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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure under Article 5(3) of Regulation (EC) No 726/2004

Invented name: Vaxzevria

Active substance: Chimpanzee Adenovirus encoding the SARS-CoV-2 Spike glycoprotein (ChAdOx1-S)

Procedure number: EMEA/H/A-5(3)/1507

Note:

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



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1. Information on the procedure

Following the conclusion of a possible link between Vaxzevria (previously known as AstraZeneca vaccine) and very rare cases of unusual blood clots with low blood platelets, the European Commissioner for Health and Food Safety requested a further analysis and stratification of data to be performed, to better characterise the benefit and risk of the vaccine in different age groups and/or sex, as well as possible other risk factors that could be identified. The European Medicines Agency was also 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) therefore triggered a procedure under Article 5(3) of Regulation (EC) No 726/2004, and requested the Agency for a scientific opinion on the above issues, in order to inform national vaccination campaigns.

In order to support Member States, national medicines regulators and healthcare professionals, the European Commission requested the Agency to give its opinion – possibly in an interim form – by 22 April 2021.

The current report relates only to the interim CHMP opinion based on the limited data available at this time. This interim opinion is without prejudice to any further outcome of the ongoing review under Article 5(3) of Regulation (EC) No 726/2004.

2. Scientific discussion

2.1. Introduction

Vaxzevria is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of SARS-CoV-2. The SARS-CoV-2 S immunogen in the vaccine is expressed in the trimeric pre-fusion conformation; the coding sequence has not been modified to stabilise the expressed S-protein in the pre-fusion conformation. Following administration, the S glycoprotein of SARS-CoV-2 is expressed locally stimulates neutralising antibody and cellular immune responses, which may contribute to protection against COVID-19.

Vaxzevria is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older; the use of this vaccine should be in accordance with official recommendations.

In March 2021, a signal assessment was initiated at PRAC for embolic and thrombotic events with Vaxzevria (previously COVID-19 Vaccine AstraZeneca). The review of data analyses from EudraVigilance (EV) with individual case review (EV search with cut-off date: 22 March 2021) and “observed versus expected” analyses, input from an ad hoc expert group and available literature pointed to signals of embolic and thromboembolic events, cerebral venous sinus thrombosis, splanchnic vein thrombosis and arterial thrombosis, with or without thrombocytopenia, mainly occurring in women below 60 years old, and with a time-to-onset within 2 weeks following vaccination.

On 7 April 2021, PRAC concluded that a causal relationship between vaccination with Vaxzevria and adverse events of thrombosis in combination with thrombocytopenia (TTS) was at least a reasonable possibility¹. The product information was updated with information on thrombocytopenia and coagulation disorders to warn that *a combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with Vaxzevria. This*

¹ [AstraZeneca's COVID-19 vaccine: EMA finds possible link to very rare cases of unusual blood clots with low blood platelets](#)

includes severe cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia. Some cases had a fatal outcome. The majority of these cases occurred within the first fourteen days following vaccination and occurred mostly in women under 60 years of age.

Healthcare professionals should be alert to the signs and symptoms of thromboembolism and or thrombocytopenia. Those vaccinated should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg swelling, persistent abdominal pain following vaccination. Additionally, anyone with neurological symptoms including severe or persistent headaches or blurred vision after vaccination, or who experiences skin bruising (petechia) beyond the site of vaccination after a few days, should seek prompt medical attention.

Further, thrombosis in combination with thrombocytopenia (thrombosis with thrombocytopenia syndrome - TTS) was added as an adverse drug reaction with the frequency very rare and thrombocytopenia with the frequency common.

As an outcome of this review, it was also decided to conduct a number of studies to identify the exact pathophysiological mechanism for the occurrence of these thrombotic events and better define the magnitude and characteristics of the risk. At that time, experience with exposure to the second dose of the vaccine was still limited with all cases of TTS reported after administration of the first dose of Vaxzevria.

On 9 April 2021, the EC triggered a procedure under Article 5(3) of Regulation (EC) No 726/2004, and requested the Agency to perform a further analysis and stratification of data to better characterise the benefit and risk of the vaccine in different age groups and/or sex, as well as possible other risk factors that could be identified. The European Medicines Agency was also requested to provide, if possible, a recommendation on the administration of the second dose of Vaxzevria on the basis of the available data².

2.2. Risk contextualisation

The first aspect which the Agency was asked to consider was to contextualise the reports of TTS with the benefits of the vaccination by age and/or sex, as well as to identify possible additional risk factors for the occurrence of the TTS reactions.

2.2.1. Measures

Based on public health relevance and availability of data as of 21 April 2021, the following parameters were used.

2.2.1.1. Potential benefits

Potential benefits of vaccination with Vaxzevria were described for the following three outcomes:

- 1) COVID-19 related hospitalisations prevented
- 2) COVID-19 related intensive care unit (ICU) admissions prevented
- 3) COVID-19 related deaths prevented

² [AstraZeneca's COVID-19 vaccine: EMA to provide further context on risk of very rare blood clots with low blood platelets](#)

As potential benefits depend on the level of exposure to the circulating virus and individual characteristics (i.e. age) this analysis takes into consideration the following factors:

- Age categories: 20-29; 30-39; 40-49; 50-59; 60-69; 70-79; ≥ 80
- Background SARS-CoV2 virus exposure, divided into three categories, using overall COVID-19 incidence as submitted by MSs:
 - “Low” exposure: using virus circulation for September 2020 (incidence: 55/100,000 population)
 - “Medium” exposure: using virus circulation for March 2021 (incidence 401/100,000 population)
 - “High” exposure: using virus circulation for January 2021 (incidence 886/100,000 population)

Analyses are at a population level. Analyses based on individual risks, including occupation and other medical conditions that might increase exposure or the seriousness of the infection, have not been analysed. Neither has the analysis taken into account reduced vaccine efficacy against SARS CoV-2 variants.

2.2.1.2. Potential harms

Potential harms were assessed based on the number of spontaneously reported cases in EudraVigilance of TTS in patients having received Vaxzevria.

