NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES

VACCINE BENEFIT RISK EXPERT WORKING GROUP

Title of paper: Update on COVID-19 Vaccines and risk of thromboembolic events with concurrent thrombocytopenia **Type of paper:** For advice

Active(s) rINN	COVID-19 Vaccine AstraZeneca solution for injection COVID-19 Vaccine (ChAdOx1 S [recombinant]) BNT162b2
Product name(s)	AstraZeneca COVID-19 vaccine Pfizer-BioNTech COVID-19 vaccine
Marketing Authorisation Holder(s)	AstraZeneca Pfizer-BioNTech
Legal status	Prescription only medicines
Therapeutic classification **(ATC code)**	Vaccines, other viral vaccines ATC code: J07BX03
Previous assessments	VBR EWG: 16 & 24 March 2021 CHM: 27 March 2021
Assessor(s)	Name: [redacted] Email: [redacted] Name: [redacted] Email: [redacted] Name: [redacted] Email: [redacted] Name: Dr Gary Peters Email: gary.peters@mhra.gov.uk Name: Patrick Batty Email: patrick.batty@mhra.gov.uk

1. Introduction

The Pfizer/BioNTech COVID-19 vaccine was authorised for use under Regulation 174 by the MHRA on 2 December 2020. It is estimated that over 14 million doses have been administered in the UK as of 29 March 2021. The AstraZeneca COVID-19 vaccine (Vaxzevria) was authorised for use under Regulation 174 by the MHRA on 30 December 2020, and over 20 million doses have been administered in the UK as of 29 March 2021.

Since the previous EWG meeting on 25 March 2021, this review has been discussed at an extraordinary meeting of CHM on 27 of March 2021.

An ad hoc EMA Expert group met on 29 March 2021, as stated in the statement issued by the EMA on 25 March 2021.

This paper provides an update of the available data since the previous discussion with conclusions from the EMA expert group.

2. Summary of CHM discussion

CHM heard the following criteria were applied to ascertain the likelihood of a report being an identified case and to facilitate validation of reports:

CONFIRMED:	Any venous/arterial thrombosis	**+**	Platelet count <150 x 10^9/L	**+**	D-dimer >4000ng/mL	**+**	Anti-PF4 Abs
PROBABLE:	Any venous/arterial thrombosis	**+**	Platelet count <150 x 10^9/L	**+**	D-dimer >4000ng/mL		
POSSIBLE:	Any venous/arterial thrombosis	**+**	Platelet count <150 x 10^9/L				
UNLIKELY:	Criteria met for any of the above BUT alternative diagnosis more likely to explain the event.						
CRITERIA NOT MET:	One or none of the criteria are met.						

CHM agreed a previous MHRA review found that the available evidence does not suggest that venous thromboembolism in the absence of low platelet count is caused by COVID-19 vaccines.

The following key conclusions were made:

- **Benefit/Risk remains favourable**

After analysing the evidence presented, CHM's advice remains that the benefits of the vaccines against COVID-19 continue to outweigh any risks and that the public should continue to get their vaccine when invited to do so. CHM noted the analyses from Public Health England which have

found that COVID-19 vaccines have prevented over 6000 deaths up to the end of February in England alone[1].

- **Review of evidence**

A further review of cases of blood clots with simultaneous low platelet counts has found that while there is a similarity in the timing and nature of these reports after vaccination with COVID-19 vaccine AstraZeneca, we cannot be sure that the events are caused by the vaccine in the absence of mechanistic data.

The review of the available evidence identified 22 cases of cerebral vein blood clots and 8 cases of other major blood clots with simultaneous low platelet count, reported from the start of AstraZeneca vaccine roll out on 4th January 2021 up to 24th March 2021. This indicated that the potential risk is small, with these events are occurring at a rate of 1.7 cases per 1 million doses of AstraZeneca vaccine given.

- **Distribution of adverse events by age**

CHM noted that cerebral sinus vein thrombosis (CVST) is very rare and is usually more common in younger adults than in older people. As of 24 March, the UK data suggest that cerebral sinus vein thrombosis or other major blood clots with a low platelet count in people who have received the COVID-19 Vaccine AstraZeneca were more common in younger adults than older adults. The estimated incidence-based data as of 24 March was [redacted] 1 million adults aged 20 – 29, with lower incidences in older age groups. Given the known high effectiveness of the vaccine, in a wave of the pandemic similar in size and severity to that seen in the UK during December 2020 to Feb 2021, we would expect to prevent [redacted]. In older adults even more hospitalisations and deaths are prevented for every 1 million people vaccinated. Based on current available evidence, the benefits of the vaccine therefore outweigh the risks for all adults, but especially for older adults.

