24 March 2021
EMA/PRAC/157045/2021
Pharmacovigilance Risk Assessment Committee (PRAC)

Signal assessment report on embolic and thrombotic events (SMQ) with COVID-19 Vaccine (ChAdOx1-S [recombinant]) – COVID-19 Vaccine AstraZeneca (Other viral vaccines)

EPITT no:19683

Confirmation assessment report	12 March 2021
Preliminary assessment report on additional data	17 March 2021
Adoption of first PRAC recommendation	18 March 2021

Administrative information

Active substance (invented name)[Error! Bookmark not defined.]	AZD1222 (COVID-19 Vaccine AstraZeneca)
Marketing authorisation holder	AstraZeneca
Authorisation procedure	
☒	Centralised
☐	Mutual recognition or decentralised
☐	National

Adverse event/reaction:	embolic and thrombotic events

Signal validated by:	BE
Date of circulation of signal validation report:	11 March 2021
Signal confirmed by:	Belgium
Date of confirmation:	12 March 2021
PRAC Rapporteur appointed for the assessment of the signal:	**Jean-Michel Dogné (BE)**

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1. Background

Seriousness: 258 serious cases, 45 fatal.

Evidence: 269 cases in EudraVigilance for the SMQ 'Embolic and thrombotic events'

ROR: NA

Exposure: as of 11 March 2021, over 5.5 million doses of the AstraZeneca vaccine had been administered in EU/EEA countries [source: ECDC COVID-19 Tracker] [1]; in the UK, exposure was approximately 9.7 million doses as of 28 February 2021 [source: weekly summary of Yellow Card reporting] [2].

At the time of the PRAC meeting on 18 March 2021, it was noted that the latest overall exposure in EU/EEA and UK combined, as of 14 March 2021, was close to 20 million first doses administered [1].

Regulatory context: NA

COVID-19 Vaccine AstraZeneca is an adenovirus vector vaccine which received a conditional marketing authorisation in the EU on 29 January 2021 for active immunisation against COVID-19 in individuals 18 years of age and older.

Cases of thromboembolic events have been reported following administration of COVID-19 Vaccine AstraZeneca in several EEA countries, some leading to local suspensions of specific batches or to the use of the vaccine itself. An observed-to-expected analysis performed on 8 March 2021 identified no increased risk of thromboembolic events following administration of the vaccine although there were limitations.

Venous thromboembolism is an important potential risk included in the RMP of the recently approved COVID-19 Vaccine Janssen, another adenovirus vaccine, due to an imbalance in clinical trials. Natural infection with SARS-COV-2 has been associated with hypercoagulability, microangiopathy and venous or arterial thromboembolic events. One of the mechanisms hypothesised for the hypercoagulable state seen in patients with severe COVID-19 is related to the high-grade systemic inflammatory response.

2. Initial evidence

2.1. Signal validation

A search performed in EudraVigilance on 11 March 2021 for cases of 'Embolic and thrombotic events' (SMQ) yielded 269 cases, mostly from the UK (224 cases). Thrombotic thrombocytopenic purpura was not reported as such in any of the cases. Two additional cases were retrieved under the MedDRA PT 'coagulopathy', both from the UK, but were excluded from the review due to limited information. The majority (60%) of cases occurred in female patients. Median age was 70 years. Forty-five (45) cases had a fatal outcome.

Thirty (30) cases originated from the EEA: Germany (6), Sweden (5), Austria (5), Ireland (2), France (2), Denmark, Norway, Italy, Finland, Croatia, Latvia, Cyprus, Estonia, Greece, Czech Republic (1 each).

Of these, 19 were in women, 11 in male; 8/30 were consumer reports. Time-to-onset ranged from 0 to 16 days. Thrombotic events were reported in 10 cases, e.g. deep vein thrombosis, hepatic vein thrombosis, mesenteric vein thrombosis, portal vein thrombosis, carotid artery thrombosis, peripheral

artery thrombosis, cerebral venous sinus thrombosis. Other reported events included pulmonary embolism (8), thrombocytopenia (6), disseminated intravascular coagulation (4), deep vein thrombosis (4), hepatic vein thrombosis (2). In 14 cases the vaccinee had risk factors for thromboembolic events such as hypertension, thyroiditis, obesity or chronic hepatitis B. Fourteen (14) cases have limited information. Seven (7) cases had a fatal outcome, in vaccinees were aged 24 to 60; disseminated intravascular coagulation occurred in 3 of them.

2.2. Signal confirmation

In total there were 269 cases of 'Embolic and thrombotic events' , median age was 70 years. Thirty (30) cases originated from the EEA. Seven (7) cases had a fatal outcome, in vaccinees aged 24 to 60; disseminated intravascular coagulation occurred in 3 of them. Thrombotic thrombocytopenic purpura was not reported as such in any of the cases. Although an observed-to-expected analysis performed on 8 March 2021 identified no increased risk of thromboembolic events following administration of the vaccine, further investigation is needed as these cases led to local suspensions of specific batches or the use of the vaccine itself. Besides, Venous thromboembolism is an important potential risk in the RMP of the recently approved COVID-19 Vaccine Janssen, another adenovirus vaccine, due to an imbalance in clinical trials.

Therefore the signal is confirmed.

2.3. Proposed recommendation

Following the suspension of a batch (number ABV5300) of COVID-19 Vaccine AstraZeneca [3] and the pause of the vaccination campaign with COVID-19 Vaccine AstraZeneca in Denmark and some other Member States [4], the MAH has been requested as part of a late breaking request for the Summary Monthly Safety Report (due date 15 March 2021) to provide:

A cumulative review of reports of Embolic and thrombotic events (SMQ Broad). The review should include at a minimum a discussion of fatal and serious events, if any batch clustering is observed with focus on ABV5300 batch, other risk factors – if they can be identified, an observed versus expected analysis, and risk-benefit considerations.

3. Additional evidence

3.1. Assessment of additional data

3.1.1. Introduction

The COVID-19 Vaccine AstraZeneca was granted a conditional marketing authorisation by the European Commission on 29 January 2021. Over 6.9 million doses have been administered in the EU/EEA countries [1] and over 9.7 million doses in the UK [2]. In EU countries, COVID-19 Vaccine AstraZeneca was administrated mainly in adults <60 years, while e.g. Comirnaty has been more evenly administered in all age groups and COVID-19 Vaccine Moderna more in adults >60 years [5].

The following events highlight the ongoing insights regarding the issue of thromboembolic events:

- On 7 March 2021, the Austrian National Competent Authority suspended the use of one batch of the COVID-19 vaccine AstraZeneca (batch number ABV5300) as a precautionary measure following reports of events of thromboembolic events occurring with use of the vaccine[4].

- On 11 March 2021, the Danish Health Authority paused its vaccination campaign with COVID-19 Vaccine AstraZeneca. This was decided as a precautionary measure while a full investigation is ongoing into reports of blood clots in people who received the vaccine, including one case in Denmark where a person died [4]. This has since been followed by suspension in multiple other countries, in the EU.
- On 13 March 2021, Norway issued a Rapid alert following a cluster of three healthcare professional cases reporting apparent immune thrombocytopenia in conjunction with cerebral venous sinus thromboses in young individuals (aged between 30-49) within 7 to 10 days of vaccination.
- On 15 of March, the Paul Ehrlich Institute issued a statement on the specifically noting cases of cerebral venous sinus thrombosis and thrombocytopenia. They received reports of cases of thrombotic events with concomitant thrombocytopenia in six women aged between 20 – 49 years and one young man aged between 20-29 years who became symptomatic four to 16 days apart after receiving COVID-19 AstraZeneca vaccine. The six women developed central sinus vein thrombosis, two of which were fatal. A first Observed versus expected analysis concluded that more cases of sinus thrombosis have been reported than would be expected by statistical chance .

On 16 March, a preparatory PRAC meeting was held to discuss the ongoing signal of embolic and thrombotic events.

Based on above evolution and pattern of cases, the focus of the signal shifted from overall thromboembolic events to specific entities, specifically cerebral venous sinus thrombosis with thrombocytopenia and Disseminated intravascular coagulation.

This assessment is based on information which was available up to the 17th March 2021, including the EMA assessment of EudraVigilance (EV) data and preliminary information provided by the Biologics Working Party (BWP).

The assessment report is structured as follows:

- Background on specific clinical entities
- Review of Clinical, non-clinical and Quality information
- Review of the Embolic and thrombotic events by the MAH, following the current signal request
- EMA evaluation of EV data and expert review
- MHRA conclusion
- Discussion on possible hypothesis
- Conclusions and recommendations

3.1.2. Background information on specific clinical entities

Cerebral venous sinus thrombosis (CVST) is a rare manifestation of thrombosis with an incidence that varies between studies (Capecchi, 2018) [6]. In adults, the annual incidence of CVST is 2 to 5 cases per million individuals, but it is likely to be underestimated because of the lack of well-designed epidemiological studies. Two recent studies in The Netherlands and southern Australia found a higher

incidence than previously reported of 13.2 and 15.7 annual cases per million, respectively (Coutinho, 2012; Devasagayam, 2016) [7, 8].

At variance with arterial stroke that is more prevalent in the elderly, CVST typically affects young adults with a mean age of 35 years and is more common in women than in men (2.2:1) because of sex-specific risk factors (Capecchi, 2018) [6].

Because symptoms of CVST are variable and aspecific, diagnosis is often delayed to a median period of 7 days from the onset of clinical manifestations (Ferro, 2004) [9]. The most common presenting symptoms are: headache (88.8%), seizures (39.3%), paresis (37.2%), papilledema (28.3%) and mental status changes (22%).

Risk factors are associated with a multitude of acquired and inherited events, these include other central nervous system events such as intracranial neoplasias and infection, procedural events such as surgery and lumbar puncture as well as other systemic risk factors for thrombotic events eg: nephrotic syndrome, vasculitis, oral contraception and pregnancy (Alvis-Miranda, 2013) [10].

CVST is more common in women of reproductive age than in men, as a result of the use of oral contraceptives or hormone replacement therapy, pregnancy and the puerperium (Bousser, 2012) [11]. Oral contraceptive use is by far the most common risk factor, reported in more than 80% of women in various series and associated with a pooled estimate of approximately 6-fold increased risk of CVST (Dentali, 2006) [12]. In 85% of patients at least one risk factor is identified and 50% of events are triggered by the interaction of more risk factors (Capecchi, 2018) [6].

Cerebral venous sinus thrombosis, along with other paradoxical thromboembolic events, have been known to rarely occur in other immune thrombocytopenic states such as immune thrombocytopenia (ITP) (Hernandez, 2015; Sarpatwari 2010 [13]) and heparin-induced thrombocytopenic thrombotic syndrome (HITT). Plausible mechanisms for the clinical paradox associating immune thrombocytopenia particularly with venous thromboembolic events have been postulated, including increased platelet microparticle thrombogenicity following peripheral destruction, increased antiphospholipid antibody activity and increased levels of von Willebrand factor antigen (Rasheed, 2020) [14].

A recent literature review of CVST in COVID-19 identified 9 studies and 14 patients (Tu, 2020) [15]. The median age was 43 years and majority had no significant past medical conditions (60.0%). The time taken from onset of COVID-19 symptoms to CVST diagnosis was a median of 7 days.

Type 2 HITT is the more serious of the two types of HITT. It is a rare condition occurring in approximately 1- 3% of patients receiving heparin (Arepally, 2017) [16]. Events manifest secondary to an immunological response leading to thrombocytopenia, bleeding and thrombosis. The time to onset is typically 4-10 days following heparin therapy. Clinical events occur secondary to an immune response to PF4/heparin, although the immune response is recognised to occur more frequently than clinical manifestations of thrombocytopenia or thrombosis (Arepally, 2017) [16]. Patients can experience thrombocytopenia concurrent with thrombosis, with thrombosis being the more severe complication and can be life-threatening (Arepally, 2017) [16]. Thrombotic events primarily affect the venous system, although arterial involvement can also occur (Majeed, 2010) [17].

Thrombotic thrombocytopenic purpura (TTP) presents with thrombocytopenia along with microvascular thrombosis and haemolytic anaemia with characteristic red cell fragments on peripheral smear (Louw, 2018) [18]. Secondary forms can result from extrinsic triggers including autoimmune disorders, pregnancy and viral infection. This arises from antibodies to ADAMTS13, a protease that cleaves von Willebrand factor (VWF) multimers into smaller ones. This protease's deficiency leads to VWF giant multimers that bind to platelets, and coagulation factors promote the coagulation cascade.

Thrombocytopenia and thrombosis have also been associated with **COVID-19 disease.** The incidence of thrombocytopenia in patients with COVID-19 has been variable across studies. Mild thrombocytopenia has been observed in up to one-third of these patients, with even higher rate in patients with severe disease (57.7%) compared with non-severe disease (31.6%). ITP has also been known to occur with onset occurring in 20% of cases 3 weeks after onset of COVID-19 symptoms, with reports occurring after clinical recovery (Bhattacharjee, 2020) [19]. Cases of TTP have also been reported to occur (Bhattacharjee, 2020) [19]. The proposed mechanisms of thrombocytopenia with COVID-19 involve inhibition of platelet synthesis due to direct infection of the bone marrow cells or platelets by the virus (possibly via CD-13 receptors) and dysfunctional marrow microenvironment; virus-mediated liver damage leading to decreased thrombopoietin production; pulmonary endothelial damage followed by platelet aggregation in the lungs, subsequent formation of microthrombi, and platelet consumption; and finally, the destruction of platelets by the immune system.