2.2.2. Methods and analysis

2.2.2.1. Calculation

COVID-19 related events prevented per 100,000 vaccinated patients over a four-month and three-month period were estimated by applying Vaxzevria effectiveness data and the background incidence of virus exposure to the number of COVID-19 related hospitalisation, ICU admission and death events.

Within each age strata, the following calculation was used:

$$\text{events prevented} \begin{bmatrix} \text{hospitalised} \\ \text{ICU admitted} \\ \text{deaths} \end{bmatrix} = \text{COVID incidence rate} \times \text{proportion with event} \times \text{vaccine effectiveness}$$

Potential harms were defined as TTS cases in persons exposed to Vaxzevria per 100,000 per month as reported to EudraVigilance:

$$\text{potential harms} = \frac{\text{observed events (EudraVigilance)}}{\text{persons exposed to AZ vaccine}}$$

2.2.2.2. Data sources

Data sources included data on COVID-19 infection and vaccination from the MS obtained either directly or through European Centre for Disease Prevention and Control (ECDC)³, the literature, and EudraVigilance.

³ Data from The European Surveillance System – TESSy, provided by Austria, Croatia, Czech Republic, Denmark, Finland, Germany, Ireland, Italy, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Slovakia, Sweden and released by ECDC. The views and opinions of the authors expressed herein do not necessarily state or reflect those of ECDC. The

2.2.2.2.1. Potential benefits

EEA MS were asked to submit the below information by age group (0-19; 20-29; 30-39; 40-49; 50-59; 60-69; 70-79; ≥80) by sex (F/M/Unknown) for their respective MS. The same information was requested from ECDC. The request included:

- The number of vaccinated persons with Vaxzevria by week up to the most recent date stratified by dose (1st and 2nd)
- Number of COVID-19 infection, hospitalisations, ICU admissions, and deaths by month from January 2021 to March 2021
- Population size by month

Incidence rates of COVID-19 infection were received from the ECDC⁴ and directly from Member States and these were broken down by age categories (20-29; 30-39; 40-49; 50-59; 60-69; 70-79; ≥80). Age distributions were extrapolated to those countries that did not report data according to requested age categories.

The proportions of hospitalisations, ICU admissions and deaths following COVID-19 infection across EEA MS were estimated from across EEA MSs, based on a subset of EEA MS as provided by ECDC and collected from the MSs. The data from the two sources were compared for validation.

Data broken down by sex was received from a subset of MS, but were insufficient to allow validation of extrapolation to all EEA MS. Therefore, no stratification by sex could be performed.

No further stratification on other risk factors for severe COVID disease, including underlying health condition or obesity, was performed as relevant data were not available.

The proportion of prevented hospitalisations is assumed to be the same as the proportion of prevented ICU admissions and deaths. Health policy measures in the recent months may have led to different exposures of populations across MS over months, and this may have led to different risks.

Data sources for efficacy and risk (TTS) are described under the contextualisation section (Section 2.2.3)

2.2.3. Contextualisation: analyses and additional sensitivity analyses

To contextualise the robustness of effect estimates of the effectiveness of Vaxzevria and the occurrence of TTS, several approaches were developed with different assumptions regarding efficacy level, benefit window and potential harms. Analyses relate to average benefits and risks for individuals.

Efficacy level

Vaxzevria effectiveness (VE) is estimated using different data sources and assumptions.

- Firstly, effectiveness is derived from observational studies. Two studies in the public domain have results on VE against hospitalisation.^{5,6} VE increased with time in the month following the

accuracy of the authors' statistical analysis and the findings they report are not the responsibility of ECDC. ECDC is not responsible for conclusions or opinions drawn from the data provided. ECDC is not responsible for the correctness of the data and for data management, data merging and data collation after provision of the data. ECDC shall not be held liable for improper or incorrect use of the data.

⁴ ECDC. Weekly surveillance report on COVID-19. Available from: <https://www.ecdc.europa.eu/en/covid-19/surveillance/weekly-surveillance-report> (accessed 16-Apr-2021)

⁵ Vasileiou, Eleftheria and Simpson, et al. Effectiveness of First Dose of COVID-19 Vaccines Against Hospital Admissions in Scotland: National Prospective Cohort Study of 5.4 Million People. Preprint: <http://dx.doi.org/10.2139/ssrn.3789264>

⁶ Jamie Lopez Bernal, Nick Andrews, Charlotte Gower, et al. Early effectiveness of COVID-19 vaccination with BNT162b2 mRNA vaccine and ChAdOx1 adenovirus vector vaccine on symptomatic disease, hospitalisations and mortality in older adults in England. Preprint: <https://doi.org/10.1101/2021.03.01.21252652>

first dose to 80% overall. A constant vaccine effectiveness from these observational studies of 85% in the 18-64 years of age, 79% in the 65-79 years of age and 81% in those above 80 years of age was used. This approach is seen as the best-case scenario.

- Secondly, from observational studies and based on the available knowledge from clinical trials and the literature, effectiveness levels of the Vaxzevria after 1st dose are increasing over the first weeks following administration of the first dose. The second analysis was performed assuming no effectiveness of 1st dose of Vaxzevria for the first three weeks and after the third week a constant effectiveness of 18-59yrs=85%;60-79yrs=79%; ≥80=81% based on the two observational studies.
- Thirdly, effectiveness is extrapolated from clinical trials at 60% for symptomatic COVID-19 infection.⁷ It is noted this might be a conservative estimate given that pooled VE in the time period starting 21 days after dose 1 until dose 2 (censored at 12 weeks post dose 1) in subjects who received standard dose for each doses (SD/SD) is estimated at 73.2% (95% CI: 54.3, 84.3). Effectiveness at 60% is therefore seen as a conservative scenario.

Benefits window

Benefit parameters were estimated as prevented cases per 100,000 occurring in a four-month and a three-month window. While data for benefits in a three-month window are more comprehensive, in clinical practice, a four-month benefit window is considered a less conservative scenario based on demonstrated persistence of immune response beyond the three months. A proportion of subjects in the pivotal clinical trials were administered the second dose of the vaccine beyond three months of the first dose. Although there is no direct evidence that the protection afforded by the first dose would extend beyond 12 weeks, based on antibody kinetics and Kaplan Meier (KM) curves for efficacy a sharp drop in level of antibodies past that time is considered unlikely, and therefore protection can be assumed to reasonably persist over the first 4 months, or longer, but sufficient data are yet lacking.