- **Distribution of adverse events by gender**

The CHM noted that cerebral sinus vein thrombosis on its own usually affects more women than men. As of 24 March, 17 of the reported cases of cerebral sinus vein thrombosis with a low platelet count that happened after vaccination with COVID-19 Vaccine AstraZeneca were in women, and 8 were in men. The evidence is insufficient to reach a conclusion on whether these events are more common in women than in men following vaccination with COVID-19 Vaccine AstraZeneca. The demographics of the population vaccinated with COVID-19 Vaccine AstraZeneca may have affected the number of reports in men and women, given the higher proportion of women who have received the vaccine that are less than 50 years of age compared to men, and chance may also have played a role, considering the relatively small number of reports.

- **Background rate of cerebral sinus vein thrombosis**

It is currently not known exactly how often cerebral sinus vein thrombosis with concurrent low platelet count occurs in people who have not received a COVID-19 vaccine, and it will be important to gather more data on this as part of the continued monitoring of the issue.

[1] https://www.gov.uk/government/news/covid-19-vaccines-have-prevented-thousands-of-deaths-in-older-adults-new-data-shows

- **Possible mechanism for an effect of COVID-19 Vaccine AstraZeneca on thromboses with thrombocytopenia**

The CHM agreed that the current evidence does not confirm a mechanism by which COVID-19 Vaccine AstraZeneca might increase the risk of cerebral sinus vein thrombosis with a low platelet count. It will be important to carry out further scientific studies to investigate this as part of the continued monitoring of the issue.

- **Ongoing clinical trials of COVID-19 Vaccine AstraZeneca**

The CHM advised that clinical trials studying the effectiveness of COVID-19 Vaccine AstraZeneca in children and pregnant women should continue, , but there needs to further evaluation of the pregnancy trials, and pregnancy exposure to date.

3. Case summaries and discussion

3.1. Astra Zeneca Vaccine

The evaluation focused on any thromboembolic events reported in conjunction with thrombocytopenia, for completeness this included arterial and venous emboli with a data lock point of the 29th of March 2021.

There were 69 reports of interest in total (increased from 35 at the last DLP of the 24th of March). Of these, 39 reported CVST, cortical venous thrombosis or cerebral thrombosis, 19 reported pulmonary embolus, 8 reported portal vein thrombosis and 7 cases reported arterial (femoral/renal/superior mesenteric artery, carotid artery, ischaemic stroke etc.).

Of these reports 62 were considered “confirmed”, “probable” or “possible”. 5 were “unlikely” and 2 did not meet the case criteria.

Table 1: Summary table of reports of thrombosis with thrombocytopenia by category of validation

Category	Number	Notes
Confirmed	8	
Probable	9	
Possible	45	
Unlikely	5	Bleed preceded thrombus (immobility possible risk factor), AIH, pancreatic cancer, cerebral amyloid angiopathy on post-mortem, vulval intra-epithelial neoplasia
Criteria not met	2	No thrombosis, unclear platelet count

The introduction of a proforma to gather relevant follow-up clinical information on potential cases has improved the quality and quantity of data collected.

Causality assessments using the WHO-UMC system

An assessment of causality using the WHO-UMC system has been attempted but was challenging. The committee should be aware that the nature of the signal creates problems that hamper an objective assessment of causality using this tool. The 'certain' category requires that the reported event is definitive pharmacologically or phenomenologically (that is, an objective and specific medical disorder or a recognised pharmacological phenomenon) and a plausible drug withdrawal response. The 'probable/likely' category requires an event that is unlikely to be attributed to disease or other drugs and a reasonable response to drug withdrawal. The 'possible' category is used when the reported events could be explained by other drugs or disease and there is no clear data on drug withdrawal. The response to drug withdrawal may be difficult to assess for a vaccine.