3.1.3. Clinical and non clinical (CHMP) and Quality (input from BWP)

A summary is presented below of non-clinical and clinical data assessed within the marketing authorisation application and related to thromboembolic events .

- Clinical data were reviewed from clinical trials assessed as part of the marketing authorisation (MA) application and additional data submitted after the MA, including data currently under evaluation . These data did not suggest an association of thrombotic events with the use of the AZ1222 vaccine.
- There were no adverse events of leukopenia, thrombocytopenia, or neutropenia reported for the AZD1222 group. A slightly higher frequency of platelet decrease was observed post second dose of the AZD1222 vaccine [3.1%] than post first dose [1.8%], however this was also true in the control group [0.6% and 1.1% respectively]. All clinical laboratory results in the AZD1222 group were within normal clinical range and were not considered Adverse Events.
- Available data from studies with other ChAdOx1 vectored vaccine candidates demonstrated the vector is well tolerated at all dose levels investigated, with no SAEs related to the vaccine reported. Local and systemic AEs were predominantly self-limiting and shortlived.
- Non-clinical data of AZ1222 show strong immunogenicity response following two dose administration in animals. In addition, available data show a favourable safety profile. Adverse effects are limited to the site of administration and all findings reported were reversible by the end of the recovery period.
- Regarding inflammatory response after vaccination, it was concluded that the only relevant signs observed following immunisation in primary pharmacology studies in animal models are restricted to respiratory tract tissues following challenge and no apparent signs of inflammation are observed as a result of immunisation.

Quality aspects were discussed at the BWP on 16 March 2021. It was concluded that there is no indication thus far that SAE are linked to quality of the vaccine. As a further follow-up, the MAH was requested to provide a full batch analysis for specific lots and batch data from UK supplied lots, to understand if there are any clear differences between that and the EU product.

PRAC Assessment

Based on the input provided by the CHMP Rapporteur on the clinical and non-clinical data (DLP 7 Dec 2020), there was no evidence to suggest an association of thrombotic events with the use of the

AZ1222 vaccine. A slightly higher frequency of platelet decrease was observed post second dose of the AZD1222 vaccine compared to post first dose, however this was also true in the control group. All clinical laboratory results in the AZD1222 group were within normal clinical range and were not considered as Adverse Events.

Moreover, the BWP concluded that there is no indication so far that SAE are linked to the quality of the vaccine (16 March 2021). Follow-up questions for specific batches were asked to the MAH.

3.1.4. MAH report

3.1.4.1. AstraZeneca response:

A search of the company's safety database was undertaken on 08 March 2021 for cumulative adverse event data (up to 08 March 2021) from spontaneous and solicited reporting sources using PTs under SMQ Embolic and thrombotic events (MedDRA version 23.1) in association with the use of post-marketing use of COVID-19 VACCINE ASTRAZENECA.

The search identified 267 cases involving 286 events (PTs) from post marketing sources. 279 events (PTs) were serious and 7 were non-serious. After the search was carried out, two additional cases of pulmonary embolism were identified, as of 10 March 2021. These 2 cases with 2 events (MedDRA Preferred Term [PT]) have been added to the analysis of pulmonary embolism. An additional case with PT Pulmonary Embolism was also included in the below analysis. The 288 events are listed Table 1 below:

Table 1 Post-marketing adverse event preferred terms identified in database search

AE Preferred Term	PT Count	PT Serious Count
Acute myocardial infarction	5	5
Amaurosis fugax	2	2
Aortic embolus	1	1
Blindness transient	3	3
Brain stem infarction	1	1
Brain stem stroke	1	1
Cerebral infarction	1	1
Cerebral thrombosis	2	2
Cerebral venous sinus thrombosis	4	4
Cerebrovascular accident	57	53
Cerebrovascular disorder	1	1
Deep vein thrombosis	15*	15*
Diplegia	8	8
Disseminated intravascular coagulation	1	1
Embolic stroke	1	1
Embolism	1	1
Embolism arterial	1	1
Haemorrhagic infarction	1	1

Table 1 Post-marketing adverse event preferred terms identified in database search

AE Preferred Term	PT Count	PT Serious Count
Haemorrhagic stroke	3	3
Hemiparesis	15	15
Hemiplegia	6	6
Hepatic vein thrombosis	1	1
Ischaemic stroke	11	11
Mesenteric vein thrombosis	1	1
Monoparesis	10	10
Monoplegia	31	31
Myocardial infarction	34	34
Paraparesis	2	2
Paraplegia	1	1
Paresis	3	2
Pelvic venous thrombosis	1	1
Portal vein thrombosis	1	1
Pulmonary embolism	22	22
Pulmonary infarction	1	1
Quadriplegia	1	1
Splenic infarction	1	1
Splenic vein thrombosis	1	1
Superior sagittal sinus thrombosis	1	1
Thrombophlebitis	1	1
Thrombophlebitis superficial	2	
Thrombosis	3	3
Transient ischaemic attack	28	28
Vascular stent occlusion	1	1
Total:	**288**	**281**

* After the listings were run, follow-up information was received on 10 March 2021 . Based on the follow-up information the initially reported PT of Deep vein thrombosis was no longer valid and removed. The case report remains included in the analysis, although no longer qualifying for the scope of the search. There was a duplicate case in the safety database .This case is not included in the analysis.

The reports were received from United Kingdom (246), India (8), Austria (3), France (2), Germany (2), Poland (2), Bangladesh (1), Finland (1), Ireland (1), Latvia (1), Norway (1) and Sweden (1). The 269 cases described 166 females, 95 male and in 8 reports gender was not identified.

Two cases were from non-interventional/post-marketing sources and 267 were spontaneously reported.

Out of the 269 cases, 102 were medically confirmed. 40 events had a fatal outcome.

The case level outcomes were: Not Recovered (75), Recovered (44), Recovering (73), Recovered with Sequelae (13) Unknown (24) and Fatal (40). Follow-up information was received on 10 March 2021 for one case. Based on the follow-up information the initially reported PT of Deep vein thrombosis was no longer valid and this case should not have been part of this analysis. The case report remains included in the demographic and other information details, although no longer qualifying for the scope of the search.

PRAC Assessment

The search in the AstraZeneca global safety database (DLP 8 March 2021) using the SMQ Embolic and thrombotic events identified 269 cases, with 288 PTs. In decreasing order, these PTs were Cerebrovascular accident (n=57), Myocardial infarction (n=34), Pulmonary embolism (n=22), Monoplegia (n=31), Deep vein thrombosis (n=15), Ischemic stroke (n=11), [..], Cerebral venous sinus thrombosis (n=4),[…] DIC (n=1) […]. These cases originated mainly from the UK (91%) with female predominance (64%).

The estimated number of doses administered according the 2nd MSSR was 1,903,293 doses for the EU and 9,589,941 doses in the UK (DLP 28 February 2021).

3.1.4.2. Fatal case reports

There were 39 fatal cases occurring in 25 females and 14 males, aged 32-97 years (mean 71 years). Age was not reported in 2 cases. The cases originated from the United Kingdom (32), India (6), and Austria (1). Of the 39 cases, 26 were medically confirmed.

There were 18 fatal cases with a cause of death of **Myocardial infarction (MI)**. Of the 18 cases, 10 occurred in vaccinees aged 70 years and older. A summary of the remaining 8 cases aged less than 70-yeasr old is provided below:

- A total of 8 patients (7 males and 1 female), experienced an event of myocardial infarction with fatal outcome. Three reports were from the UK and 5 were reported from India. It was noted in each of the 5 reports of MI from India government officials, that the deaths were not related to the vaccine.
- The patients ranged in age from 42-67 years, with a mean age of 53 years. For 7 cases where the time to onset was reported, the range was from 1 to 9 days. The cause of death was reported as: MI or Heart attack in 7 reports, and Cardiogenic shock with myocardial infarction in 1 report.
- Five (5) of these 8 patients had a medical history of cardiac disease, aortic stenosis due for upcoming surgery, hypertension, diabetes and hypercholesterolemia, all of which were likely to have contributed to the fatal events of myocardial infarction. The remaining 3 reports lacked sufficient information such as medical history concerning cardiovascular disease, diabetes, renal function, smoking, and obesity, to be able to assess a causal relationship.

There were 8 fatal cases of **Cerebrovascular accident** all occurring in vaccines aged 79 years and older.

All other fatal events (8 events) were singular or were reported at two occurrences (Table 2) apart from 5 fatal cases of Pulmonary embolism/infarction that are described below.

Table 2 Summary of Fatal Cases with One or Two Occurrences

	Case Medically Confirmed		Sex	Age range in Years	Cause of Death Disease PreferredTerms	AE Preferred Term	Time To Onset
1	YES		M	79+	Transient ischaemic attack; Lymphoproliferative disorder in remission; Asthenia	Transient ischaemic attack	Unknown
2	YES		M	60-69	Cardiac arrest	Acute myocardial infarction	Unknown
3	YES		F	30-39	Cerebral thrombosis	Cerebral thrombosis	1 week 5 days
4	YES		F	60-69	Cerebral thrombosis	Cerebral thrombosis	1 week 1 day
5	YES		M	30-39	Brain stem infarction; Superior sagittal sinus thrombosis; Haemorrhage intracranial; Cerebral haemorrhage	Brain stem infarction	1 week 3 days
						Cerebral venous sinus thrombosis	1 week 1 day
						Superior sagittal sinus thrombosis	Unknown
6	YES		F	70-79	Death; Aortic embolus	Aortic embolus	Unknown
7	NO		F	60-69	Haemorrhagic stroke	Haemorrhagic stroke	Unknown
						Hemiplegia	Unknown
8	NO		F	Unknown	Death	Acute myocardial infarction	2 days

PRAC Assessment

Review of the fatal case reports (n=39) indicated that the majority originated from the UK (n=32). There were 6 cases from India and 1 from Austria. Main cause reported was Myocardial infarction (n=18), occurring in > 70 years for 10 cases and in 42-67 years for 8 cases.

Other causes reported were: Cerebrovascular Accident (n=8), all in patients > 79y, Pulmonary embolism (n=5) with 4 cases from the UK (70-89y) and 1 case from Austria (40-49y). Other PTs in remaining cases (8) include cerebral thrombosis (n=2), cerebral venous sinus thrombosis (n=1), aortic embolism (n=1), haemorraghic stroke (n=1).

3.1.4.3. Lot Numbers

Batch numbers were not reported in 139 cases or events. The three batches with the highest number of cases are: AB0006 (491,700 doses distributed, 17 SAEs reported), AB0001 (533,100 doses distributed, 12 SAEs), PV46662 (700,800 doses distributed, 10 SAEs). There was no cluster of events for any of these batches. In addition to the above batches, 2 cases from Austria have been received with batch no ABV5300 (1,060,200 doses distributed); no other thrombotic events were reported from this batch.

PRAC Assessment

The MAH stated that there was no cluster of events for any of the batches. The MAH should clarify in the next MSSR how this was concluded.

3.1.4.4. Observed versus Expected analyses for Pulmonary Embolism and Deep vein thrombosis

Observed-to-expected (O/E) analyses were performed by the MAH for deep vein thrombosis and pulmonary embolism. Background incidence rates were defined by the number of incident reports of a condition or event occurring naturally in the population, expressed in person-time and these background estimates were obtained from the literature. The observed number of cases were found to be significantly less than the expected number of events, the results of the O/E analysis are presented in Table 3. See section 3.2.2 of the Summary Safety Report for more information on process of O/E calculation.

Table 3 Observed versus expected analysis for Pulmonary embolism and Deep vein thrombosis

Medical Concept	Observed cases	Expected cases	Rate ratio (CI 95%)	Conclusion
Deep vein thrombosis	15	704.87	0.02 (0.01 - 0.04)	Observed significantly < expected
Pulmonary Embolism	22	861.7	0.02 (0.02 - 0.04)	Observed significantly < expected

CI Confidence Interval

PRAC Assessment

The observed number of cases for deep vein thrombosis and pulmonary embolism was well below the expected number of cases. This results in a rate ratio with a value clearly close to zero and an upper bound of the 95% confidence interval well below unity; that is, the results of this analysis show that the number of observed cases is statistically significantly lower than expected.

The findings of the O/E analysis are reassuring. However, O/E analyses are often subject to many important sources of uncertainty and the findings should be interpreted cautiously.

In this particular case, the following information was not provided: 1) there is no presentation of the

literature search strategy or the results of the search for backgound incidences, 2) there is no discussion about the comparability between the source population of observed cases and the populations used to derive the background incidences, and there are no stratified analyses (by age, gender), 3) there are no sensitivity analyses presented to explore the impact of potential sources of uncertainty (e.g., under-reporting, background incidence). With regard to the latter, it should be noted that reasonable changes in the parameter values in the uncertainty analysis would probably not change the main conclusions, given the large difference between expected and observed figures and 4) there is no details on the risk period applied.

In conclusion, the analysis is reassuring but: 1) it should not be used as the only source of information for decision-making, 2) on the basis of the document, it is of limited value because questions remain to be answered in order to better assess the quality of the analysis (sources for incidence rates, lack of sensitivity analyses, lack of stratified analyses, assessment of the comparability of the source populations of the observed cases and for the calculation of incidence rates). The MAH is requested to provide a more detailed section to address these issues in the next MSSR.