Potential harms

The number of TTS cases in patients exposed to Vaxzevria is extracted from EudraVigilance, the European database of reports of suspected adverse drug reactions. The analysis uses cases that occur within 1-month of vaccination. This time window was chosen as it covers all cases of TTS occurring in the EEA in EudraVigilance. Therefore, extending the time window beyond 30 days has currently no impact on the analysis. There were 16 cases where the time of the occurrence of the event after vaccination was not reported; these were all considered likely to have occurred within 1-month of the vaccination.

A search was therefore performed in EudraVigilance (data cut off: 13 April 2021) with the MedDRA SMQ 'Embolic and thrombotic events' and specific preferred terms (PT: acquired amegakaryocytic thrombocytopenia, anti-platelet antibody, autoimmune heparin-induced thrombocytopenia, heparin-induced, thrombocytopenia, heparin-induced thrombocytopenia test, heparin-induced thrombocytopenia test positive, immune thrombocytopenia, megakaryocytes abnormal, megakaryocytes decreased, non-immune heparin associated thrombocytopenia, platelet aggregation abnormal, platelet anisocytosis, platelet count, platelet count abnormal, platelet count decreased, platelet disorder, platelet maturation arrest, platelet production decreased, platelet toxicity, plateletcrit abnormal, plateletcrit decreased, spontaneous heparin-induced thrombocytopenia syndrome, thrombocytopenia, thrombocytopenia neonatal, thrombocytopenic purpura, thrombotic thrombocytopenic purpura) with COVID-19 VACCINE ASTRAZENECA (CHADOX1 NCOV-19), to identify

⁷ [Assessment report COVID-19 Vaccine AstraZeneca EMA/94907/2021](#)

all cases of TTS. Therefore, cases were identified based on structured reporting, and were not subjected to individual case causality assessment.

A total of 142 cases were identified in EudraVigilance.

Background rates of TTS

TTS associated with vaccination with Vaxzevria is usually associated with anti-PF4 antibodies, and thromboses are found in large vessels at unusual locations including cerebral veins and splanchnic vessels. This represents a distinct pattern of features compared to thrombosis associated with thrombocytopenia in the background population; thus no measurable background incidence is assumed.

A standard methodology of measuring excess adverse events following vaccination is to measure the background rate of events and subtract this from the observed cases; the difference is assumed to be the excess, associated with vaccination. However, considering the distinct pattern of features of thrombosis associated with thrombocytopenia in people vaccinated with Vaxzevria, background incidence rates were not used in the analysis and the harms are estimated by considering only the cases observed in EudraVigilance without any adjustment for expected background rates.

Under reporting to EudraVigilance

For the analysis of harm, the number of TTS cases was taken as reported from the EEA in EV. Because of the established under-reporting seen in spontaneous reporting systems, a second (sensitivity) analysis was made assuming an under-reporting of TTS cases reported to EV. For this analysis an underreporting of TTS cases to EV was assumed as follows; 0% in the first seven days; 20% between day 8 and day 14; 50% after day 14 (Lévy, 2002; Prevots, 1994)^{8,9}. The level of underreporting is difficult to estimate.

2.2.4. Outcomes

The outcomes for the different analyses under the different scenarios are provided in the Appendix of this document and the spreadsheet attached. Table 3 provides the numbers assessing potential benefits over a four-month period, and Table 4 provides the numbers assessing potential benefits over a three-month period. It should be noted that all estimates are accompanied by uncertainties, both based on estimation uncertainty and based on the limitations of the data discussed above.

This exercise has put the very rare cases of TTS in the context of the benefits of vaccination. The analyses conducted show that the benefits of vaccination increase with increasing age and increasing infections rates. Details on different scenarios of age and infection rate for hospitalisation, ICU admission and death, together with TTS risk are presented in this assessment report based on different assumptions of vaccine effectiveness and risk.

While the COVID-19 events prevented and the TTS cases (risks) are presented in detail in the annexes, it is illustrative to make observations based on a reasonable set of assumptions.

If one considers the analysis using 80% effectiveness (the best-case scenario) over a four-month window compared to the unadjusted TTS cases, the following observations can be made:

- Hospital admissions prevented are numerically higher than TTS cases across all age categories, and all virus exposure levels;

⁸ Lévy-Bruhl D, Desenclos JC, Rebière I, Drucker J. Central demyelinating disorders and hepatitis B vaccination: a risk-benefit approach for pre-adolescent vaccination in France. *Vaccine* 2002; 20: 2065-2071.

⁹ Prevots R, Sutter R, Strebel P, et al. Completeness of reporting for paralytic poliomyelitis, United States, 1980 through 1991: implications for estimating the risk of vaccine-associated disease. *Arch Pediatr Adolesc Med* 1994; 148: 479-485.

- ICU admissions prevented are numerically higher than TTS cases across all age categories for medium and high virus exposures and above 60 years at low virus exposure and;
- Deaths prevented are numerically higher than TTS cases in those above 30 years for high and medium virus exposures; and above 60 years for low virus exposure.

If one considers the analysis using 60% effectiveness (the conservative scenario) over a four-month window (effectiveness assumed to start from three weeks onwards) compared to the unadjusted TTS cases, the following observations can be made:

- Hospital admissions prevented are numerically higher than TTS cases across all age categories, and all virus exposure levels;
- ICU admissions prevented are numerically higher than TTS cases across all age categories for medium and high virus exposures and above 60 years at low virus;
- Deaths prevented are numerically higher than TTS cases in those above 30 years for high virus exposure; above 40 years for medium virus exposure and above 60 years for low virus exposure.

The analyses detailed in the Appendix to this assessment report are based on the data currently available. Assumption and extrapolation have been made that need to be considered when interpreting the results.

Analyses are at a population level. Analyses based on individual risks including occupation and other medical conditions that might increase exposure or the seriousness of infection, have not been performed.