The main risk factors for isolated thromboembolic events, including CVST, and isolated thrombocytopenia are relatively well known. However, the clinical and biological risk factors associated with immune-mediated thrombotic events in heparin-induced thrombocytopenia are not well defined (Arepally 2021). There is no evidence that thrombophilia disorders are a risk factor although polymorphic variations in the FcγIIA receptor and its functional regulation by tyrosine phosphatases, CD148 and TULA-2 may be pre-disposing factors with a genetic basis. Greinacher et al. (2021) have listed pre-existing autoimmune and coagulation disorders in the only published case series of 9 patients with vaccine induced prothrombotic immune thrombocytopenia (VIPIT) associated with the AZ COVID-19 vaccine. VIPIT is described as a disorder that clinically resembles HIT and no risk factors were mentioned beyond the possible vaccination trigger.

Updated case features thromboembolic events with thrombocytopenia considered "confirmed", "probable" or "possible"

Table 2: Overview of other thromboses with thrombocytopenia cases by age

Classification	Age range (years)	Mean age (years)	No. cases
Confirmed	22-49	39	8
Probable	34-73	57	9
Possible	18-73 (unknown in 10)	44	45

Demographics

Ages ranged from 18 to 73 (mean 45.7). 22 were in patients under 50 years of age (22/62), age was unknown in 10 reports. 43 were female and 19 were male. Over half the cases (36/62) were described as British/ white British/Caucasian/Irish/other white background, 3 as Asian/ Indian and ethnicity was not reported in 23.

Time to onset

Time to onset ranged from 8- 28 days. 57/62 cases stated that events occurred in relation to first doses, dose was not stated in the remaining cases.

Comorbidities or pre-existing risk factors

15/62 cases reported no past medical history or no significant past medical history. In 5/62 this was not reported or unknown.

27/62 had some comorbidities of note these include autoimmune hepatitis, inflammatory bowel disease in two individuals with use of 5ASA drugs, known alcohol excess with suspected cirrhosis, ANA+ individual with a family history of rheumatological conditions, motor neurone disease in 2 individuals, previous DVT or PE in at least 3 individuals, obesity, non-Hodgkins lymphoma, unspecified immunodeficiency and recently excised superficial spreading malignant melanoma. One individual [redacted]

3 female patients were taking hormonal contraception.

Information was also sought on any additional concurrent risk factors for thrombocytopenia or thrombophilia. Malignancy was reported as suspected in one individual [redacted] however limited information was provided about the type of malignancy and this diagnosis was not confirmed. In 2 patients [redacted] anti-phospholipid syndrome was queried as a diagnosis. Two additionally reported weakly positive lupus tests.

In 11/62 cases relatively detailed information excluding potential risk factors for both thrombocytopenia and thrombosis were provided (including infectious viral screen, autoimmune screen, exclusion of malignancy, thrombophilic screen), 28 other cases provided less detailed information on risk factors excluded, for example one case said there was no infectious screen performed but reported that there was no evidence of malignancy or lymphoproliferative disorder. Information on pregnancy was not provided for any patient.

Anti-PF4 antibodies

8 cases reported positive anti-PF4 antibodies, these cases were considered confirmed per the case validation criteria. Additionally 3 report a negative HIT screen (1 reports testing with Acustar, in 2 the diagnostic assay not provided), 2 additional cases report pending HIT screens and in 1 case HIT was reported as weakly positive (this was not considered confirmed).

Platelet counts

Platelet counts ranged from 2 – 103 x 10^9/L. 27/62 events involved a platelet count <50x 10^9/L, 5/62 events involved platelet counts <5 x 10^9/L.

COVID-19 status

Only 1 case [redacted] In all other cases no information on serology was provided. 7 cases specifically report tests were performed, in 4 these were reported as PCR tests, 1 was [redacted] and the test type was not specified in the remaining cases.

Concomitant medications

In terms of concomitant medications, of note 1 case describes [redacted] 1 also reports [redacted]. [redacted] It was noted some individuals were on medication rarely associated with thrombocytopenia including levetiracetam, sertraline, venlafaxine, amitriptyline, indapamide, sodium valproate and citalopram. As previously stated, 3 individuals report use of hormonal contraceptives. In 11/25 cases no information was provided.

9 cases had no concomitant medications reported, were reported as having no regular medication or were reported as not having any medication within the last 12 months. In 27 cases it was unknown if the individuals in question were taking any concomitant medications.

Outcomes

16 cases were reported as having a fatal outcome. Fatal cases ranged from ages 18- 73 years (mean 41.3). 10/16 were aged under 50, 4 of these were under the age of 30. A further case describes [redacted]

In 35/62 cases the event was reported as ongoing, recovering or not recovered. In 5 at least one event was reported as recovered, additionally 1 individual [redacted] and 1 [redacted] In 2 cases outcome was unknown.