3.1.4.5. Pulmonary embolism and pulmonary infarction

There were 22 cases of Pulmonary embolism, one of which also included Pulmonary infarction.

The cases originated in the United Kingdom (18), France (1) and Austria (3).

All three cases from Austria were reported in females.

Two cases from Austria were reported from the lot ABV5300 and one from the lot ABV3025.

All 22 cases were spontaneously reported and were serious. Five reports had fatal outcome and 14 of the 22 cases were medically confirmed.

Outcomes of the adverse events of Pulmonary embolism/Pulmonary infarction were: Recovering (8), Recovered with sequelae (2), Not recovered (1), Fatal (5) and Unknown (6).

The demographics and time to onset of the vaccinees are presented in Table 4:

Table 4 Cases with Pulmonary embolism by age interval

Age interval, years	Gender			Time to Onset			
	Male	Female	Unknown	< 1 day	1-7 days	8-18 days	Unknown
18 to <65	1	5	0	0	2	1	3
≥65	6	6	0	1	5	2	4
Unknown	0	2	2	1	1	0	2

3.1.4.5.1. Fatal Pulmonary Embolism

There are 5 cases with fatal outcome. These are described below.

- A 79+ year-old female patient of unknown ethnic origin with unknown past medical history and concomitant medication of calcium carbonate, cholecalciferol for osteopenia received COVID-19 VACCINE ASTRAZENECA (batch number AB0007). On day 1, she collapsed while walking and was admitted to hospital. She was diagnosed with new atrial fibrillation, bilateral

pulmonary embolisms, acute congestive cardiac failure, and was intubated. On day 2, the patient experienced multiple organ failure, mitral incompetence and pneumothorax. On day 2, the patient died. It is not known whether an autopsy was performed. Patient had not shown symptoms associated with COVID-19.

- A 79+year-old female patient of unknown ethnic origin with past and current medical history of dementia and unknown concomitant medications received COVID-19 VACCINE ASTRAZENECA (batch number AB0001). On an unknown date, the patient experienced pulmonary infarction, deep vein thrombosis leg and pulmonary embolism. On day 5, the patient died from pulmonary infarction. An autopsy was performed which showed the cause of death was 1. Pulmonary infarction, 2. Left leg deep vein thrombosis (DVT) and 3. Ischaemic heart disease. The reporter concluded that the DVT may have occurred after a fall prior to receipt of her COVID vaccine.
- A 70-79-year-old female patient of unknown ethnic origin with past and current medical history of stroke, type 2 diabetes mellitus, essential hypertension and hypothyroidism and unknown concomitant products received COVID-19 VACCINE ASTRAZENECA (batch number AB0006). On day 3 post-vaccination, the patient experienced unilateral leg pain, leg swelling and deep vein thrombosis. On day 4, the patient experienced pulmonary embolism, hypotension, and hypoxia. On an unknown day, the patient died from the event of pulmonary embolism. An autopsy was not performed. The cause of death was pulmonary embolism. The history of stroke and the concomitant type 2 diabetes suggests that the patient was at risk of thrombotic events.
- A 70-79-year-old female vaccinee received COVID-19 VACCINE ASTRAZENECA (batch number unknown) and 4 days later experienced pulmonary embolism and malaise. The vaccinee died on the same day, cause of death was reported as pulmonary embolus. No other information was available.
- A 40-49-year-old female with a family history of fatal pulmonary embolism in immediate family received COVID-19 Vaccine AstraZeneca (batch number ABV5300). The patient experienced splenic vein thrombosis, mesenteric vein thrombosis, thrombocytopenia, pulmonary embolism, portal vein thrombosis and hepatic vein thrombosis. On an unknown date, the patient experienced gastrointestinal bleeding. The patient experienced asystole and died 10 days later. Cause of death was reported as pulmonary embolism, splenic vein thrombosis, portal vein thrombosis, asystole, gastrointestinal bleeding, hepatic vein thrombosis and vein thrombosis mesenteric. It was not known whether an autopsy was performed.

3.1.4.5.2. Non-Fatal Pulmonary Embolism

There are 13 cases reported with very limited medical information to evaluate/assess the case for relatedness/association.

One case was related to a potential vaccination error and there was no information on pulmonary embolism from the narrative. It is not clear based on the available information if this a case of pulmonary embolism.

Three cases had confounding medical history:

- Case one has a past history of pulmonary embolism and was treated with Rivaroxaban but had missed a dose on the day of the event.

- Case two has a past history of unknown neoplasm which could have contributed to the pulmonary embolism.
- Case three experienced pulmonary embolism on the same day as receiving the vaccine; the case was confounded as the vaccinee had suspected COVID-19.

3.1.4.6. Summary

In summary, a review of the cases of pulmonary embolism indicated no pattern of events and no clustering of risk factors were identified. Further, there were no trends seen for any batches that were included in this analyses.

The observed number of cases is significantly less than the expected number of events. Past history of pulmonary embolism, neoplasm, current history of deep vein thrombosis and missed dose of anti-coagulant were noted as risk factors for pulmonary embolism in cases where this information was available.

3.1.4.7. Deep vein thrombosis

There were 15 cases of Deep vein thrombosis occurring in 11 females and 4 males. All cases were from the United Kingdom. All cases were spontaneous, and serious and 7 were medically confirmed.

Outcomes of the adverse events of Deep vein thrombosis were: recovering (6), recovered with sequelae (1), not recovered (3), died (1) and unknown (4).

Lot/Batch numbers were available in 9 case reports, 1 report each from AB0001, AB0002, AB0005, AB0008, AB0011, AB0012, PV46662, and 2 reports from AB0006.

Table 5 Cases with Deep vein thrombosis by age group

Age group, years	Gender			Time to Onset			
	Male	Female	Unknown	< 1 day	1-7 days	8-13 days	Unknown
18 to <65	1	3	0	1	3	0	0
≥65	3	8	0	0	4	1	6

Follow-up information was received on 10 March 2021 for one Case (incorrectly considered to be a fatal DVT case). Based on the follow-up information this case did not involve a DVT. This case is nevertheless included in this analysis. In 2 cases, DVT was reported together with Pulmonary embolism and these cases were fatal and discussed above in Section 3.1.4.5.1.

In 4 cases the vaccinee had confounding medical history:

- Case : history of DVT
- Case : concurrent COVID-19 illness
- Case : history of testicular cancer with metastasis to liver
- Case : history of clotting disorder

In one of the 15 cases, there was a non-fatal case received which included a PT of DVT. However, reported verbatim was reported as "Suffered Nausea". No other details were provided in the narrative about DVT.

In the remaining 7 cases, available information was too limited to assess.

3.1.4.8. Summary

In summary, there was no trend seen after reviewing the cases of DVT. There were no cases of DVT associated with lot number ABV5300. There were no trends seen for any batches that were included in this analyses. The observed number of DVT cases is significantly less than the expected number of events.

Overall conclusion

Based on the data available from post-marketing experience, it is AstraZeneca's opinion that the information in the current document and the AstraZeneca Core Data Sheet continues to accurately reflect the known benefit-risks for COVID-19 Vaccine AstraZeneca.

PRAC Assessment

The MAH revised cases of Pulmonary embolism and Deep vein thrombosis. It is agreed that based on these cases, no specific pattern or clustering of risk factors could be identified.

However, based on the evolution of events, input from MS and analysis from EMA, the scope of the concerns should be directed to specific issues including Disseminated intravascular coagulation, haemorrhagic stroke, Cerebral venous sinus thrombosis and thrombosis with thrombocytopenia (see Global discussion and conclusion).

3.1.5. EMA analysis of EudraVigilance data

3.1.5.1. Observed to expected analysis

Based on data available in EudraVigilance up until 12 March 2021.

EMA provided an assessment of the signal of embolic and thrombotic events for COVID-19 Vaccine AstraZeneca, including an observed to expected analysis (DL 12 March 2021).

PRAC Assessment

An exploratory analysis for thromboembolic events was conducted based on EV data. There was a lower proportion of overall serious thromboembolic events for COVID-19 Vaccine AstraZeneca compared to the other COVID-19 vaccines. However, a higher fatality rate was noted.

The observed vs expected analysis for COVID-19 Vaccine AstraZeneca for events including DIC, Cerebral venous sinus thrombosis and Haemorrhagic stroke showed a disproportionality in younger age groups, specifically those aged 18-54 years. However several limitations for this type of analysis apply, and should be taken into account, as discussed in the report, including:

(i) Code lists used to identify expected cases may not match the MedDRA classification used to identify observed cases in EV;

(ii) Cases of cerebral venous sinus thrombosis from published article identified by review of medical records in 2008-2010; uncertainty on comparability of diagnostic criteria with

2021 cases;

(iii) Background incidence rates are from one database/country only;

(iv) There might be under-reporting when the observed number of cases is calculated from spontaneous reporting systems such as EV;

(v) There might be delay in reporting: during a mass vaccination some case reports might not have been submitted yet to EV;

(vi) There might be more intensive case ascertainment in vaccinated individuals.

It also has to be considered that the populations exposed to the different COVID-19 vaccines can vary overall and between Member States, for example in terms of age, gender and prevalence of relevant co-morbidities.

In conclusion, for overall thromboembolic events this analysis is reassuring. However, a signal of disproportionality was noted for rare events, such as DIC, Cerebral venous sinus thrombosis and Haemorrhagic stroke warranting further investigation.

Updated OE analyses performed with data (DLP including data available in Eudravigilance up to the 16th March 2021 at 6pm)

EMA performed an updated observed to expected analysis (DLP including data available in Eudravigilance up to the 16th March 2021 at 6pm) .

Data sources used in the OE analysis

Data provided by the ACCESS consortium, stratified by age group, based on the average of the period from 2017-2020

- The databases used for the main analysis for the three events investigated are:
  - Coagulation disorder (this was used to compare with the SMQ Embolic and thrombotic events): ARS from Italy
  - Disseminated intravascular coagulation: FISABIO from Spain
  - Cerebral venous sinus thrombosis: ARS from Italy

- Different data sources were chosen according to the event considered, the reason was that when several incidence rates estimates existed (also considering other sources and literature), the data source with the median rate was chosen.

In addition a conservative sensitivity analysis was performed using the database with the lower incidence rate estimate

Background rates used for the specific events (including age stratification)

- The rate are expressed by 100,000 person years
- Coagulation disorder: ARS from Italy

Age category	IR
20-29	40.14
30-49	85.08
50-59	200.73
60-69	427.56
70-79	912.00

80+	2055.95

- Disseminated intravascular coagulation: FISABIO from Spain

Age category	IR
20-29	0.60
30-49	1.09
50-59	3.07
60-69	4.67
70-79	8.37
80+	11.66

- Cerebral venous sinus thrombosis: ARS from Italy

Age category	IR
20-29	0.64
30-49	1.80
50-59	1.00
60-69	1.29
70-79	1.91
80+	1.55

Results

		EEA			EEA and UK		
Disseminated intravascular coagulation	IR per 100,000 Person years From FISABIO	Expected 14d	Observed 14d From EV	**OE 14d with 95% c.i.**	Expected 14d	Observed 14d From EV	**OE 14d with 95% c.i.**
20-29	0.60	0.04	1	23.26 (0.30 - 129.41)	0.04	1	23.26 (0.30 - 129.41)
30-49	1.09	0.78	4	5.12 (1.38 - 13.11)	1.99	4	2.02 (0.54 - 5.16)
50-59	3.07	1.48	1	0.67 (0.01 - 3.75)	4.38	1	0.23 (0.00 - 1.27)
60-69	4.67	1.84	1	0.54 (0.01 - 3.03)	9.24	1	0.11 (0.00 - 0.60)
70-79	8.37	0.83	0	0.00 (0.00 - 4.42)	11.30	0	0.00 (0.00 - 0.32)
80+	11.66	0.90	0	0.00 (0.00 - 4.09)	5.37	0	0.00 (0.00 - 0.68)
Total		**5.87**	**7**	**1.19 (0.48 - 2.46)**	**32.31**	**7**	**0.22 (0.09 - 0.45)**

		EEA			EEA and UK		
Cerebral Venous Sinus Thrombosis	IR per 100,000 Person years From ARS	Expected 14d	Observed 14d From EV	**OE 14d with 95% c.i.**	Expected 14d	Observed 14d From EV	**OE 14d with 95% c.i.**
20-29	0.64	0.05	1	21.80 (0.28 - 121.32)	0.05	1	21.80 (0.28 - 121.32)
30-49	1.80	1.29	11	8.55 (4.26 - 15.31)	3.27	12	3.67 (1.89 - 6.41)
50-59	1.00	0.48	1	2.07 (0.03 - 11.53)	1.43	2	1.40 (0.16 - 5.06)
60-69	1.29	0.51	0	0.00 (0.00 - 7.23)	2.55	0	0.00 (0.00 - 1.44)
70-79	1.91	0.19	0	0.00 (0.00 - 19.37)	2.58	0	0.00 (0.00 - 1.42)
80+	1.55	0.12	0	0.00 (0.00 - 30.74)	0.71	0	0.00 (0.00 - 5.14)
Total		**2.63**	**13**	**4.94 (2.63 - 8.45)**	**10.58**	**15**	**1.42 (0.79 - 2.34)**

** Based on cases retrieved using a search in Eudravigilance with the Preferred Terms, "cerebral venous thrombosis" and "cerebral venous sinus thrombosis"*

Embolic and thrombotic events	IR per 100,000 Person years From ARS	EEA Expected 14d	EEA Observed 14d From EV	OE 14d with 95% c.i.
20-29	40.14	2.88	11	3.82 (1.91 - 6.84)
30-49	85.08	60.95	79	1.30 (1.03 - 1.62)
50-59	200.73	96.89	40	0.41 (0.29 - 0.56)
60-69	427.56	168.22	33	0.20 (0.14 - 0.28)
70-79	912.00	90.40	5	0.06 (0.02 - 0.13)
80+	2,055.95	158.30	8	0.05 (0.02 - 0.10)
Total		**577.64**	**182**	**0.32 (0.27 - 0.36)**

Of note, 9 cases without TTO assigned to the shortest risk period; 6 cases without age added only to the total, 1 cases with age group 10-19 not included in the analysis

Exposure data used within the OE analysis including age stratification and source (i.e. ECDC)

Age category	Vaccinated in EEA with AZ
20-29	211,917
30-49	2,133,764
50-59	1,428,787
60-69	1,190,833
70-79	309,743
80+	226,536

Number of vaccinated with AZ (~5.5 millions) up to 7th March based on ECDC data extracted on Monday 15th March (data are publicly available at https://covid19-vaccine-report.ecdc.europa.eu/) Most of the countries report data by detailed age groups to ECDC; however, some may report in a simplified way (<60 and 60 years and above) or do not provide details. When detailed data by age group was not available, information from countries where this information was provided was used to impute a distribution.