2.2.5. Additional discussion and limitations

The outcomes presented in this analysis provide an EEA contextualisation of the harms of Vaxzevria using major clinical events prevented by vaccination using different assumptions. In addition to the assumptions and sensitivity analyses described above, additional assumptions and limitations should be taken into consideration.

Parameters used for this analysis are estimated on the data available to the EMA at the time of the analysis. While age-specific data have been obtained from the majority of MSs, it has been assumed that the age specific distribution is representative for MSs from which data were not obtained. Sex-specific data was obtained from a small subset of MS, which did not allow to a validated an extrapolation to the remaining MS, and this was not further pursued. The proportion of patients hospitalised, with ICU admission and death following COVID-19 infection was estimated on a subset of EEA MS as provided by ECDC and collected from the MS and was considered representative of the whole EEA.

It is known that there is heterogeneity¹⁰ across the EU MSs. For example, country specific values depend on the vaccination policies and strategies at MS level and these are not fully harmonised. In addition, the circulation of the virus differs in both temporal and geographical terms in Europe. As MSs only reported data from 2021 onwards, the COVID-19 incidence rate for the low exposure scenario (virus circulation in September 2020) was estimated based on the case-based data submitted to ECDC by MSs).

An alternative approach to assessing the benefits of vaccination was tested as a sensitivity analysis: this simply multiplied the vaccine effectiveness by the incidence rate for each outcome derived from

¹⁰ [ECDC Managing heterogeneity when pooling data from different surveillance systems](#)

ECDC / MS data. This was found to have little impact on the estimated vaccine benefits. Additionally, this approach did not fully allow contextualisation with a “low” background COVID-19 incidence because event-specific background data are only available for the past three months. As a result, this alternative approach is not included in the assessment report.

The effectiveness data for Vaxzevria was derived from two observational studies and complemented with two additional analyses, one based on varying effectiveness over time and one based on the clinical trial estimate of efficacy for symptomatic disease. Evidence from observational studies can be questioned based on potential confounders (notably the impact of social distancing measures imposed in temporal association with vaccination roll-out). On the other hand, the external validity of clinical trials efficacy can be considered as valid and results thereof have been considered in parts of the scenarios.

It should be noted that equal effectiveness is assumed across all three benefit parameters.

The lag-time between vaccination of individuals, TTO and then reporting to EudraVigilance as well as the impossibility to investigate the platelet count in the event of sudden death due to multiple thromboses and bleedings, may have led to a few fatalities not having been considered, with a consequence of some underestimation in cases. Certainty around this will improve with more data becoming available.

2.3. Current evidence on administration of a second dose

The second aspect which the Agency was asked to consider as part of this procedure was to provide, if possible, a recommendation on the administration of the second dose of Vaxzevria, on the basis of available data.

As part of the assessment of this matter, the MAH was asked to submit the following information:

- A search of the AstraZeneca safety database for AE reports of “embolic and thrombotic events” in association with the use of a second dose of Vaxzevria covering the period up to 12 April 2021.
- A search of the EudraVigilance Database undertaken on 14 April 2021 for adverse event reports of “embolic and thrombotic events” in association with the use of a second dose of Vaxzevria.
- An overview of “embolic and thrombotic events” in ongoing and completed clinical trials.
- Information on exposure to the second dose, stratified by 10-year age groups where available, for the EEA (per Member State), for the UK and worldwide.
- Available non-clinical and clinical data of heterologous prime-boost regimens as well as a discussion thereof.

Note that data from the US study D8110C00001 (*A Phase III Randomized, Double-blind, Placebo-controlled Multicenter Study in Adults, to Determine the Safety, Efficacy, and Immunogenicity of AZD1222, a Non-replicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19*) are not available yet and therefore have not been considered in this assessment.

In the context of the above-mentioned [signal procedure](#), which concluded with the amendment of the Product Information to include information on thrombosis in combination with thrombocytopenia (TTS), an ad hoc expert group was convened to address questions posed by the Pharmacovigilance Risk Assessment Committee (PRAC). Due to the risk of severe thrombosis + thrombocytopenia following

vaccination with Vaxzevria as identified following the first dose of this vaccine, the question has been raised whether a second dose can be given safely or whether offering another vaccine or delaying the second dose may be more optimal. The ad hoc expert group noted that the implication of administering the second dose is not clear at this stage.

Vaxzevria is intended to be given as two doses given 4 to 12 weeks apart. Data submitted in support of the marketing authorization application suggested that a single dose would provide some level of protection, however there was uncertainty on both the level as well as the duration of protection. Therefore, it is recommended in the SmPC that a second dose should be given within a 4 to 12 weeks interval.

The available evidence and uncertainties for the administration of a second dose of Vaxzevria with an interval of 4 to 12 weeks after the first dose are summarised in Table 1.

Three alternative scenarios can be considered with regards to the administration of a second dose as follows:

- Vaxzevria is given as a second dose but delayed,
- No second dose is given,
- An mRNA vaccine dose is given as a second dose,

The available evidence and uncertainties for each of these three alternative scenarios are summarised in Table 2.

Whilst it could also be considered to offer individuals who received a single dose of Vaxzevria a full two-dose mRNA vaccine regimen, the added benefit of restarting the vaccination course is questionable based on immunological principles. This possibility is not considered further in this assessment as uncertainties in this scenario are comparable to the scenario in which a single mRNA dose is given, as a second dose, following a single first dose of Vaxzevria.