3.2. Pfizer-BioNTech Vaccine

Up to and including 29 March 2021, a total of 11,024,779 first doses of the Pfizer vaccine had been administered in the UK. A further 3,227,045 2nd doses had also been administered.

UK cases

UK Yellow Card reports of arterial or venous thromboembolic events occurring in conjunction with thrombocytopenia were retrieved for review (DLP 29 March 2021).

One case reporting a thrombotic event with thrombocytopenia was identified. The details are as follows:

Patient Details	[redacted]
Medical history	[redacted]
Concomitant medications	[redacted]
COVID-19 infection	[redacted]
Suspected reactions (Outcome)	**Thrombocytopenia (not recovered)** **Pulmonary embolism (not recovered)**
Time to onset	[redacted]
Case narrative	[redacted]
Investigations	[redacted]

	[redacted]

This case is a [redacted] urther information has been requested.

This is the first UK case reported for the Pfizer-BioNTech vaccine to meet any of the criteria in the case definition.

Three UK cases of cerebral venous sinus thrombosis have been reported for the Pfizer-BioNTech vaccine. None of these cases reported thrombocytopenia or low platelets alongside the CVST; therefore, these cases do not meet the case definition.

A single case of thrombotic thrombocytopenic purpura has also been reported for the Pfizer-BioNTech vaccine. This case also does not meet the case definition.

All cases, except the [redacted] (pulmonary embolism, thrombocytopenia) were included in the data presented to CHM at its Extraordinary meeting on 27 March 2021.

Non-UK cases

Up to 28th March, six cases of interest reporting venous or arterial thrombotic events with thrombocytopenia (platelets <150) were identified. These include 1 report identified from a line listing provided by the marketing authorisation holder (MAH); 2 reports identified in a line listing provided by the EMA (DLP 22 March 2021); 2 reports identified in a publication from the US (Lee et al, 2021) and 1 report identified in the MHRA's non-UK ADR database. These cases are summarised as follows:

Patient Age (years), Sex, Country **(Case definition)**	**Case Details**	**Source**
[redacted] (Probable)	[redacted] **thrombocytopenia** [redacted] **sinus cerebral** thrombosis. [redacted] The outcome was **fatal**.	MAH
[redacted]	[redacted] **pulmonary embolism, thrombocytopenia** [*platelet count not provided*], [redacted]	EMA

(Possible – other factors)	[redacted]	
[redacted] (Possible but Unlikely – other factors)	[redacted] **mural thrombus**. [redacted] **Developed severe thrombocytopenia** [*platelet count not given*] [redacted]	EMA
[redacted] (Possible, limited details)	[redacted] Diagnosed with **myocarditis** but did not require treatment for **thrombocytopenia**. [redacted]	Publication (Lee et al, 2021)
[redacted] (possible, limited details)	**Thrombocytopenia**, neutropenia and **pulmonary embolism** [redacted] The outcome was **fatal**.	Publication (Lee et al, 2021)
[redacted] (Possible, other factors)	[redacted] **TIA and transient motor dysphasia**, [redacted] **M2 branch thrombus.** [redacted]	MHRA non-UK ADR database

All non-UK cases were included in the data presented to CHM at its Extraordinary meeting on 27 March 2021. No further information has been received regarding these cases since then. No new non-UK cases of relevance have been reported/identified since then.

Overall summary of the UK and non-UK cases

There is 1 UK case and 6 non-UK cases reporting a venous or arterial thrombotic event with thrombocytopenia/low platelets following vaccination with the Pfizer-BioNTech COVID-19 vaccine.

Where age and sex are known (6/7 cases) all concerned patients aged 44 years or older; there is no pattern in sex distribution of the cases.

Five out of the seven cases (including the UK case) involved a thrombotic event in vessels outside of the brain. One case of thrombosis in a vessel in the brain involved a venous thrombosis (cerebral venous sinus thrombosis) the other was an arterial thrombosis (M2).