3.1.5.2. Specific Case assessement

Review of data received in EudraVigilance up to 12 March 2021

EMA conducted a search in the Eudravigilance database with a data lock point on 12 March 2021. The search terms were SMQ 'Embolic and trhombotic events', PT 'coagulopathy'.

General results (Data lock point 12/03/2021)

A total of 293 case reports were retrieved. After exclusion of possible duplicates, non-serious cases and consumer reports, 202 serious cases from healthcare professionals were selected for further review.

Most of the 202 cases originate from outside the EEA, with UK accounting for the highest number (158); of note, 5 cases from India. The 37 EEA cases (18%) originate from Austria, Germany (8 each),

France (4), Sweden (3), Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, Greece, Ireland, Italy, Korea and Spain (1 each).

The majority of cases (122) are in female patients, 76 are in men and in 4 cases the gender is not reported. Age ranges from 16 to 99 years with a median of 47.

25 different batch numbers were reported in 106 cases with this information. The batch number most frequently reported was mentioned 14 times.

The 10 most frequently reported thromboembolic terms were cerebrovascular accident (49), myocardial infarction (30), pulmonary embolism (24), monoplegia (16), ischaemic stroke (15), transient ischemic attack (15), deep venous thrombosis (13), hemiparesis (12), monoparesis (9), and acute myocardial infarction (6).

In 45 cases (22%), the outcome was fatal.

Time-to-onset for the thromboembolic events was specified in 181 cases, ranging from 0 to 34 days.

In 44 cases, the TE events were preceded by flu-like symptoms. Thrombocytopenia was reported in 7 cases. In 120 cases, there were underlying risk factors for the reported events such as a history of hypertension, cerebrovascular accident, diabetes, cardiac disorders, pulmonary embolism or comedications such as oral contraceptives. In a further 9 cases, there was a history of confirmed or suspected COVID-19. In 55 cases there was insufficient information for causality assessment. In 18 cases, there were no clear alternative explanation for the events. Of note, a history of autoimmune disorders such as rheumatoid arthritis, multiple sclerosis or thyroiditis was reported in 29 cases.

Among the trombotic events of special interest: a cerebral venous sinus thrombosis (CVST) was reported 5 times, disseminated intravascular coagulation (DIC) was reported 4 times, and superior sagittal sinus thrombosis was reported once. (DLP 12/03)

Updated review including data available in Eudravigilance up to the 16th March 2021 at 6pm

A search in EudraVigilance for cases of 'embolic and thrombotic events' (SMQ) for the high level active substances COVID-19 VACCINE ASTRAZENECA CHADOX1 NCOV-19 and COVID 19 VACCINE (CHADOX1 S[RECOMBINANT]) was performed. The results included reports sent to EV up to 16 March 2021 18:00 CET.

A total of 469 reports was retrieved, which may include duplicates. Of these , 436 (93%) were serious, including 59 fatal (13%). One-hundred and ninety-one (191) reports originated from the EEA (41%) and 276 from the UK (59%). The majority of reports (312 [67%]) were from healthcare professionals. Reports were predominantly in female vaccinees (295 [63%]) with a median age of 60 years. Thrombocytopenia (and related PTs) was co-reported as a reaction in 26 cases. Disseminated intravascular coagulation was reported in the 6 of the retrieved cases, and a follow-up version of one of the previously submitted cases was being processed at the time the query was performed, thus there were 7 cases in DIC in total. There were 18 cases of cerebral venous sinus thrombosis including some reported as 'cerebral venous thrombosis' or 'cerebral thrombosis'. There were also 4 cases of mesenteric vein thrombosis.

Disseminated intravascular coagulation (DIC) (Data lock point including data available in EVDAS up to the 16th March at 6pm)

Six cases (+ 1 case re-submitted after cut-off) of DIC were received in Eudravigilance based on data available in Eudravigilance up to the 16th March 2021 18:00 CET) (table below). All cases originated from the EEA.

An overview of the 7 cases of DIC is presented within Table 6 below:

Table 6: Overview of DIC cases

Case	1	2	3	4	5	6	7
Age	20-29	30-39	60-69	40-49	30-39	50-59	30-39
Gender	F	M	F	F	F	F	F
Pre-existing condition	NA	Chronic hepatitis B Migraine BMI 32 Malaise, fainting, headache with normal tests	Hypertension Hypercholesterolaemia Hashimoto	Family history of polytropic thrombocytopenia	Allergy No family history of thrombosis		NA
Baseline treatment			Losartan K Levothyroxine Na Simvastatin	None	ethinyl estradiol and drospirenone(10 years) Desloratadine		NA
COVID-19	PCR neg Serology neg	27/01: PCR- 03/02: PCR- 27/02: False-pos Serology neg					
Initial reaction	Day1: flu like syndrome vomiting, chills	Pyrexia, headache	Headache		Fever and myalgia during 1-2 days		
Clinical course	Day 7: recurrence of digestive symptoms and headache unresponsive to paracetamol Day 9: Thrombectomy for ischemic stroke - Hemiplegia and aphasia	Day 10: lost consciousness, hemiparesis, pyrexia (38.1 C)	Headache Day 5: Tiredness, Speech impairment Day 7 : Hospital with Abdominal pain, Motor restlessness, Sytematic inflammatory response, Adrenal bleeding Day 8 : One-sided paralysis, Cerebral artery occlusion, ischemic cerebral infarction, Thrombocytopenia Day 10: Increase intracranial pressure Day 12 : Multiorgan failure	(dates unknwon) thrombosis in splenic vein and kidneys Necrotic intestine Pulmonary embolism	Day 6: fever, acute headache Visual disturbance in the lower right cadran Day 8: hospitalisaiton with Thrombosies of Venous sinuses, CID, thrombocytopenia Day 9: coma (Glasgow scale)	Day 11CID, haemorrhagic stroke, pulmonary thromboembolism, coma, hemiplegia, aphasia, acute coronay syndrome	Headache vasomotor Thrombopenia Disseminated Intravscular Coagulation
Fatal		Yes	Yes	Yes	Yes		
Stroke	Yes	Yes	Yes	PE	CVST		
Thrombocytopenia	Yes: 58 G/L peripheral	Yes: 14 G/L	Yes	severe	22 G/L		Yes
DIC	resolved	Fatal	Yes	Fatal	Yes		Yes
Imaging	Sinusitis	CT scan: thrombosis	Cerebral artery		Day 8CT, MRI:		

		af areria carotis interna and areteria cerebri media. Small subarachnoid hemorrhage	occlusion (right internal carotid artery and arteria cerebri media ipsilateral)		Veous sinus thrombosis, of sigmoid and transverse sinuses, Thrombosis internal jugular vein (all lef side) Day 9: MRI: Sub-arachnoid haemorrhage + are reported Cerebellar oedema, cerebrellar haemaoma		
Labo	Myelogram normal AutoAb negative SAPL test, PNH negative	RBC 5,15x10*12/l; Hct 45,6%; PLT 14x10*9/l; IPF 9,9% (N 1,3-7%) - activation of thrombopoiesis. INR 1.09. D-dimers in plasma >35 (ref<0.5 mg/l), plasma fibrinogen 1.02 (ref 1.7..4.2 g/l).	Day 8 : Systematic hypercoagulative disorder, DIC	Consumptive coagulopathy (DIC)	Day 8: Fibrin D Dimer >7 mg/L, Fibrinogen 1.3 g/L		
Diagnosis	Thombus left proximal M1	Ischemic stroke involving arteria carotis media, DIC	DIC Ischemic cerebral infarction Adrenal bleeding Systematic hypercoagulative disorder	Autopsy: pulmonary embolism, DIC Association with vaccine considered unlikely	CVST CID Important cerebral damage not compatible with life		
Expert opinion	Moderate thrombocytopenia unfrequent in stroke	Ischemic stroke withthrombocytopenia in the context of DIC	Ischemic stroke, Transfusions could contribute to DIC, Thombocytomenia in the context of DIC	Unclear case, poorly documented	Oral contraceptives increases 7x the risk of CVST in women. Expert 2: normal aPTT, normal INR and normal fibrinogen go against DIC. More like HIT-type clinical picture: Thrombocytopenia and thrombosis leading to treatment with heparin.	Acute coronary syndrome although troponin level can also be increased in PE [pulmonary emboly]. Haemorrhagic stroke and DIC with elevated D-Dimers, thrombocytopenia.	

PRAC Assessment

Seven cases[1] reported with the PT "Disseminated Intravscular Coagulation" (DIC) were identified from the Eudravigilance report. Three were less documented.

The Disseminated Intravascular coagulation (DIC) events were identified mainly in women (6/7) and in young adults (aged 26 to 60 years). COViD-19 results were provided for two cases only and both test were negative (one of the case had 1 PCR positive on 4 and was considered as false positive) No information was found for the other cases. A fatal outcome was reported in four cases. In five cases, severe thrombocytopenia was reported.

An initial reaction to the vaccine is reported in four cases with no specific pattern. Those immediate reactions are followed by a period of improvement, most patients continuing their activities, before rapid deterioration 5 to 10 days after vaccination.

No risks factors for DIC can be clearly identified from this overview of cases. Clearly, the occurrence of neurological signs from 4 days after vaccination should alarm and request further imedical investigation. However, in the early phase of clinical deterioration, signs and symptoms can be difficult to interpret.

Cerebral venous sinus thrombosis (CVST)/Cerbral venous thrombosis (CVT) (DLP including data available in EVDAS up to 6pm on the 16th March 2021)

A total of 16 cases, reported under the MedDRA PTs 'cerebral venous thrombosis' or 'cerebral venous sinus thrombosis' were available in Eudravigilance up to the 16th March 2021 at 6pm. A further two cases, reported as 'cerebral thrombosis' were considered relevant following review by haematologist (expert opinion).

Of the 18 cases, six were fatal. In one of these fatal cases, an event of disseminated intravascular coagulation was also co-reported. Therefore, a total of 9 fatal cases were reported for events of DIC/CVST.

Cases originated from 5 countries: DE (7), IT (3), UK (3), IN (2), NO (2), ES (1). The majority (16) were in women, the median age was 42 (range: 22 to 64). The time-to-onset ranged from 1 to 14 days with a median of 8 days. Thrombocytopenia occurred in 12 cases (67%). Several cases possibly confounded by medical history and/or co-medications.