Table 1. Available evidence for Vaxzevria given as a second dose with an interval of 4 to 12 weeks as recommended in the SmPC¹¹

Second dose	Available Data Benefits	Available Data Risks	Uncertainties Benefits	Uncertainties Risks
<p>Vaxzevria given at 4-12 weeks</p>	<p>Protection against symptomatic COVID-19 demonstrated for two standard doses given 4 to 12 weeks apart (VE=58.8%, 95% CI: 44.6 – 69.6, 65/5,849 vs 156/5,763). Protection has been demonstrated for 3 months after the second dose.</p>	<p>There is clinical trial data (COV001, COV002, COV003, COV005) available in 24,244 persons of whom 12,282 received Vaxzevria (either 1 or 2 doses). Of these, 8,705 subjects received two doses at the recommended (standard) dose level. No cases of thrombosis combined with thrombocytopenia (TTS) have been reported in these trials.</p> <p>Three cases of thrombosis + thrombocytopenia have been reported so far following the second dose post licensure [AZ Global Patient Safety Database, cut off 19-04-2021, 40-49M/>79M/UnkM, TTO 3 and 7 days after the 2nd dose, and on the day of the second dose]. These have not been validated according to the Brighton Collaboration case definition.</p>	<p>Although protection has been demonstrated for 3 months after the second dose, it is likely to remain for longer however the exact period is not known at the moment.</p> <p>Level of protection against severe COVID-19 unknown due to low numbers in the clinical trials.</p> <p>In clinical studies in 11,612 persons (5,849 in the Vaxzevria group vs 5,763 in the control group) who received two standard doses with a 4 to 12 week interval, there were 8 hospital admissions (0 in the Vaxzevria group vs 8 in the control group), 1 severe case (in the control group) and no deaths.</p>	<p>There is no insight in the risk TTS after 2nd dose.</p> <p>There is limited exposure to second dose:</p> <ul style="list-style-type: none"> - n=10,448 received 2 doses in COV001, COV002, COV003 and COV005. The median exposure was 81 days post dose 2. In total, n=8,705 received two standard doses. - According to the MAH n=89,186 post licensure in the EEA (as of 4 April 2021). In addition, MS France that 3,514 persons received a second dose, not included in the data from the MAH. - n=2,093,158 post licensure in the UK (as of 11 April 2021); <p>The interval between the two doses for post licensure exposure data is unknown.</p> <p>The follow up after the second dose for the post licensure data is unknown.</p> <p>It is not clear if the risk of complications will be increased or decreased or similar after a second dose.</p>

¹¹ Data from clinical trials are obtained from the preliminary AR for variation II/02, based on DCO2 (7 December 2020) and the CMA, based on DCO1 (4 November 2020).

Table 2. Overview of current evidence of benefits and risks of alternative scenarios for completion of vaccination schedule¹²

Second dose	Available Data Benefits	Available Data Risks	Uncertainties Benefits	Uncertainties Risks
Vaxzevria given at >12 weeks	<p>Protection against symptomatic COVID-19 demonstrated in 2,359 subjects who received the second dose with a >12week interval; (8/1,146 in the Vaxzevria group vs 38/1,213 in the control group, VE: 77.6%, 95% CI:52.0, 89.6).</p> <p>The second dose was administered up to 26 weeks after the first dose.</p>	<p>See Table 1.</p> <p>In clinical trials 1,146 (seronegative) persons received the second dose of Vaxzevria with an interval >12 weeks after the first dose, up to 26 weeks. There were no cases of TTS.</p>	<p>At the time of the marketing authorisation there was no evidence that the protection afforded by the first dose would extend beyond 12 weeks. Therefore, if the second dose is extended beyond this interval, vaccinees may be unprotected for a period of time before receiving the second dose.</p>	<p>See Table 1.</p>
No second dose is given	<p>Protection starts from approximately 3 weeks after 1st dose of vaccine and persists up to 12 weeks.</p> <p>The VE in participants who received at least one dose of the Vaxzevria vaccine was estimated at 50.5% (95% CI: 36.5, 61.5)¹³ against COVID-19.</p>	<p>See Table 1.</p> <p>There are no additional risks other than lack of effect.</p>	<p>It is not known whether the protection lasts beyond the 12 weeks demonstrated in clinical trials.</p>	<p>None identified.</p>
mRNA vaccine (Pfizer or Moderna)	<p>None</p>	<p>None</p>	<p>There is no data to inform the efficacy of a single dose of an mRNA vaccine following a single dose of Vaxzevria.</p>	<p>There is no data on the safety of an mRNA vaccine following a single dose of Vaxzevria.</p> <p>The reactogenicity profile may differ with a heterologous regimen</p>

¹² Data from clinical trials are obtained from the preliminary AR for variation II/02, based on DCO2 (7 December 2020) and the CMA, based on DCO1 (4 November 2020).

¹³ Data submitted in support of the CMA (DCO 4 November 2020 : Any dose for Efficacy Analysis set, seronegative at baseline, participants who received at least one dose with follow up from the first dose).

Second dose	Available Data Benefits	Available Data Risks	Uncertainties Benefits	Uncertainties Risks
			<p>There is no data to inform the optimal timing of a dose of mRNA vaccine following Vaxzevria. As a first dose of Vaxzevria is likely to provide (some) protection up to 12 weeks, this interval could be considered.</p> <p>The mode and pattern of SARS-CoV-2 spike antigen presentation (on the surface of muscle cells and fibroblasts at IM injection sites, and by antigen-presenting cells in draining lymph nodes) of Vaxzevria is shared with mRNA vaccines, which also employ similar Wuhan-based spike immunogens.</p> <p>Differences in the spike protein as included (wild-type non stabilized S-protein vs pre-fusion stabilized S-protein) are not expected to impact the response of a second dose such that there would be no protection. If anything, some parallels can be drawn with natural infection after a second dose.</p>	<p>compared to homologous regimens, both in frequency as severity.</p>

Searches in the MAH's safety database and EV identified three cases of thrombosis in combination with thrombocytopenia following a second dose of Vaxzevria:

- one case of thrombocytopenia combined with pelvic venous thrombosis and a pulmonary embolism in a 40-49 year-old male. Time to onset was 10 days post dose 2. The patient was recovering. There is no further information on this case; hence no causality assessment could be performed.
- one case of thrombocytopenia and pulmonary embolism in an > 79-year-old male 3 days after the second dose of Vaxzevria. Due to the TTO, causality is possible; however, the presence of comorbidities and age are alternative risk factors.
- One case of thrombocytopenia combined with cerebral venous sinus thrombosis in a male patient on the day of the second dose. The age was not reported, and the outcome is not known. The information available did not allow to conduct causality assessment.