None of the cases report PF4 antibodies; 2 report a thrombotic event with thrombocytopenia and D-dimer >4000 and therefore meet the criteria for a 'Probable' case. One of these cases has other factors which are known risk factors for thrombotic events in isolation, but as discussed for the AZ vaccine, risk factors for concurrent thrombosis with thrombocytopenia are less well defined. Two cases report recent COVID-19 infection or IgG positive (SARS COV-2). Both thrombocytopenia and thromboses have been noted to occur in the context of COVID-19 infection.

Epidemiological analysis of the data with updated incidence rates is provided in a separate slide set.

4. Recent Publications

The British Society for Haematology issued preliminary guidance on the 'Syndrome of thrombosis and thrombocytopenia, possibly occurring after coronavirus vaccination' on 22 March 2021 (available at https://b-s-h.org.uk/media/19475/guidance-on-management-of-thrombosis-with-thrombocytopenia-occurring-after-coronavirus-vaccine-20210324_-003-002.pdf).

Greinacher et al. (2021) have published the clinical and laboratory features of a prothrombotic thrombocytopenia disorder resembling HIT following coronavirus vaccination in their case series of 9 German and Austrian patients. This is a preliminary report that has not been peer reviewed.

Table 3: summary of cases of prothrombotic immune thrombocytopenia associated with AZ COVID-19 vaccine (taken from Greinacher et al. 2021).

Cases	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Age, sex	49F	35F	48F	35F	43F	22F	36F	46F	24M
Lowest platelet count (per mm^3)	13	100	31	9	23	75	29	60	11
Site(s) of thrombosis	CVST, splanchnic vein, aorta	PE	CVST						
TTO (days)	5	10	8	4	13	7	8	14	16
Autoimmune disease	no	no	no	yes*	yes*	no	no	no	no
Outcome	fatal	recovering	fatal	fatal	recovering			In-hospital	fatal

*1 had demyelinating disorder & another had antiphospholipid antibodies. 2 had von Willibrand disease & an unspecified coagulation disorder.
CVST=cerebral venous sinus thrombosis, PE=pulmonary embolus

For the index case (patient 1), the peak d-dimer was increased at 142 µg/mL (normal <0.5) with a low fibrinogen of 101 mg/dL (normal 200-400). The highest APPT was minimally prolonged at 41.6 secs (normal <35), possibly after a dose of enoxaparin, and an INR was 1.4.

None of the patients were reported as having tested positive for COVID-19 infection. The case fatality rate was 44% (4/9).

All 4 patient sera tested were positive for anti-PF4 antibodies using an immunoassay with optical densities >3 (reference value <0.50). All reactivities were inhibited to normal values by the addition of heparin 100 IU. All 4 patient sera activated platelets strongly, either in the presence of PF4 10 µg/mL (3 of 4 sera) or the AZ COVID-19 vaccine (1). One patient showed strong platelet activation in the presence of heparin. All reactions were blocked by monoclonal antibody IV.3 which blocks platelet Fcγ receptors. Normal sera and 20 serum samples from control individuals who had received the AZ COVID-19 vaccine showed no platelet activation.

The authors concluded that the identified anti-PF4 antibodies bind to non-complexed PF4 alone but it is not clear whether these autoimmune antibodies are induced by the strong inflammatory stimulus of a vaccination or if the vaccine itself triggers them. Direct binding of the adenoviral vector to platelets could explain the observed enhanced reactivity of sera *in vitro*. It is proposed that this clinical entity should be named vaccine induced prothrombotic immune thrombocytopenia (VIPIT).

Medline searches conducted on the PubMed.gov site on 30 March 2021 using broad search terms, including coronavirus and vaccine and thrombosis or thrombocytopenia or heparin-induced thrombocytopenia, did not identify any other relevant articles published since 24 March 2021. There were also no relevant recent online first articles published by the Lancet on its website.

5. Other Regulatory Action

5.1. EMA

On 25 March 2021, the EMA provided an update on their ongoing evaluation of blood clot cases associated with the AZ COVID-19 vaccine, including rare cases with thrombocytopenia. The PRAC has finished its preliminary review, confirmed that the vaccine is not associated with an increase in the overall risk of blood clots and concluded that the benefits of the vaccine continue to outweigh the risk of adverse reactions. The amended product information (Annex 1) and the associated direct healthcare professional communication are now available:

https://www.ema.europa.eu/en/documents/product-information/vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-product-information_en.pdf

https://www.ema.europa.eu/en/documents/dhpc/direct-healthcare-professional-communication-dhpc-vaxzevria-previously-covid-19-vaccine-astrazeneca_en.pdf

An expert group convened on 29 March 2021 has provided advice to PRAC on plausible mechanisms, possible risk factors and on any required additional data for risk characterisation. The PRAC will discuss this advice and update their recommendations during their meeting on 6-9 April 2021.