An overview of the 18 cases of CVT/CVST are presented in the table 7 below

[1] Summary and DIC table updated by EMA on 19 March 2021

Table 7: Overview of cases concerning CVT/CVST

Case	Age	Gender	Medical history	Concomitant medication	TTO (days)	Other reactions	Fatal
1	40-49	F	Asthma, Intervertebral disc protrusion, Autoimmune thyroiditis		9	Acute respiratory failure, Cerebral venous sinus thrombosis, Chills, Coordination abnormal, Dizziness Gait disturbance, Headache, Hemiparesis, Pain in extremity, Pyrexia, Seizure, Thrombocytopenia Vomiting	Yes
2	30-39	F			7	Brain death, Haemorrhage intracranial, thrombocytopenia	Yes
3	40-49	F			13	Haemorrhage intracranial, headache, Immune thrombocytopenia, Peripheral artery thrombosis, Pulmonary embolism, pyrexia, tachycardia	
4	20-29	F			7	Epilepsy, Subarachanoid Haemorrhage	
5	30-39	F			8	Thrombocytopenia	
6	40-49	F			13	Cerebral haemorrhage, Conversion disorder, Headache, Hemianopia homonymous, language disorder	
7	40-49	F			6	Immune thrombocytopenia	
8	40-49	F			3	Thrombocytopenia	
9	50-59	M			12		

10	30-39	M			8	Fever, pyrexia, Headache, platelet count decreased, Brain stem infarction, cerebral haemorrhage, haemorrhage, haemorrhage intracranial, , Nervous system disorder, superior sagittal sinus thrombosis, CVST	Yes
11	60-69	F			8	Headache, vomiting, photophobia	Yes
12	30-39	F			12	Headache, vomiting, gastritis	Yes
13	30-39	F			8	Severe headache, vomiting, weakness, thrombocytopenia, haemorrhagic infarction	
14	40-49	F		Ethinylestradiol, Etonogestrel	12		
15	50-59	F			1	Thrombophlebitis superficial	
16	40-49	F	Factor II deficiency		12	Hepatic vascular thrombosis	
17	30-39	F	Hypersensitivity	Deloratadine, Drospirenone & Ethinylestradiol	6	Brain oedema, Cerebellar haematoma, Disseminated intravascular coagulation, subarachanoid haemorrhage, thrombocytopenia.	Yes
18	40-49	F		Ethinylestradiol, Etonogestrel	10	Cerebral haematoma, Haemorrhagic cerebral infarction, thrombocytopenia	

Other selected cases of interest (based on review of data received to EV up to 12 March conducted by EMA clinical experts in cardiology, haematology and neurology)

Of the 27 cases of interest, 16 concerned female patients, 8 concerned male patients and in 3 cases gender was not specified. Their age ranged from 21 to 80 years, with 3 persons in their twenties, 8 in their thirties, 3 in their Fourties, 6 in their Fifties, 3 in their Sixties and one in their Eighties.

Among the 27 cases, 18 were not considered by the experts to be related to the central nervous system (CNS). Those includes cases of Venous thromboembolism (5), pulmonary embolism (7), deep vein thrombosis (2), portal vein thrombosis (1), splenic infaction (1), vena cava thrombosis (1), local site reaction (1), anxiety reaction (4). Most case of pulmonary embolism were associated with venous thromboembolism. DIC was identified as possible in two cases. Of note that patients could experience various of those terms and that the level of certainty of the diagnosis were variable.

Among CNS-related events, other causes were identified: in one patient, vascular condition (e.g. aneurysm) or effect of another drug (apixaban) could not be excluded, reaction at the injection site (1), a pseudo-relapse of multiple sclerosis due to fever, and one case not interpretable.

The PRAC selected five cases from this previous list. Two of those cases report stroke episodes (in yellow in the following table), two report CVST (in orange), and on haemorragic case (blue). For one of the latter, an haematologist expert suggested the possibility of Heparin-induced thrombocytopenia (HIT).

Case	Demographics and pre-existing conditions	Summary of clinical course	Experts' opinion
1	40-49♀ Hashimoto's thyroiditis, Asthma, Intervertebral disc prolapse	D0 Vaccination NA: headache + typical subacute vascular symptoms Thrombosis of venous sinuses	Neurologist: Pattern compatible with thrombosis of venous sinuses Cardiologist: Chills, fever, pain in limb, dizziness, headache, vomiting, gait instability, hemiparesis, seizure. – clinical picture could be of CVST (cerebral venous sinus thrombosis). Haematologist: Thrombocytopenia in the context of DIC
2	20-29♂ Concomitant medication was not reported	D0 Vaccination NA Death. Brain swelling (Confusion and Hemiparesis) but also stated intracerebral bleed and decompression craniotomy and thrombopenia. Systemic symptoms present including Micturition urgency and Painful urination and Nausea and Vomiting and Petechiae Scleral hyperaemia and Macroscopic haematuria.	Neurologist: Personally, the most probable situation is a Haemorrhagic lobal stroke treated with craniectomy. There were also systemic symptoms so the CNS haemorrhagic may be in a broader context. Haematologist: In my opinion, the only case that could fit into the clinical presentation of TTP (although DIC is also likely)
3	40-42 likely man No cardiovascular risk factors.	D0 Vaccination D1 Flu-like syndrome + injection site reaction D2 Left hemiparesis + sensitive symptoms during few minutes. Hospitalization. NRL exploration normal but a micro-ischemia in DWI+ FLAIR- D4 NRL normal CSF high-proteins only. MRI same lesion now DWI- FLAIR+	Neurologist: Ischemic Stroke of unknown etiology in a young person without vascular risk factors and normal cardiac study (except for the finding of FOP but nothing supports the embolic etiology, so it is probably not related with the current stroke) Cardiologist: Clinical picture of possible TIA event in young patient with PFO. PFO is a risk factor for stroke or TIA within 24 hours after administration of vaccine.
4	30-39♂	D0Vaccination D1Fever, generalised aching D9 Headache, thrombocytopenia (30 and fell to 10 – 15 $x10^9/l$, clotting time: normal Blood test: no red cells fragments cerebral venous sinus thrombosis (CVST), intracranial haemorrhage D10Superior sagittal sinus thrombosis, brain stem infarction, intracranial haemorrhage, cerebral haemorrhage D10 Death, no autopsy	Cardiologist: Clinical picture of rapidly developing thrombocytopenia of unknown trigger associated with CVST, brain stem infarction and intracranial haemorrhage in patient 9 days after administration of vaccine. Limited blood tests provided do not point to DIC (normal clotting time), do not point towards TTP (no red cell fragments). Unclear how the signs of inflammation the day after vaccination are linked to neurological picture that developed thereafter. The predominant etiologies of CVST in male patients are haematological disorders, a hypercoagulable state, trauma, cancer. Haematologist: intriguing because it fits very well with the "HIT-like theory". This patient had an inflammatory syndrome (aches, fever) followed by thrombocytopenia and thrombosis, but without any signs of DIC (normal clotting factors) or TTP, and ended up having bleeding, probably due to severe thrombocytopenia. Strong suspicion of HIT like reaction.
5	60-69♀ Psoriasis (no systemic treatment) Hypertension, dyslipidaemia Hypertensive heart disease amlodipine, valsartan and hydrochlorothiazide, Betaine,Potassium Hydrogen Carbonate, Nebivolol Rosuvastatin, nebivolol hydrochloride, Acetylsalicylic acid	D0 Vaccination D2 Stroke (carotid artery thrombosis) -> thrombolysis stopped due to thrombocytopenia worsening. Then decompressive craniectomy D2 Femoral artery thrombosis + embolectomy	Neurologist: Ischemic stroke The appearance of two events in different locations (CNS + Femoral) suggest that even atrial dilation was considered as mild by the Cardiologist, the origin may be embolic. Cardiologist: Clinical picture of possible AF with resulting emboli to CNS and leg (increased size of the atrium in echocardiography in patients with HTN, CHF [nebivolol] and hypercholesterolaemia). Haematologist: Agree, but also moderate thrombocytopenia, not very frequent in pts with stroke (0.3%)

PRAC Assessment

From the list of other cases selected in Eudravigilance report, 9 were identified as CNS-related. The PRAC selected five of those cases for further review, i.e. two cases of thrombosis, two cases of CVST and one case of cerebral haemorrhage. A possibility of DIC was mentioned for two of those patients, one with stroke and one with haemorrhage.

Those cases highlight the need for further research into occurrence of CVST and DIC in Eudravigilance.

Cases not reported in Eudravigilance at the time of the report

In addition to the cases identified in Eudravigilance, additional cases were communicated to the PRAC with a recording date in the database after the data lock point of the report.

Cases are summarised here-after with special focus on the cases with a suspicion of CVST:

Case	**1**	**2**	**3**	**4**	**5***
Age	20-29	40-49	20-29	40-49	30-39
Gender	F	F	F	F	F
Pre-existing condition	No smoking, no contraception	Healthy		obesity, gestational diabetes, allergic rhinitis, psoriasis, and methrorragias associated to endometrial polypus	
Baseline treatment		etonogestrel/ethinylestradiol			
COVID-19	No information	No information	No information	No information	No information
Initial reaction		D1: headache			Severe reaction 7 hours after vaccination
Clinical course	D7: Convulsion (cerebral aneuvrism and tumor excluded)	D7: Headache, backpain, pain in the leg D10 : found unconscious D11: hemiocraniotomy		Day 2: intense oppressive holocraneal cefalea with vomiing	D7: hospital admission with abdominal pain Persisting headache
outcome	Recovering	UKN - Cerebral status unclear		Recovering (enoxaparin)	Discharged
Thrombocytopenia	75 G/L	Yes	No	47 G/L D-Dimer 21,000	117 G/L
Diagnosis	Sinus venous thrombosis saggittlais superior and transversus) Cerebral haemorrhage	Haemorrhagic venous infarction Sinus venous thrombosis	Isolated venous sinus thrombosis	Extensive cerebral venous thrombosis, including longitudinal superior sinus, recturs sinus, transvers sinus, and left sigmoid sinus) Parieto-occipital infarction	Severe thrombosis in v. jugularis, the tisht sinus and in the sinus rectus, Cerebellar bleed
Expert opinion					

* Case submitted at the extraordinary PRAC (16 March 2021).

Three additional cases with **CVST** were reported on 16 March 2021:

> Case 6 30-39-year-old woman who experienced sinus vein thrombosis with thrombocytopenia 8 days after vaccination.The patient is still in the hospital, and further data have been requested.
>
> Case 7 : 40-49-year-old woman who experienced sinus vein thrombosis with thrombocytopenia (60,000/uL) 14 days after COVID-19 vaccination AstraZeneca. Further information is currently being sought.
>
> Case 8: 40-49 year old female developed sinus thrombosis and thrombocytopenia 6 days after vaccination with AstraZeneca.

Two other cases in women were communicated and were not identified in the Eudravigilance search:

Case 9 : Female, 30-39. Fatal case involving hospital admission 10 days after vaccination with left side hemiparesis, aphasia, and gradually reduced consciousness. CT showed cranial bleed. Thombocyts measures at 37. An autopsy report is requested

Case 10 : Female , 50-59, with hypertension under treatment. Case of pulmonary embolism, with symptoms starting 7 days after vaccination.

One additional case **of portal vein thrombosis** was communicated on 16 March 2021:

Case 11 : M, 30-39. Diagnosis of portal vein thrombosis whose symptoms started 7 days after vaccination. Thrombocytopenia at 10 G/L. The patient developped abdominal purpura annd easy bleeding. The outcome is currently unknown.

PRAC Assessment

Eight additional cases of cerebral venous sinus thrombosis were identified after the data lock point of the EudraVigilance report. All patients were women with ages ranging from 22 to 46 years. Thrombocytopenia was reported in 7 cases of the eight cases. No result for COVID-19 testing is reported.

Those cases follow the same chronological pattern of events, with first reactions in the 2 or 3 days following vaccination and secondary degradation in the 6 to 14 days following vaccination.

Those cases are not sufficiently documented to identify potential risk factors beside the fact that all cases are women.

In the other cases communicated, we note one case of deep vein thrombosis, one case of portal vein thrombosis, one fatal case of cranial haemorrhage, and one case of pulmonary embolism.

The cases identified after the data lock point of the Eudravigilance search were reported ad hoc by member states because considered as potentially relevant to the assessment. Their identification does not result from a systematic search.

Review of the cases: Overall PRAC comment

The Eudravigilance search permitted to identify 202 serious cases from which 22 % were fatal. Most cases (122) were female.

In this report, the PRAC reviewed more specifically the cases of disseminated intravacular coagulation (DIC) and cerebral venous Sinus thrombosis (CVST). Several observations were made and should be further discussed.

1) A **chronological pattern** is observed, with a first reaction to the vaccine observed in the first days after vaccination. This episode usually last 2 or 3 days and is followed, often after a healthy interval, by a period of deterioration 6 to about 12 days after vaccination. The clinical evolution is rapid.
2) A high proportion of cases are **female**. This may be due to a higher proportion of women vaccinated or a higher risk of thrombotic events in this population;

3) The persons affected are mainly **young adults**, with some cases in their twenties. Again, this could reflect the population currently vaccinated in many countries although many adverse events in older population are reported from UK. The identification of more cases in the younger population could reflect a higher risk in this population. Eventually, it could also reflects the fact that thrombotic events being less expected in this population, those cases attract more attention.

4) **Thrombocytopenia** is documented in most cases of thrombotic events. Thrombocytopenia is often severe and most likely peripheral. The association of cerebral thrombosis and thrombocytopenia is unusual and the pathophysiological mechanism of these thromboses may differ from classical ischemic strokes.

The review of the cases did not permit to clearly identify **risk factors** beside those already mentioned (i.e. potentially age and sex). It was also not possible to identify **prodromes**. High reactogenicity is documented for this vaccine and signs and symptoms reported here are not specific. Also, the first signs at the time of the degradation varied, although **neurological signs and a resurgence or increase of symptoms a few days after vaccination should be taken in high consideration.**

Finally, those cases did not permit to document a possible association with **COVID-19 infection**. However, when the results of the tests were made available, they were negative.

3.1.6. Information received from MHRA

Information received on 16th March

Following the reports of temporarly pause of the vaccination programme with COVID-19 Vaccine AstraZeneca in several EU member states the MHRA conducted a review, focusing on specific UK data on venous thromboembolic events occurring more generally along with an evaluation of cases of thrombocytopenia, with and without venous thromboembolic events.

