updates are needed to inform of any new events in the SOC of Nervous System disorders or any serious or severe events with a neuro-inflammatory aetiology. Therefore, these have been identified as a potential important risk in the RMP with adequate surveillance measures.

Safety data in participants with severe immunodeficiency, or participants with severe underlying disease (including autoimmune or inflammatory disorders) are lacking, as all these populations were excluded from the studies. The MAH has submitted a safety study protocol in immunocompromised adults ≥18 years which was agreed at CHMP (MEA 009.1). The results are pending, the primary clinical study should be submitted in February 2023 and the final CSR in November 2023.

Over a third of participants in the University of Oxford studies and in study D8110C00001 had comorbidity at baseline. There were no imbalances in the unsolicited AEs, SAEs and AESIs between the AZD1222 and control group for either comorbidity subgroup and between individual comorbidity subgroups.

Further, there is only very limited clinical experience in pregnant women, with 14 pregnant women in the safety database who were exposed to AZD1222. Data from non-clinical studies do not indicate any harm during pregnancy. In the absence of clinical data to confirm lack of risks, risks during pregnancy remain, albeit theoretical. The MAH has presented a protocol for a pregnancy register of women exposed to AZD1222 (MEA 006.1).

The available data (non-clinical, clinical, neutralizing capacity of antibodies) from clinical trials and post-marketing exposure do not raise a concern regarding vaccine-associated -enhanced disease. However, the possibility of enhanced disease cannot be excluded with certainty. Vaccine-associated enhanced disease (VAED) should continue to be considered as an important potential risk in the RMP.

Benefit-risk assessment and discussion

The available clinical data for Vaxzevria, including the induction of immune responses and the demonstrated vaccine efficacy, establish the benefits to prevent COVID-19 in immunized individuals 18 years of age and older. The available safety data for subjects aged 18 years and above allows concluding on a positive benefit/risk balance in the proposed indication. The quality related SOBs are ongoing according to plan and expected to be concluded by February 2021. The fulfilment of the clinical SOBs are due on 31 May 2022 and 31 March 2024.

Importance of favourable and unfavourable effects

Not applicable

Balance of benefits and risks

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

7. Recommendations

Based on the review of the available information on the status of the fulfilment of Specific Obligations, the marketing authorisation holder has complied with the specific obligations and the benefit-risk balance for Vaxzevria in its approved indication (please refer to the Summary of Product Characteristics) continues to be favourable, and therefore the renewal of the conditional marketing authorisation is recommended, subject to the conditions and obligations as detailed in this assessment report.

Amendments to the marketing authorisation

The renewal requires some minor amendments to SmPC and labelling.

Please refer to the Attachment which includes all agreed changes to the Product Information.

Conditions of the marketing authorisation

The marketing authorisation is subject to the following conditions:

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **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 elucidate the possible mechanisms of platelet activation after vaccination and to identify the possible triggers, the MAH should conduct and submit the final report for a non-clinical study to test in-vitro expression of the S protein of Vaxzevria.	7 July 2021[1]
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

[1] This Annex II condition is under assessment within procedure EMEA/H/C/005675/II/0031

Specific obligations to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Number	Description	Due date
SOB 013	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.	30 December 2021
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.	30 June 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 studies COV001, COV002, COV003 and COV005.	31 May 2022
SOB 019	In order to confirm the efficacy and safety of Vaxzevria, the MAH should provide the final analysis from the pooled pivotal studies.	Final pooled analysis: 31May 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 final clinical study report for study D8110C00001.	Final CSR: 31 March2024

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.

8. EPAR changes

The table in the "Steps after" module of the EPAR will be updated as follows:

Scope

Renewal of conditional marketing authorisation

Summary

The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated

and therefore recommends the renewal of the conditional MA for Vaxzevria, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.