A summary of the expert group meeting is provided below. The meeting of the EMA Extraordinary Ad-Hoc group considered the following:

- The panel agrees there are likely to be various clinical entities involved for thromboembolic and thrombocytopenic events or combinations of the two;
- The group considered there to be an association with vaccine as events of CVST with thrombocytopenia are very uncommon, and there seems to be a plausible mechanism with evidence suggesting this is specific to the AstraZeneca vaccine;

- The group considered there was no current data on the exact mechanism of antibodies and therefore was unable to make a conclusion on causality, much more information on mechanisms was needed.

[redacted]

- [redacted]

The group finally noted that although most events have been seen with the 1st dose so fat, the 2nd dose may cause a magnitude more complications then currently seen if the vaccine is causally associated with these events. The group noted the importance of this in any ongoing evaluation of these events.

5.2. Germany

On 30 March 2021, the Standing Committee on Vaccination (STIKO) recommended using the AZ COVID-19 vaccine only in people aged at least 60 years, unless they are at high risk from COVID-19 or are health workers. 31 cases of unusual blood clots, including CVST, have been reported following the administration of 2.7 million doses of the AZ COVID-19 vaccine. All but 2 of the cases were females aged 20 to 63 years and 9 were fatal (https://www.reuters.com/article/us-health-coronavirus-astrazeneca-berlin-idUSKBN2BM13E). There was no official confirmation of this news report on the Paul-Ehrlich Institute website on 30 Mar 2021. Other news reports also state that Sweden, France and Finland have suspended use of the AZ COVID-19 vaccine in younger people until more data is available.

5.3. Canada

On 24 March 2021, Health Canada issued guidance to HCPs on the risk of thrombosis with thrombocytopenia following immunisation with the AZ COVID-19 vaccine and provided information for vaccine recipients on the signs and symptoms requiring immediate medical attention (https://covid-vaccine.canada.ca/info/pdf/astrazeneca-covid-19-vaccine-letter.pdf

The product information was also updated to add a warning and a description of the post-marketing cases:

7 WARNINGS AND PRECAUTIONS

[…] ***Hematologic***

Thrombocytopenia and coagulation disorders

A combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with AstraZeneca COVID-19 Vaccine. 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. 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.

8 ADVERSE REACTIONS

[…]

8.3 Post-Market Adverse Reactions

[…] A combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with AstraZeneca COVID-19 Vaccine. 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. See WARNINGS AND PRECAUTIONS

On 29 March 2021, Health Canada published a statement on further action to confirm the benefit-risk profile of the AZ vaccine. No cases of thrombosis with thrombocytopenia have been reported in Canada. Health Canada will be issuing additional terms and conditions on the authorisations of the AZ and Verity Pharmaceuticals/Serum Institute of India vaccines. These will include a requirement that the manufacturers conduct a detailed assessment of the benefits and risks of their vaccine by age and sex in the Canadian context. This will allow Health Canada to determine if there are specific groups of people who may be at higher risk. The Public Health Agency of Canada also paused the use of the AZ vaccine in individuals aged less than 55 years, pending further risk/benefit analyses by Health Canada (https://www.canada.ca/en/public-health/news/2021/03/use-of-astrazeneca-covid-19-vaccine.html). Patients are advised to seek immediate medical attention if they develop any of the following symptoms starting between 4 and less than 20 days after vaccination: shortness of breath, chest pain, leg swelling, persistent abdominal pain, sudden onset of severe or persistent worsening headaches or blurred vision, and skin bruising (other than at the site of vaccination). Decisions on the type of second dose offered to those receiving the AZ vaccine will be based on the latest evidence.

5.4. Australia

The Therapeutics Goods Administration granted provisional approval for the AZ vaccine allowing legal supply on 26 March 2021. A safety alert from 19 March 2021 states that European and UK reviews found no proven link with blood clots including DIC but no alerts have been published after this date. The TGA have not received any reports of blood clots following AZ COVID-19 vaccination in Australia. However, the Australian Technical Advisory Group on Immunisation has recommended that immunisation with any COVID-19 vaccine should be deferred as a precautionary measure in those with medically confirmed histories of CVST and/or HIT. HCPs are advised to be alert for persistent, unexpected and/or severe adverse events following immunisation, particularly those occurring 1-2 weeks after vaccination.