The report mentions the following:

With AstraZeneca the pattern seen with venous thromboembolic events more generally is in keeping with expected background trends and usage of the vaccine. There have been a small number of cases reported of thromboses with thrombocytopenia which appear to be in keeping with the cases reported from the EU, however this remains at a low incidence given the usage to date. The available evidence is insufficient to establish a causal association, and MHRA continues to monitor cases reporting thrombocytopenia, immune thrombocytopenia and associated events.

In summary, venous thromboembolism (VTE) occurs naturally, in all ages, and is not uncommon. We have been closely reviewing reports of VTE and their consequences following vaccination with COVID 19 vaccines. Amongst the more than 24 million doses of both vaccines administered so far, several hundred cases of VTE are expected to have occurred by chance within a short time after vaccination. The analyses show no evidence that VTE, overall, is occurring more than what would be expected in the absence of vaccination, for either vaccine.

The action taken by some EU countries over the past week to temporarily pause the use of the AstraZeneca vaccine has been based mainly on isolated reports of cerebral sinus vein thrombosis concurrent with thrombocytopenia and bleeding shortly after vaccination. This form of blood clot can also occur naturally in the absence of vaccination, can occur in association with COVID disease and is extremely rare, and a causal association with the vaccine has not been established. The reporting rate of this following vaccination in Germany has been 4 per million doses of the vaccine. In the UK, 4

possible cases of this form of blood clot with low platelets after 11 million doses of the AstraZeneca vaccine have been identified so far.

Whilst this requires further review, a causal association with the vaccine cannot be established based on available information. Given the extremely rare rate of occurrence of these events, the benefits of the AstraZeneca COVID vaccine, with the latest data suggesting an 85% reduction in hospitalisation and death from COVID disease, far outweigh any possible risks of the vaccine.

3.1.7. Hypotheses and Comments from Member States

3.1.7.1. Background COVID 19 disease and thrombothic disease

Coagulation abnormalities (including thrombocytopenia) have been associated with COVID-19 disease, with variable incidence.

EMA report on Coagulation abnormalities in context of COVID-19 2021-03-12 (last update) Information overview v1.2

The EMA has released an analysis report on the COVID 19 coagulation abnormalities based on current status of knowledge in the information available in the literature and case studies.

Relevant sections of this report are summarized below.

Mechanistic and pathophysiological aspects

As regard mechanistic and pathophysiological aspects, coagulation abnormalities in COVID-19 are described as a consequence of both, cell and tissue damage that results from invasion of SARS-CoV-2 (in particular into type II pneumocytes with their ACE2 expression) with local inflammatory responses (endotheliitis), and also general changes such as associated with systemic inflammation, critical illness and reduced mobility (stasis). Some have referred to this as "viral coagulopathy", which in COVID-19 is notable for the high frequency and severity of microthrombosis, in addition to macro-thromboembolic events (such as also occurring in sepsis).

It seems to be held that microthromboses can lead to macrothrombosis and subsequently to clinical events (e.g., as in review by Ortega-Paz Luis et al. 2021; Manolis et al. 2021), in both the venous and arterial circulation.

The local mediator and link between inflammation, coagulation abnormalities and microthrombosis is reported to be neutrophil extracellular traps (NETs), in a process dubbed NETosis (reports predate COVID-19). This mediation occurs at both levels, local (microvascular) and systemic (macrovascular), for reasons including that NETs can enter vessels and cause platelet activation (through Toll-like receptors, TLR), factor V activation and thrombin generation. NETs are large extracellular, web-like structures of former cytosolic and granule proteins that assemble on a scaffold of chromatin, and these have been described to kill extracellular pathogens (Lee and Grinstein 2004).

These pathophysiological events can occur in the absence of an obvious systemic cytokine storm.

The coagulation abnormalities can lead to comorbidities and events such as VTE, stroke, diabetes, lung, heart attack, acute kidney injury and liver injury. Conversely, cardiovascular risk factors can exacerbate the dysfunction of endothelium cells and platelet and contribute to coagulopathy**.**

Consistent laboratory findings of coagulation abnormalities in COVID-19 are: elevated factor VIII and elevated fibrinogen. Unusual findings are: bleeding, thrombocytopenia, "very long" (a)PTT (e.g., more than 6 s longer than normal [25-35 s] and / or aPTT is out-of-proportion longer than PT is longer). D-dimers are recommended to be measured (see below) and to be better reported to avoid misinterpretation (Favaloro and Thachil 2020).

Risk factors

In COVID-19 hospitalised patients, the "D-dimer level at presentation was independently associated with thrombotic events, consistent with an early coagulopathy", based on more than 3300 consecutive admissions in New York state (Bilaloglu et al. 2020). Baseline D-dimer levels seem useful for stratification of investigational interventions (such as done in the REMAP-CAP trial), but at this time they have no systematic impact on clinical management.

Of note are estimated adjusted hazard ratios (HR) for a thrombotic event (ibidem, table 2): male 1.5, myocardial infarct 1.4, congestive heart failure 1.3 and D-dimer from 1.2 to 7, whereas HRs for age and BMI were around unity. (Reasons for the prognostic importance of sex can be addressed in an update of this document.) A systematic review quantified risk factors for VTEs in around 30,000 COVID-19 patients (table 4 in Nopp et al. 2020), reporting that men at higher risk to develop VTE but finding no association between comorbidities or age with the risk of VTE, possibly because the high VTE risk associated with COVID-19 masks general VTE risk factors such as age.

Strong clinical risk factors for VTEs in the general population are high age, obesity, reduced mobility, history of cancer or active cancer, intensive care treatment, history of VTE or thrombophilia; inherited thrombophilia conditions may or may not be known at the time of a TE, but they concern up to 12% of the general population (considering for example factor V Leiden; further such conditions are prothrombin mutations, deficiency of AT or protein S or C, anti-phospholipid syndrome).

The ISTH scoring system is an important tool to synthesise risk factors in patients with conditions that predispose to disseminated intravascular coagulation (Levi et al. 2009), which in some patients predominates as thrombosis, arterial or venous thromboembolism, purpura fulminans associated with peripheral ischemia or vascular skin infarction. In the case of a predisposing condition, the score ranges from 3 (minimum) to 8 points (maximum):

- Platelet count: 1 point if 50,000 to 100,000/µl, 2 points if <50,000/µl
- PT: 1 point if 3 to 6 s, 2 points if more than 6 s prolonged
- Fibrinogen: 1 point if <100 mg/dL
- D-dimer: 2 points for moderate, 3 points for "strong" increase [cut-off values have not been defined but "3- to 4-fold increases" are proposed (Thachil et al. 2020)]

COVID-19 as a severe infection should qualify as predisposing condition so that the score can be used to gauge the risks of patient for coagulation-related events. With respect to coagulopathy, it has been recommended to monitor PT, D-dimers, platelet counts and fibrinogen for determining the prognosis of Covid-19 patients (Thachil et al. 2020).

Other risk factors for coagulation abnormalities and / or TEs in COVID-19 are currently suggested (e.g., deficiencies of vitamin D, magnesium, phosphate), with recommendations to correct obvious deficiencies.

In the paediatric population, the Multisystem inflammatory syndrome in Children (MIS-C) involves multi-organ function impairment according to a literature review (Hoste, Van Paemel, and Haerynck

2021); thrombotic complications affected only 13 out of 928 paediatric patients with MIS-C but included serious events (2 splenic infarctions and 5 cerebral strokes during ECMO).

PRAC Assessment

The association between coagulation abnormalities and COVID-19 disease is now rather well documented including in recent literature review papers. The literature review by Raadsen M et al. (2021) can be cited as an example. The authors discuss the Thrombocytopenia in Virus Infections and there is a paragraph on SARS-COV2. Consistently with the EMA report, the authors describe several mechanisms involving hypercoagulability and inflammation interact resulting in thrombotic phenomena, both in the microvasculature and in the larger, mostly pulmonary blood vessels.

Current recommendations in the EMA report for clinical management of coagulation abnormalities in COVID-19 are based on medicines and approaches that are used widely and generally for prophylaxis and treatment as for other critically ill or ICU-hospitalised patients.

Raadsen, Matthijs et al. "Thrombocytopenia in Virus Infections." Journal of clinical medicine vol. 10,4 877. 20 Feb. 2021, doi:10.3390/jcm10040877.

3.1.7.2. Hypothesis based on cases:

1. Heparin induced thrombocytopenia- like syndrome (HIT)

This hypothesis is less documented and further information is still being collected.

The hypothesis was presented by {Member State} and is presented below. Based on this hypothesis, the etiology of the clinical presentation observed in patients would be a cascade of reactions triggered by the combination of heparin with Platelet Factor 4.

This hypothesis would be consistent with the HIT-like syndrome associated with thrombocytopenia and sometimes evolving into Disseminated intravascular coagulopathy or Cerebral venous sinus thrombosis also associated with thrombocytopenia.

The hypothesis of HITT-like syndrome is supported by some thoughts and comments by EMA haematologist experts and by Member States.

Analysis from EMA experts

Haematologist: A heparin-induced thrombocytopenia-like syndrome could be a possibility and explain the triad of thrombocytopenia, thrombosis and bleeding. Indeed, pseudo-HIT would fit better than TTP. Some factors supporting this theory are:

- HIT is more common in women than men.

- HIT is more frequent when there is some inflammatory background (surgery/trauma) than when heparin is administered in other contexts. I believe that something in common to all fatal cases from this series is a systemic inflammatory syndrome.

There are, however, some differences:

- HIT is a serious disease, with a mortality that can reach 20%, but the cause of death is typically thrombosis (e.g. stroke). DIC is a rare complication of HIT.

- The importance of thrombotic events explains why anticoagulation with an alternative agent (e.g. danaparoid) is a very important part of therapy. The fatal cases from this series all ended up having DIC, where anticoagulation would have been difficult/controversial.

- In HIT, heparin is administered continuously, and this continuous "antigen" administration self-perpetuates the immune response, whereas stopping the heparin typically improves the problem. Indeed, HIT is clearly associated with length of heparin therapy. The same applies to many other immune-related drug reactions. In contrast, here we are dealing with a single administration of a "drug", so the mechanism must be somewhat different. Or, for these patients this was not the first encounter with the antigen. This raises the question as to whether fatal cases went through COVID-19 disease before vaccination.

Cardiologist: Agree with these comments and in particular the difference related to the prolonged (or repeated) administration of antigen in immune-mediated HIT vs single administration of vaccine. Also the recovery from thrombocytopenia follows within day when the administration of heparin is stopped. But similar to what is observed with several cases here there is often in HIT this few days/weeks delay in development of thrombocytopenia/clinical picture (unless repeated exposure where the symptoms develop more rapidly).

Analysis from Member State

Some of the case stories including the Member State case, involve primarily younger, previously relatively healthy women (and two men) who developed thrombocytopenia, bleeding and thrombosis all within 7-10 days of vaccination with the AZ vaccine. A theory has now been raised that the mechanism behind the clinical presentation could be similar to what is seen in cases of heparin induced thrombocytopenia (HIT), except that the immunological response could be triggered by the AZ vaccine rather than heparin.

Heparin induced thrombocytopenia occurs very rarely and it is not possible to pinpoint in advance which patients are at increased risk of developing this condition. Heparin triggers an immunological response leading to thrombocytopenia, bleeding and thrombosis. The time to onset is typically 5-7 days. The cases with the AZ vaccine had time to onset of the serious adverse event within 7-10 days in patients with a clinical presentation very similar to that seen with HIT.

Given that the factor(s) involved in the development of thrombocytopenia, bleeding and thrombosis, it is difficult, from quality perspective, to know what to look for. Although, at this stage, it does not seem likely, that the events seen is quality related, this should not be excluded. While it is clear that the AZ vaccine does not contain heparin, the question remains whether something else, related to the quality of the AZ vaccine, could have been involved in causing the events seen. Any possible option should be taken into consideration, such as: possible quality defects, a particular excipient, or a product- or process related impurity, originating from a particular step in the manufacturing process, and which may trigger a similar immunological response as seen in cases of HIT. It should also be considered if batches involved in the currently reported events is from a particular drug substance- or drug product site.

PRAC Assessment comment on HITT hypothesis

It should be noted that the relevant information to substantiate this hypothesis is still being collected and more data is expected from experts and from MAH by the time of PRAC discussion of 18 March 2021.

The possibility of heparin-induced thrombocytopenia (HIT)-like syndrome triggered by a component in the vaccine is evaluated by experts. The clinical picture is quite similar. It seems that the pathophysiological mechanism involved may mimic the HIT entity, with platelets as a direct target. This remains to be demonstrated.

2. Other hypothesis:

- ***COVID-19 disease***

As described above, COVID-19 is known to be associated with coagulation abnormalities (see section 3.1.7.1). Confounding effect or underdiagnosis of covid-19 disease cannot be excluded.

Comments from Member State

We note that in the 4 Member State cases, the time to onset is 10 days or less after what seems to be the first dose of the vaccine in the three that specify TTO. It takes 3 weeks for protection to start after the first AZ dose, hence these patients would not yet have immunity to COVID-19. We also noted the temporal relationship described in the fatal and complex cases in the signal AR. Case 1 had a fever when she presented with headache. Of note, in addition to thrombocytopenia, she also had elevated D-dimer.