At this moment, the exact mechanism behind the observed TTS thought to be triggered by Vaxzevria is not known. Several hypotheses were discussed in the context of the signal procedure.

The Ad Hoc Expert Group consulted by the PRAC considered that an atypical heparin induced thrombocytopenia (aHIT) like disorder was the most plausible hypothesis given the similarities observed in both the serological profile and clinical presentation of affected patients. It was considered likely that the syndrome, which resembles aHIT, concerns autoantibody against PF4, which exhibits a high binding affinity¹⁴.

As an immunological mechanism is considered most likely, an increased risk with the second dose is possible due to boosting of potential anti-pF antibodies that were elicited (subclinical) following the first dose. Alternatively, persons who have not developed this complication following the first dose may also be less likely to develop it after the second dose. Only 3 cases of TTS have been reported so far following a second dose of Vaxzevria. However, underreporting is possible, and both exposure to the second dose and follow-up time are far more limited than for the first dose. Therefore, the risk of TTS following a second dose of Vaxzevria is not known.

There is no data to suggest that delaying the second dose may lower the risk of TTS. Also, persons may be unprotected for a certain amount of time if the second dose is delayed beyond 12 weeks.

A scenario where no second dose is given could be considered in order to avoid an additional risk of TTS after a second dose. Whilst clinical studies demonstrated protection following the first dose, it was only demonstrated up to 12 weeks. There is, at present, no data to inform the duration of protection after this period, and therefore, there can be no reassurance that individuals not given a second dose of any vaccine would maintain an adequate level of protection that would avoid an increase in infection levels.

There is currently no clinical data with a heterologous prime/boost regimen (i.e. a first dose of Vaxzevria followed by a second dose of mRNA vaccine). A (non-peer-reviewed) study in mice supports the hypothesis that Vaxzevria induces an immunologic priming that may be boosted with a subsequent approved mRNA vaccine¹⁵. However, this is not supported by any clinical data.

Currently, a study is ongoing in the UK to test heterologous regimens in humans (COM-COV). Recruitment is complete, and initial reactogenicity results should become available soon whilst

¹⁴ Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. *N Engl J Med* 2021. doi:10.1056/NEJMoa2104840. pmid:33835769

¹⁵ Spencer, AJ, McKay PF, Belij-Rammerstorfer S, et al. Heterologous vaccination regimens with self-amplifying RNA and Adenoviral COVID vaccines induce robust immune responses in mice. bioRxiv 2021.01.28.428665; doi: <https://doi.org/10.1101/2021.01.28.428665>

immunogenicity data are expected in May 2021. This data should be submitted by the MAH for assessment as soon as it is available.

3. Overall discussion and conclusion

Vaxzevria is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older. The overall benefits of Vaxzevria in the prevention of COVID-19 outweigh risks from adverse events including thrombosis in combination with thrombocytopenia (TTS).

The favourable effects of vaccination with Vaxzevria have been demonstrated in clinical trials. Vaccination has benefits in protecting against COVID-19 and observational studies suggest that it reduces the risk of hospitalisation from COVID-19.

Vaxzevria has been associated with an increased risk of TTS. The frequency of those events has been characterised as very rare based on current reporting rates. No risk factors have been identified for TTS at present.

To support decision making relating to vaccination campaigns at national level, the reports of TTS are presented in the context of the benefits of vaccination stratified by age and considering the background infection rate. The analysis does not take into consideration individual risk of infection, e.g. occupation or risk of severe COVID-19 based on comorbidities. When conducting this analysis, the benefits of the vaccine were described using data from the marketing authorisation dossier of Vaxzevria, published studies, data provided by the Member States and ECDC and were estimated in terms of:

- COVID-19 related hospitalisations prevented
- COVID-19 related ICU admissions prevented
- COVID-19 related deaths prevented

In this analysis, it was not possible to further stratify risk by sex, as data on sex was received from only a subset of Member States and it was not possible to validate extrapolation to the remaining Member States.

Benefits were expressed as a function of age and level of viral circulation. The risk of TTS was estimated based on a number of spontaneously reported cases in EudraVigilance in patients having received Vaxzevria and the exposure data for Vaxzevria.

In order to reflect the different situations in the different MSs and changing situation over time and understanding that different parameters may be important for decision making, different scenarios have been assessed, which gave different estimates of benefits and risks. Infection rate and hospitalisation, ICU and death are used to contextualise the occurrence of TTS.

Different assumptions on estimates on the level of benefit and level of risk have been made:

- several assumptions on the level and duration of protection provided by the vaccine;
- two assumptions for risk using the absolute number of cases of TTS reported to EudraVigilance and adjusting this number based on presumed underreporting.

In addition, the circulation of the virus differs in both temporal and geographical terms in Europe. As Member States only reported data from 2021 onwards, the COVID-19 incidence rate for the low exposure scenario (virus circulation in September 2020) was calculated based on the case-based data from the ECDC (drawn from 9 Member States).

This exercise has put the very rare cases of TTS in the context of the benefits of vaccination. The analyses conducted show that the benefits of vaccination increase with increasing age and increasing infections rates. Details on different scenarios of age and infection rate for hospitalisation, ICU admission and death, together with TTS risk are presented in the assessment report based on different assumptions of vaccine effectiveness and risk.

For example, if one considers the analysis using 80% effectiveness (the best-case scenario) over a four-month window compared to the unadjusted TTS cases, the following observations can be made:

- Hospital admissions prevented are numerically higher than TTS cases across all age categories and all virus exposure levels;
- ICU admissions prevented are numerically higher than TTS cases across all age categories for medium and high virus exposures and above 60 years at low virus exposure and;
- Deaths prevented are numerically higher than TTS cases in those above 30 years for high and medium virus exposures; and above 60 years for low virus exposure.

If one considers the analysis using 60% effectiveness (the conservative scenario) over a four-month window (effectiveness assumed to start from three weeks onwards) compared to the unadjusted TTS cases, the following observations can be made:

- Hospital admissions prevented are numerically higher than TTS cases across all age categories and all virus exposure levels;
- ICU admissions prevented are numerically higher than TTS cases across all age categories for medium and high virus exposures and above 60 years at low virus;
- Deaths prevented are numerically higher than TTS cases in those above 30 years for high virus exposure; above 40 years for medium virus exposure and above 60 years for low virus exposure.