The national regulatory authorities in the USA, New Zealand and Switzerland have not issued any press announcements of regulatory action or safety alerts concerning the risk of thrombosis and thrombocytopenia associated with any coronavirus vaccine.

6. Risk Management Plan

Safety specification

The company propose inclusion of thromboembolic events with thrombocytopenia in the list of safety concerns as an important potential risk. The list of safety concerns would therefore read:

Important identified risks	None
Important potential risks	• Neuroinflammatory disorders • Vaccine associated enhanced disease • **Thromboembolic events with thrombocytopenia**
Missing information	• Use of AZD1222 in pregnant and breastfeeding women • Use of AZD1222 in subjects with severe immunodeficiency • Use of AZD1222 in subjects with severe and/or uncontrolled underlying disease • Use of AZD1222 with other vaccines • Long term effectiveness

Additional pharmacovigilance

Additional pharmacovigilance is proposed to characterise these events.

Plans are still in the early stages and work is ongoing to establish feasibility and to avoid duplication of work however, the company have proposed the following approach:

Study Topic	Study Questions	Study Design	Data Sources
1. Disease epidemiology of Thrombocytopenia occurring with and without thromboembolic events	1. Prevalence and the incidence rate of TP occurring with and without concurrent TE 2. Describe the demographic characteristics and medical history of patients with prevalent and incident TP, respectively, occurring with and without concurrent TE 3. Evaluate associations between known risk factors for TE and TE incidence in association with prevalent and incident TP, respectively, with and without concurrent TE	Secondary data analysis using a cohort design. Three study periods will be considered based on calendar time: - Pre-COVID: Jan 01 2019-31-Dec 2019 (inclusive) - COVID: Jan 01 2020-31-Dec 2020 (inclusive) - COVID vaccination roll-out: Jan 01 2021-end of data availability o If feasible, event rates will be further broken down by prior to vs. on or after 7th March; the date of initial media reports and Austria's batch suspension of COVID-19 Vaccine AstraZeneca	Integrated digital health system in England consisting of main linkages for general practice data, hospital records and Public Health England (PHE) as well as other linkages (The Oxford-Royal College of General Practitioners sentinel network; ORCHID) [JMIR Public Health Surveill. 2020 Jul-Sep; 6(3): e19773; doi: 10.2196/19773]
2. AstraZeneca COVID-19 vaccine safety study reporting the risk of thromboembolic disease with thrombocytopenia	1. Evaluate if there is an association between AstraZeneca COVID-19 vaccine exposure and thromboembolic events occurring with thrombocytopenia	Study feasibility and appropriate study design to be informed by Disease Epidemiology Study #1	ORCHID database, see above

Further detail is needed to assess the likelihood of these plans to provide meaningful information and linkage of primary and secondary care data may well be crucial in order to identify cases where thrombocytopenia is reported with a thromboembolic event as coding of thrombocytopenia and or platelet count is likely to be lacking in many data sources.
In order to minimise overlap and splitting of available subjects and data for this rare event MHRA is liaising with the company to ascertain which aspects are better approached with MHRA expertise and access to data, in conjunction with PHE and which aspects AstraZeneca is best placed to concentrate their efforts.

Routine risk minimisation measures
As an aspect of routine pharmacovigilance, a proforma has been created with input from haematology experts which is used for follow-up so that cases can be quickly classified and contain sufficient information for assessment. The proforma questions have also been deployed as additional questions put to reporters who are reporting a thromboembolic or thrombocytopenic event via the Yellow Card website. Similarly, Public Health England have now deployed an online snap survey which includes questions from the proforma and facilitates reporting to the Yellow Card Scheme by requesting a Yellow card report identifier at the end of the survey.
The proforma will also be used to shape company follow up forms for cases reporting these events. It is also proposed to add thromboembolic events with concurrent thrombocytopenia to the list of Adverse events of special interest in the RMP.

7. Discussion

Reports of thromboembolic events occurring with thrombocytopenia have increased with the AstraZeneca COVID-19 vaccine in the 2 weeks following the MHRA and EMA statements. In the period between the previous discussion of these events at CHM with a data lock point 24 March 2021 to the current data lock point of the 29th of March, the number of reports considered to be “Confirmed”, “Probable” or “Possible” has increased from 30 to 62. As with the previous data lock point, only a minority of reports fall within the “Unlikely” or “Criteria not met” categories (7 in total).