Thrombotic events may be the presenting feature of COVID-19 which causes a hypercoaguable state, including thrombocytopenia, elevated D-dimer levels and prolonged PT (Jafari 2020) [20]. VTE in COVID includes PE, DVT and as well as 'immunothrombosis' in smaller pulmonary arteries and capillaries (BTS Guidance on Venous Thromboembolic Disease in patients with COVID-19, 2021) [21]. Thrombotic complications in COVID-19 also include MI and ischaemic stroke (Piazza & Morrow 2020) [22].

There are also numerous literature publications specifically concerning cerebral venous sinus thrombosis (CVST) in young patients with COVID-19 (e.g. Abouhashem 2020) [23], even without risk factors for VTE, and it has been described as a presenting feature (Hughes 2020) [24]. We note one case series in which one patient was on oral contraception additionally (Cavalcanti 2020) [25], and there is a further case in which CVST was accompanied by coagulopathy (Sugiyama 2020) [26]. There is also a further case which was accompanied by internal iliac vein thrombosis related to paucisymptomatic infection with COVID-19 (Beretta 2020). In this case, nasopharyngeal swab, repeated twice, tested negative for SARS-CoV-2 – it was serological tests that confirmed SARS-CoV-2 infection.

A recent literature review of CVST in COVID-19 identified 9 studies and 14 patients (Tu 2020) [15]. The median age was 43 years (IQR=36-58) and majority had no significant past medical conditions (60.0%). The time taken from onset of COVID-19 symptoms to CVST diagnosis was a median of 7 days (IQR=6-14). A significant proportion of patients had raised D-dimer (75.0%). Overall mortality rate was 45.5%. It also seems that women may be affected more frequently (Nwajei 2020) [27]. A further publication advises that COVID-19 patients with a preexisting hypercoagulable state, such as pregnant/ postpartum women, women using OCPs, those in a fasting state, and those with history of thrombophilia, malignancy, and chronic inflammatory diseases are high-risk groups (Shakibajahromi 2020) [28]. Indeed, we note that three of the cases are on CHCs and in one, tranexamic acid is listed as a concomitant medication. This publication also highlights that elevated D-dimer, fibrinogen level, fibrin/fibrinogen degradation product (FDP), and thrombocytopenia are commonly reported laboratory abnormalities in COVID-19 patients, with higher rates in severe disease. It further noted that CVST

and COVID-19 might present with haemorrhagic infarction as the first imaging manifestation and that the presence of any unexplained and atypical haemorrhagic lesion in the initial brain CT of these patients should raise the suspicion to CVST. A meta-analysis estimated the risk of CVST among hospitalised SARS-CoV-2 infected patients to be 0.08% (95% CI 0.01% - 0.5%) (Baldini 2021) [29].

We further note that there are a number of published case reports describing portal vein thrombosis in previously healthy young males (Borazjani 2020 [30], Franco Moreno 2020 [31], Jafari 2020 [20]), and one publication describes COVID-19 as a novel aetiology of this condition (Hassan 2021) [32]. Mesenteric ischaemia can also be a presenting feature of COVID-19 or may occur at a late stage in the disease, as described in a recent case series (Singh 2021) [33].

We further note that DIC has been described in association with COVID-19 (Asakura & Ogawa 2020) [34[34]. A recent paper has proposed a definition for COVID-19-associated coagulopathy (CAC), based on clinical and laboratory features (Iba 2021) [35]. This includes proven COVID-19 test with two or more of the following four criteria: (1) decrease in platelet count (less than 150 × 109/L); (2) increase in D-dimer (more than two times the upper limit of normal); (3) >1 s prolonged prothrombin time or INR > 1.2; (4) presence of thrombosis (macrothrombosis including deep vein thrombosis/venous thromboembolism, thrombotic stroke, acute coronary syndrome, limb artery thrombosis, mesenteric artery thrombosis, etc., and/or microthrombosis including skin, acral lesions, etc.) (Iba 2021) [35]. If the patient meets one of the above 4 criteria and also one or more of following criteria: (i) increase in fibrinogen level; (ii) increased VWF (more than two times the upper normal limit); (iii) presence of lupus anticoagulant and/or high-titer antiphospholipid antibodies, they are defined as "risk of CAC".

It may also be worth considering that the accuracy of viral RNA swabs in clinical practice varies depending on the site and quality of sampling. A positive test for SARS-CoV-2 on PCR generally confirms the diagnosis of COVID, and CDC indicates that confirmatory laboratory evidence is detection of SARS-CoV-2 RNA in a clinical specimen using a molecular amplification detection test. However, false negatives may occur (Woloshin 2020) [36]. Accuracy varies by site and stage of disease and degree of viral multiplication or clearance (Watson 2020) [37]. The CDC definition of severe Covid indicates RNA to be confirmatory laboratory evidence, but it can be diagnosed on presumptive laboratory evidence including detection of specific antigen in a clinical specimen or detection of specific antibody. However, antibody testing should be undertaken at least two weeks after onset of symptoms and the sensitivity and specificity of antibody tests vary over time, hence results should be interpreted in the context of clinical history and depends not only on the accuracy of the test itself, but also the pre-test probability of infection. At days 1-7, the sensitivity of IgM testing is only 23.2%, increasing to 58.4% at days 8-14. Similarly, for IgG, sensitivity at day 1-2 will be 29.7%, increasing to 66.5% day 8-14. A single negative test result may not be informative if the pre-test probability is high (Watson 2020) [38].

We suggest that it may be warranted to consider COVID-19 an alternative aetiology, particularly in cases of VTE and ATE which are very unusual and/or associated with thrombocytopenia, elevated D-dimer levels and prolonged PT. It may also need to be considered that background rates of VTE and ATE including rare types of events measured prior to 2020 may not be reflective of the current background rate, with the virus in circulation.

PRAC assessment comment on "COVID-19 disease" hypothesis

This hypothesis is mechanistically plausible. However this is not supported by the negative PCR and serologic results in some patients experiencing coagulation abnormalities.

It cannot be excluded that COVID-19 might be part of the possible explanations but it is hardly the only one.

Many of the people affected by this clinical picture suffer from auto-immune or allergic pre-existing conditions (asthma, psoriasis, drug allergies, auto-immune thyroiditis or other auto-immune disease) or a chronic hepatitis B (2 cases) that may play a role as chronic immune stimulation.

Taking into account the fact that COVID19 infection is associated with tremendous thrombotic complications, whose complete pathophysiology is not well understood, it is logical to suspect that the immune responses associated with COVID19 infection and COVID-19 vaccination may share some similarities that would increase the risk of thrombotic event. We could imagine that the S-specific T cell immune response may induce a cross reaction with a specific human protein or antigen involved in the hemostatic system (and leading to platelet activation and/or consumption) in people particularly sensitive because of a "reactive" immune system. The phenomenon of "molecular mimicry" in the situation of vaccines has been well reviewed by Segal et al. 2018 [39]. Regarding the timing of the immune response following vaccination, we know that the immune response starts quickly after vaccine administration (as evidenced by fever or systemic symptoms starting few hours after vaccination) and, even if 3 weeks are needed to achieve immunity against COVID19, the process is launched immediately and the production of antibodies is only part of the global immune response triggered by vaccination. However, this hypothesis would not explain why a particular occurrence of this clinical picture is described after the AstraZeneca vaccine compared to other non-adenovirus COVID19 vaccines (Pfizer, Moderna).

- ***Adenovirus vector***

Some evidence that thrombocytopenia has been reported following the administration of adenoviral gene transfer vectors. impact of the ChAdOx1 in this context.

Analysis from Member State

General clinical overview of cases:

For assessment of possible pathogenicity mechanisms, a general overview of the clinical issue(s) is obviously the first step. This general clinical overview is provided in the following.

It should be stressed that the information is preliminary and incomplete, as cases are still accumulating, several patients are in intensive care or recovering (outcomes unknown), and details for the diagnostic hematology workup for patients is lacking (translation of hospital records is pending).

So far, EMA/PRAC, is aware of a total of approx. 15 cases of thromboembolic events combined with thrombocytopenia associated with use of the AZ COVID-19 vaccine.

The cases had the following in common:

Most cases occurred in individuals < 50 years of age, i.e. the younger age group (no sex predisposition).

Most cases occurred within 10 days of the 1st vaccine dose, in otherwise generally healthy individuals.

Specifically, COVID-19 is associated with thromboembolic events, but there was no history of active SARS-CoV-2 infection in these cases.

Many cases had fatal outcomes.

Most of the cases presented with one or more of the following symptoms: Thrombosis affecting different organ systems (CNS, lung, spleen, gastrointestinal tract) and including large vessels (cerebral venous sinus thrombosis in 5 individuals, in others thromboses affected portal vein, splenic vein, pelvic vein, femoral artery, common carotid artery), thrombocytopenia (presumably secondary

to thrombosis, i.e. consumptive), bleeding, petechiae and multiorgan failure.

Platelet counts were in most cases in the 15 - 80 x 1E9/L range (i.e. above the very low levels often seen with drug-induced thrombocytopenia) [40].

The following observations are also considered relevant as regards evaluation of pathogenicity mechanisms:

In 3 of the apprx. 15 cases of thromboembolic events combined with thrombocytopenia, Hashimoto's thyroiditis was reported as co-morbidity.

In 3 of 13 other cases registered with monosymptomatic thrombocytopenia within 14 days of vaccination with AZ vaccine, comprising mostly older individuals (median age 63.5 years), idiopathic thrombocytopenic purpura (IPC) was reported as co-morbidity, and in these cases, flare-up of the purpura was seen after vaccination.

Both observations above suggest a possible auto-immune/immune component behind the thrombocytopenic and thromboembolic events.

In short, the cases appear to exhibit a general clinical presentation of moderate thrombocytopenia combined with pro-thrombotic predilection, affecting also large vessels.

Interestingly, this clinical presentation is considered to be quite similar to heparin-induced thrombocytopenia [40, 41]. It should be stressed, however, that there was no history of heparin treatment prior to thrombosis in these cases (some patients were treated with heparin after thrombosis was evident).

Description of vaccine (ChAdOx1 nCoV-19/AZD1222):

The active component in the vaccine is a replication incompetent chimpanzee adenovirus vector (ChAdOx1), encoding the full-length spike protein of SARS-CoV-2 (based on the original index Wuhan-1 sequence, codon-optimized, with a tissue plasminogen activator leader sequence).

The adenovirus particles are formulated in L-histidine (pH 6.6), NaCl, MgCl2, EDTA, sucrose, ethanol, polysorbate-80 (tween 80). One dose (0.5 mL) contains ≥ 2.5E8 infectious units of adenovirus particles.

Following intramuscular injection, the adenovirus vector is thought to transduce primarily muscle cells and fibroblasts at the injection site, and professional antigen presenting cells in draining lymph nodes, causing expression of the trimeric native-like prefusion form of the SARS-CoV-2 spike protein on cell surfaces (antigen-presenting cells also expected to display processed form of the spike antigen, not detailed) [42].

This mode and pattern of SARS-CoV-2 spike antigen presentation is essentially identical between ChAdOx1 nCoV-19/AZD1222 and eg mRNA-based vaccines. Also, all currently approved COVID-19 vaccines employ spike immunogen based on the sequence of the original SARS-CoV-2 isolate from the index human case in December 2019 (Wuhan-Hu-1 SARS-CoV-2 isolate) [43].

Possible vaccine-specific pathogenic mechanisms for combined thromboembolic/thrombocytopenic effects:

The following 3 pathogenic mechanisms were considered:

Hypothetical mechanism #1: Issue is caused by the SARS-CoV-2 spike protein immunogen encoded by the chimpanzee adenovirus vector. This mechanism was considered un-likely, as the mode and pattern of SARS-CoV-2 spike antigen presentation (on the surface of muscle cells and fibroblasts at

intramuscular injection sites, and by antigen-presenting cells in draining lymph nodes) is not vaccine-specific (is shared with mRNA vaccines, which also employ very similar Wuhan-based spike immunogens).

Hypothetical mechanism #2. Issue is caused by product impurities and/or excipients: This mechanism was considered un-likely, because (i) the vaccine excipients (detailed above) are not considered to be associated with thromboembolic risk, and (ii) the issue has to our knowledge not associated with certain batches of product (which would have been expected if the cause was eg contamination with endotoxin or other pro-thrombotic compounds).

Hypothetical mechanism #3. Issue is caused by the chimpanzee adenovirus vector:

Replication in-competent adenovirus vectors based on different serotypes of human adenoviruses are known to be able to cause thrombosis, secondary (consumptive) thrombocytopenia and disseminated intravascular coagulation, potentially leading to multiorgan failure and death, especially after intravenous injection of virus particles. This has been consistently described in preclinical models eg nonhuman primates and rabbits, and one fatality has also been reported in a phase 1 clinical trial [44-49].

The pro-thrombotic effects of adenovirus vectors are considered to be caused by a combination of the following pathways/sub-mechanisms [44-49]:

Binding of adenovirus to platelets, causing platelet activation and thrombosis.

- Specifically, aggregation and activation of platelets is mediated by so called RGD motifs in the pentn base of adenovirus particles, binding to alphaIIb/beta3 integrins on platelet surfaces [44].
- Interestingly, adenovirus particles can also bind platelet factor 4, the platelet antigen considered to be responsible for triggering heparin-induced thrombocytopenia [40, 41, 50].
- Thus, it is likely that antibody production against vector and/or platelet self antigens can might aggravate platelet activation, as is known from eg histamine-induced thrombocytopenia [40, 41].