The analyses detailed in the Appendix to this assessment report are based on the data currently available. Assumption and extrapolation have been made that need to be considered when interpreting the results.

These are only interim results and may be subject to change as more is known about the risk of TTS and the favourable effects of vaccination with Vaxzevria. However, these results based on the agreed methodology can be used to help guide vaccination decisions at national level including on optimal use of Vaxzevria as part of the armamentarium.

To better support this contextualisation exercise, key aspects of this analysis have been presented graphically.

In relation to the administration of the second dose of Vaxzevria:

The CHMP considered the alternative scenarios of administering Vaxzevria with an interval longer than the recommended 4-12 weeks, of not administering a second dose at all or administering an mRNA vaccine as 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 is unclear, and there has not been enough exposure and follow-up time to determine whether the risk of TTS with a second dose will differ from that of the first dose.

For subjects that will not receive a second dose of Vaxzevria, at present there are no or limited data on alternatives for the administration of a second dose of Vaxzevria.

Appendix 1

Table 3. Model outcomes assessing COVID-19 related hospitalisation, ICU admission and deaths per 100,000 over four-months

Overview of the outputs of the models under different scenario's (prevented benefits calculated per 100,000 over four months)																					
		Model 1 Model 2 Model 3									Model 1 Model 2 Model 3 Model 4 Model 5										
Age categories	Total number vaccinated with AZ	COVID-19 incidence per/100,000 per month	COVID-19 incidence per/100,000 per four months	Hosp rate (%)	COVID-19 hospitalisation per/100,000 per four months	COVID-19 prevented hospitalisation/100,000 per four months	COVID-19 prevented hospitalisation/100,000 per four months	COVID-19 prevented hospitalisation/100,000 per four months	ICU rate (%)	COVID-19 admission per/100,000 per four months	COVID-19 prevented admission/100,000 per four months	COVID-19 prevented admission/100,000 per four months	COVID-19 prevented admission/100,000 per four months	Death rate (%)	COVID-19 death per/100,000 per four months	COVID-19 prevented death/100,000 per four months	COVID-19 prevented death/100,000 per four months	COVID-19 prevented death/100,000 per four months	Cases of TTS after 1st dose/100,000	Cases of TTS after 1st dose/100,000	Fatal TTS cases afster 1st dose of those that reported deaths status (41% of 142 cases)/100,000
Medium circulation of the virus																					
20-29	1269332	597	2389	1.8%	43	37	30	21	0%	4	3	3	2	0%	0	0	0	0	1.9	2.7	0.1
30-39	1922817	586	2342	2.7%	63	54	44	31	0%	6	5	4	3	0%	2	2	2	1	1.8	2.1	0.5
40-49	2796826	643	2571	3.7%	95	81	66	46	0%	12	10	8	6	0%	8	7	5	4	2.1	2.7	0.9
50-59	3256014	501	2003	6.7%	134	114	92	65	1%	18	15	12	9	0%	9	8	6	4	1.1	1.4	0.2
60-69	5081118	403	1610	14.3%	231	183	148	113	2%	36	28	23	17	2%	32	25	21	16	1.0	1.3	0.3
70-79	3122185	307	1228	28.6%	352	278	225	171	4%	50	39	32	24	9%	111	87	71	54	0.5	0.9	0.2
80+	786448	289	1156	35.5%	410	332	267	200	3%	36	29	24	18	21%	243	197	158	118	0.4	0.4	0.2
TOTAL						1077	871	647			131	106	79		326	262	197				
Low circulation of the virus																					
20-29	1269332	66	264	1.8%	5	4	3	2	0%	0	0	0	0	0%	0	0	0	0	1.9	2.7	0.1
30-39	1922817	52	207	2.7%	6	5	4	3	0%	1	0	0	0	0%	0	0	0	0	1.8	2.1	0.5
40-49	2796826	51	205	3.7%	8	6	5	4	0%	1	1	1	0	0%	1	1	0	0	2.1	2.7	0.9
50-59	3256014	46	182	6.7%	12	10	8	6	1%	2	1	1	1	0%	1	1	1	0	1.1	1.4	0.2
60-69	5081118	42	167	14.3%	24	19	15	12	2%	4	3	2	2	2%	3	3	2	2	1.0	1.3	0.3
70-79	3122185	50	201	28.6%	57	45	37	28	4%	8	6	5	4	9%	18	14	12	9	0.5	0.9	0.2
80+	786448	132	526	35.5%	187	151	121	91	3%	17	13	11	8	21%	110	90	72	54	0.4	0.4	0.2
TOTAL						241	194	145			26	21	16		108	87	65				
High circulation of the virus																					
20-29	1269332	1051	4205	1.8%	76	64	52	37	0%	7	6	5	3	0%	0	0	0	0	1.9	2.7	0.1
30-39	1922817	888	3551	2.7%	96	81	66	47	0%	9	8	6	5	0%	4	3	2	2	1.8	2.1	0.5
40-49	2796826	969	3877	3.7%	143	122	99	70	0%	18	15	12	9	0%	12	10	8	6	2.1	2.7	0.9
50-59	3256014	917	3667	6.7%	245	208	169	119	1%	33	28	23	16	0%	17	14	11	8	1.1	1.4	0.2
60-69	5081118	715	2860	14.3%	410	324	263	200	2%	64	50	41	31	2%	57	45	37	28	1.0	1.3	0.3
70-79	3122185	605	2421	28.6%	693	547	443	337	4%	98	78	63	48	9%	218	172	139	106	0.5	0.9	0.2
80+	786448	1077	4310	35.5%	1530	1239	994	745	3%	135	110	88	66	21%	905	733	588	441	0.4	0.4	0.2
TOTAL						2587	2087	1555			295	238	177		977	786	590				
* Explanation of the models																					
Model 1: Effectiveness Vaxzevria (18-64 years of age=85%;65-79 years of age= 79%;>80 years of age=81% (Bernal et al., Vasileiou et al.))																					
Model 2: Effectiveness Vaxzevria is assumed to start from three weeks onwards (18-64 years of age=85%;65-79 years of age=79%;>80 years of age=81%)																					
Model 3: Effectiveness Vaxzevria is assumed to start from three weeks onwards (60% effectiveness (pre-licensing trial))																					
Model 4: No underreporting of TTS cases to EudraVigilance																					
Model 5: Sensitivity analysis for underreporting of TTS cases to EudraVigilance (0% first 7 days; 20% between day 8 and day 14; 50% after day 14)																					

Table 4. Model outcomes assessing COVID-19 related hospitalisation, ICU admission and deaths per 100,000 over three-months

Overview of the outputs of the models under different scenario's (prevented benefits calculated per 100,000 over three months)																					
		Model 1* Model 2 Model 3					Model 1 Model 2 Model 3					Model 1 Model 2 Model 3			Model 4	Model 5					
Age categories	Total number vaccinated with AZ	COVID-19 incidence per/100,000 per month	COVID-19 incidence per/100,000 per three months	Hosp rate (%)	COVID-19 hospitalisation per/100,000 per three months	COVID-19 prevented hospitalisation/100,000 per three months	COVID-19 prevented hospitalisation/100,000 per three months	COVID-19 prevented hospitalisation/100,000 per three months	ICU rate (%)	COVID-19 admission per/100,000 per three months	COVID-19 prevented admission/100,000 per three months	COVID-19 prevented admission/100,000 per three months	COVID-19 prevented admission/100,000 per three months	Death rate (%)	COVID-19 death per/100,000 per three months	COVID-19 prevented death/100,000 per three months	COVID-19 prevented death/100,000 per three months	COVID-19 prevented death/100,000 per three months	Cases of TTS after 1st dose/100,000	Cases of TTS after 1st dose/100,000	Fatal TTS cases after 1st dose of those that reported deaths status (41% of 142 cases)/100,000
Medium circulation of the virus																					
20-29	1269332	597	1792	1.8%	32	27	19	15	0%	3	3	2	1	0%	0	0	0	0	1.9	2.7	0.1
30-39	1922817	586	1757	2.7%	47	40	28	21	0%	5	4	3	2	0%	2	1	1	1	1.8	2.1	0.5
40-49	2796826	643	1928	3.7%	71	61	43	32	0%	9	7	5	4	0%	6	5	3	3	2.1	2.7	0.9
50-59	3256014	501	1502	6.7%	100	85	60	45	1%	14	11	8	6	0%	7	6	4	3	1.1	1.4	0.2
60-69	5081118	403	1208	14.3%	173	137	104	78	2%	27	21	16	12	2%	24	19	14	11	1.0	1.3	0.3
70-79	3122185	307	921	28.6%	264	208	158	119	4%	37	30	22	17	9%	83	65	50	37	0.5	0.9	0.2
80+	786448	289	867	35.5%	308	249	185	138	3%	27	22	16	12	21%	182	147	109	82	0.4	0.4	0.2
TOTAL						808	598	448		98	73	55		244	182	137					
Low circulation of the virus																					
20-29	1269332	66	198	1.8%	4	3	2	2	0%	0	0	0	0	0%	0	0	0	0	1.9	2.7	0.1
30-39	1922817	52	155	2.7%	4	4	3	2	0%	0	0	0	0	0%	0	0	0	0	1.8	2.1	0.5
40-49	2796826	51	153	3.7%	6	5	3	3	0%	1	1	0	0	0%	0	0	0	0	2.1	2.7	0.9
50-59	3256014	46	137	6.7%	9	8	5	4	1%	1	1	1	1	0%	1	1	0	0	1.1	1.4	0.2
60-69	5081118	42	125	14.3%	18	14	11	8	2%	3	2	2	1	2%	2	2	1	1	1.0	1.3	0.3
70-79	3122185	50	150	28.6%	43	34	26	19	4%	6	5	4	3	9%	14	11	8	6	0.5	0.9	0.2
80+	786448	132	395	35.5%	140	113	84	63	3%	12	10	7	6	21%	83	67	50	37	0.4	0.4	0.2
TOTAL						181	134	101		19	14	11		81	60	45					
High circulation of the virus																					
20-29	1269332	1051	3153	1.8%	57	48	34	26	0%	5	5	3	2	0%	0	0	0	0	1.9	2.7	0.1
30-39	1922817	888	2663	2.7%	72	61	43	32	0%	7	6	4	3	0%	3	2	2	1	1.8	2.1	0.5
40-49	2796826	969	2908	3.7%	108	91	65	48	0%	13	11	8	6	0%	9	7	5	4	2.1	2.7	0.9
50-59	3256014	917	2751	6.7%	184	156	110	83	1%	25	21	15	11	0%	12	11	7	6	1.1	1.4	0.2
60-69	5081118	715	2145	14.3%	308	243	185	139	2%	48	38	29	22	2%	43	34	26	19	1.0	1.3	0.3
70-79	3122185	605	1815	28.6%	520	411	312	234	4%	74	58	44	33	9%	163	129	98	74	0.5	0.9	0.2
80+	786448	1077	3232	35.5%	1147	929	688	516	3%	101	82	61	46	21%	679	550	407	305	0.4	0.4	0.2
TOTAL						1940	1437	1078		221	164	123		733	545	409					
* Explanation of the models																					
Model 1: Effectiveness Vaxzevria (18-64 years of age=85%;65-79 years of age= 79%;>80 years of age=81% (Bernal et al., Vasileiou et al.))																					
Model 2: Effectiveness Vaxzevria is assumed to start from three weeks onwards (18-64 years of age=85%;65-79 years of age=79%;>80 years of age=81%)																					
Model 3: Effectiveness Vaxzevria is assumed to start from three weeks onwards (60% effectiveness (pre-licensing trial))																					
Model 4: No underreporting of TTS cases to EudraVigilance																					
Model 5: Sensitivity analysis for underreporting of TTS cases to EudraVigilance (0% first 7 days; 20% between day 8 and day 14; 50% after day 14)																					

Appendix 2

[Visual risk contextualisation EMA/234525/2021](#)