- Binding of adenovirus particles to endothelial cells, causing endothelial activation and thrombosis.
- Systemic inflammatory response syndrome (SIRS; cytokine storm), which in itself activated platelets and endothelia.
- Auto-amplification loops, where initial adenovirus vector-mediated injury to thrombocytes and endothelia self-amplify (as is also known from eg heparin-induced thrombocytopenia and disseminated intravascular coagulations) [40, 41].

None of pathways/sub-mechanisms above require active adenovirus replication in platelets or endothelia (all are triggered by simple binding of virus vectors to cell surfaces).

Due to the overall similarity in the build of adenovirus particles, it is considered likely that the abovementioned pro-thrombotic effects are also shared by chimpanzee adenoviruses such as the ChAdOx1 vector employed in the AZ vaccine.

At the same time, it is considered likely that due to the sequence differences in the RGD loops between ChAdOx1and human adenoviruses [51], the risk profile of the AZ vaccine may in this respect

differ from vaccines based on human adenoviruses.

As mentioned, while the pathways/sub-mechanisms above are triggered by binding of virus vectors to cell surfaces, the thromboembolic mechanisms thus triggered can proceed and propagate due to self-amplifying feedback mechanisms; likely for this reason, the relationship between dose of vector and toxicity is non-linear, with dramatic differences in scope and severity of toxicity noted with only modest increases of vector dose at higher doses [49].

Also, there is substantial subject-to-subject variation in the toxicity of adenovirus vectors in humans [51]. The causes for this are unknown, but may relate to known genetic polymorphisms in eg alphaIIb/beta3 integrins or Fc receptors on platelet surfaces.

It should be stressed that such pro-thrombotic effects of adenovirus vectors in humans is exceedingly rare [49].

For all the reasons above, it is concluded that if the AZ vaccine causes the observed thrombotic/thrombocytopenic events, this is most likely caused by the ChAdOx1 vector.

Finally, it should be mentioned that the mechanisms described above for adenovirus-mediated pro-thrombotic effects are very similar to the mechanisms described for heparin-induced thrombocytopenia ([40, 41, 44-51]; not further detailed here). This similarity in clinical presentations between thrombotic/thrombocytopenic events associated with AZ vaccine use and heparin-induced thrombocytopenia has also been remarked on in the latest EMA assessment.

PRAC Assessment on Adenovirus hypothesis

This hypothesis is mechanistically plausible but not supported by the fact that IV administration might be needed to observe the abnormalities. However the latter should be nuanced due to known challenges in the implementation of the "syringe-not-in-vessel" test in the context of massive vaccination.

The hypothesis is also consistent with the different O/E computed with non-adenovirus vaccines (Pfizer and Moderna) and compatible with the negative PCR and serologic results in some patients.

As mentioned by other experts, a thrombocytopenia following the administration of adenoviral gene transfer vectors has been described, involving von Willebrand factor and P-selectin. It is true that the "syringe-not-in-vessel" test is hardly ever realized by vaccinators and that the risk of intravenous injection may possibly increase the risk of activation of this thrombocytopenic mechanism. However, it is considered unlikely that the thrombotic complications possibly associated with the vaccine would be imputed to adenovirus and would have no pathophysiological link with the thrombotic complications observed with COVID19 infections.

- **ChAdOx coexpression Tissue plasminogen activator**

There might be a potential role of tissue plasminogen activator (tPA) leader sequence in a thrombotic/thromcytopenia disorder (The active substance consists of a recombinant, replication-deficient (E1 and E3 deleted) chimpanzee adenovirus (ChAdOx1) that encodes the SARS-CoV-2 (nCoV-19) spike protein combined with a tissue plasminogen activator (tPA) leader sequence).

Comment from Member State

The COVID-19 vaccine AstraZeneca does not only code for the protein S but includes a tissue plasminogen activator (tPA) signal sequence, to increase immunogenicity [42]. tPA is used as a heterologous targeting signal sequence to traffic the protein to the cell secretion pathway to increase expression membrane. This has been shown to enhance the strength of the immune response against antigens having this signal sequence [52]. It may be hypothesised that such a supplement is likely to interfere with plasminogen activator, i.e. with the coagulation system.

The entire tPA sequence is available in GenBank [53]. The signal sequence is coded by bp 63 to 167, to yield after in silico translation a 36 aa peptide (i.e. MDAMKRGLCCVLLLCGAVFVSPSQEIHARFRRGARS). Considering the length of the peptide it has been hypothesised that it may play another role in addition to targeting cellular secretion pathways. However, it is unknown if it could cause thrombosis.

Furthermore, the strong expression and the secretion of a large amount of the spike protein, per se, may cause blood clots in predisposed individuals, especially in conjunction with calling a strong immune response to the S protein.

Finally, it is not known whether this sequence is cleaved from the product before it is secreted. Usually it is, but not always. It can be checked virtually if the junction of the tPA sequence and the S protein is susceptible to induce the production of antibodies.

CHMP comment on tPA

So far as we did not receive any (non-clinical) documentation from the company for the characterization of these specific antigens.

It is considered unlikely that a signal sequence, which is meant to translocate a protein to the cellular surface, interferes with the function of proteins who happen to possess the same signal sequence.

However, this is not considered the most important aspect. tPA initiates clot lysis (through plasminogen activation to plasmin). It does not directly interfere with the coagulation pathway itself (in other words, it does not inhibit DIC, consumption of coagulation factors, and other markers of a hypercoagulable state).

Most importantly, tPA/plasmin does not interfere with platelet function, and the defining new factor of the current signals/reports is thrombocytopenia. Thrombocytopenia is the result of platelet consumption or destruction (or decreased platelet formation, which in this case also considered unlikely).

As an aside, it is important to discriminate between coagulation in the strict sense (fibrin clot formation which involves coagulation factors II-XIII) and platelet function/activation (which involves vWF and various platelet receptors). Both result in what is loosely termed hemostasis, thrombus formation and (in pathological states) thrombosis – however, these two mechanisms are quite different.

PRAC Assessment on tPA

In general, leader sequences are meant to guide proteins to the endoplasmic reticulum (ER) for

secretion. In principle the leader sequence is cleaved off. If cleavage does not occur, the fusion protein (tPA leader- Spike protein) remains anchored in the membrane of the cell and cannot be secreted. Furthermore, the tPA leader sequence has been shown to improve immunogenicity of an MVA vector vaccine by enhancing secretion of the antigen.

In principle, the leader sequence remains incorporated in the membrane and is recycled and degraded within the cell. Even if it would be released, there is no scientific evidence that this sequence could activate any pathways involved in hemostasis or coagulation.

Finally, one might speculate that the Spike protein itself could activate particular signalling pathways. However, there is no confirmed scientific rationale supporting this at this stage.

It could be also highlighted that the construct used in the COVID-19 vaccine AstraZeneca encodes for the Spike protein sequence which has not been modified. All other vaccines (Pfizer, Moderna, JNJ) have modified the sequence in order to stabilise the Spike protein in the pre-fusion state. However, this is not expected to have an impact on possible thrombosis events.

3.1.8. Conclusion

Based on the review of clinical and non-clinical data (DLP 7 Dec 2020), there is currently no evidence to suggest an association of thrombotic events with the use of COVID-19 Vaccine AstraZeneca.

The preliminary information from the BWP concluded that there is no indication so far that SAE are linked to the quality of the vaccine (16 March 2021). Follow-up questions for specific batches were made to the MAH.

Based on the available observed-to-expected analysis by the MAH and EMA, there is currently insufficient evidence to suggest there would be an increased risk of embolic and thrombotic events associated with COVID-19 Vaccine AstraZeneca.

However, a signal was noted for rare events, such as Disseminated intravascular coagulation, Cerebral venous sinus thrombosis and Haemorrhagic stroke warranting further investigation. This could be described as a heparin-induced thrombocytopenia (HIT)-like/heparin-induced thrombocytopenia with thrombosis (HITT)-like phenomenon. Available evidence is insufficient to establish a causal association and further assessement is needed.

Given the uncertainty in the case definitions of interest as this issue has progressed, further investigation on a possible underlying mechanism is needed. Following gaps in knowledge and recommendations are currently identified:

1. Importance of ruling out COVID-19 disease as an alternative diagnosis in the cases reported as thrombotic events may be the presenting feature of COVID-19;
2. Further exploration of case definitions of interest for continued monitoring and expert review;
3. Further refinement of observed to expected analsyis at the level of background rates and exposure by e.g. age-group, including sensitivity analysis. Of note is also that the rates measured prior to 2020 may not be reflective of the current background rate, with the virus in circulation.
4. Ad hoc expert group for further discussions on possible hypotheses, pathophysiological mechanisms, and possible underlying risk factors.

3.2. PRAC proposed recommendation

The PRAC recommends an update of **section 4.4 of the SmPC**, which should include the following elements:

- Description of the clinical entity i.e. a heparin-induced thrombocytopenia (HIT)-like/heparin-induced thrombocytopenia with thrombosis (HITT)-like phenomenon;
- Statement that some cases have been presenting as cerebral venous sinus thrombosis, cerebral vein thrombosis and disseminated intravascular coagulation; that there is currently insufficient evidence to establish a definitive causal relationship with the vaccine; that cases mainly occurred i.e. women < 55 year;
- Statement that the benefit/risk in individuals at increased risk of thromboembolic events (including autoimmune disease, oral contraceptive use, or prior history of thromboembolic events) should be evaluated before vaccination.

Moreover instructions to physicians and patients to be alert on specific signs and sympotoms should be included.
This information needs to be **communicated** within the SmPC /PIL and additionally via a DHPC (under discussion with the MAH).

Finally, the following issues need to be adressed:

1. Importance of ruling out COVID-19 disease as an alternative diagnosis in the cases reported as thrombotic events may be the presenting feature of COVID-19;
2. Further exploration of case definitions of interest for continued monitoring and expert review;
3. Further refinement of observed to expected analsyis at the level of background rates and exposure by e.g. age-group, including sensitivity analysis. Of note is also that the rates measured prior to 2020 may not be reflective of the current background rate, with the virus in circulation.
4. Ad hoc expert group for further discussions on possible hypotheses, pathophysiological mechanisms, and possible underlying risk factors.

These recommendations are based on **a preliminary assessement** that will be discussed during the extraordinary PRAC of 18 March 2021, where additional information will be provided by the MAH, EMA and Member States.

3.3. Adopted PRAC recommendation

The PRAC has reviewed the available evidence on the occurrence of thromboembolic events following the administration of COVID-19 Vaccine AstraZeneca, using a wide range of sources including spontaneous case reports in EudraVigilance, quality, clinical, pre-clinical and literature data and additional data from the MAH. The review of EudraVigilance data included observed-to-expected analyses that pointed to possible signals of cerebral venous sinus thrombosis and disseminated intravascular coagulation, as well as an individual case review that suggested a possible pattern in

women below 55 years with a time-to-onset within 1-2 weeks following vaccination. The PRAC has also explored possible pathophysiological explanations for the observed cases.

The PRAC has concluded that there may be a risk of rare thrombotic events accompanied by thrombocytopenia following receipt of COVID-19 Vaccine AstraZeneca that needs to be reflected in the product information, while further evidence is being collected.

The PRAC recommends by a majority of 31 out of 32 votes that the MAH for COVID-19 Vaccine AstraZeneca (AstraZeneca AB) should submit a variation by 19 March 2021 to amend the product information as described below (new text underlined/text to be removed with ~~strikethrough~~):

Summary of Product Characteristics

Section 4.4 Special warnings and precautions for use

Thrombocytopenia and coagulation disorders

A combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with COVID-19 Vaccine AstraZeneca. This includes severe cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, mesenteric vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia. The majority of these cases occurred within the first seven to fourteen days following vaccination and occurred in women under 55 years of age, however this may reflect the increased use of the vaccine in this population. Some cases had a fatal outcome.

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.

Risk of bleeding with intramuscular administration

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Package leaflet

Section 2 Warnings and Precautions

Talk to your doctor, pharmacist or nurse before you are ~~given COVID-19 Vaccine AstraZeneca~~ vaccinated:
…
...
Blood disorders

A combination of blood clots and low level of platelets, in some cases together with bleeding, has been observed very rarely following vaccination with COVID-19 Vaccine AstraZeneca. This included some severe cases with blood clots in different or unusual locations and excessive clotting or bleeding throughout the body. The majority of these cases occurred within the first seven to fourteen days following vaccination and mostly occurred in women under 55 years of age, however more women under 55 received the vaccine than other people. Some cases had a fatal outcome.

Seek immediate medical attention if you develop shortness of breath, chest pain, leg swelling, or persistent abdominal pain following vaccination.

Also, seek immediate medical attention if you experience after a few days severe or persistent headaches or blurred vision after vaccination, or experience skin bruising or pinpoint round spots beyond the site of vaccination which appears after a few days.

OnePRAC member disagreeds with the above-mentioned recommendation of the PRAC.

The MAH should distribute a direct healthcare professional communication (DHPC) according to the text and communication plan agreed with the CHMP .

The PRAC has also agreed that an *ad hoc* expert meeting should be convened to further discuss possible hypotheses, pathophysiological mechanisms, and possible underlying risk factors.

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