The ages of the individuals have diversified to include more individuals over the age of 50, and female individuals now outnumber males (the reverse was true at the start of the evaluation). The range of time to onset has also increased slightly, with 3 cases reporting times of 21-28 days. However, the majority of cases remain clustered around the 6 -16 day time period

The number of cases with a fatal outcome has also increased from 7 to 16, with just over half of the cases aged below 50 years of age. However the possibility cases on the more severe end of the spectrum would have been more likely to be reported is acknowledged.

The paper by Greinacher et al. represents the first to include data on these events in the published literature, although this has not yet been peer reviewed. It is noted that the majority events were CVSTs, although only a minority of individuals (4 out of the 9 in the paper) had sera tested for anti-PF4 antibodies.

Although the first UK case of thrombotic events with thrombocytopenia has now been reported with the Pfizer COVID-19 vaccine, the bulk of reports continue to be with the AstraZeneca COVID-19 vaccine.

Incidence rates of CVST, thromboembolic events in general and presentation of data on benefit risk is provided separately in a slide presentation.

Incidence of cerebral venous sinus thrombosis in users of hormonal contraceptives

Medicines that are associated with an increased risk of thromboembolic events might be expected to increase the risk of cerebral venous sinus thrombosis (CVST) as part of this overall thromboembolic risk. CVST occurring in association with these medicines might be different in terms of their aetiology and pathophysiology compared with the events of CVST reported following vaccination with COVID-19 vaccines, for example not occurring in the context of thrombocytopenia. But information about the absolute rate of CVST in association with oral hormonal contraceptives might provide some insight into this risk in a particular population.

Oral hormonal contraceptives are known to be associated with an increased risk of thromboembolic events generally, but published data on the incidence of CVST in women using hormonal contraceptives are limited. Some incidence data are available however, from a cohort study conducted in a large US claims database (Jick and Jick 2006). The study population was women aged 15 – 44 years who were current users of one of four different hormonal contraceptives (levonorgestrel-containing oral contraceptives (OCs), norgestimate-containing OCs, desogestrel-containing OCs, and ethinylestradiol + norelgestromin patch). Current use of a hormonal contraceptive was defined based on prescription records, starting when a prescription was filled and lasting until 45 days the last prescription. The outcome was first-time recorded claim for a clinically diagnosed CVST (including procedures consistent with CVST such as MRI) with hospitalization and prolonged anticoagulation therapy started promptly after the CVST. Potential cases were excluded if they had risk factors for CVST in the 3 months before index date.

Exposure time, numbers of CVST events, and estimates of incidence rate from the study are summarised in table 4. There was some variability in the point estimates of incidence rate between the different oral hormonal contraceptives the confidence intervals were wide, for desogestrel and levonorgestrel in particular, due to small numbers of events.

Table 4 Incidence rates of CVST in users of hormonal contraceptives. Adapted from Jick and Jick 2006.

Contraceptive	**Woman-years**	**Events of CVST**	**Incidence rate per 100,000 woman-years (95% CI)**
Desogestrel-containing OCs	185,496	5	2.7 (0.9 - 6.3)
Norgestimate-containing OCs	431,199	7	1.6 (0.7 - 3.3)
Levonorgestrel-containing OCs	299,536	2	0.7 (0.1 - 24.0)

ethinylestradiol + norelgestromin contraceptive patch	77,231	0	0.0 (0.0 - 4.8)

This study has some potential limitations, for example prescriptions were used to ascertain exposure, and it is possible that not all the medicines for these prescriptions were actually taken, although the use of data on filled prescriptions might limit this information bias. The authors were not able to obtain originally clinical records to fully validate diagnoses of CVST. The data come from a specific US population included in the PharMetrics database, which might have particular distributions of important risk factors that would limit generalisability of the findings. This was a descriptive study and did not include an unexposed comparator group, and therefore it is not possible to calculate the incidence rate of CVST cases attributable to use of hormonal contraceptive use.

Based on the data from this study for norgestimate-containing OCs, which had the most exposure-time and the most events, in 1 million women from this population taking these medicines continuously for 1 year the best estimate of the number of events of CVST would be 16, with reasonable certainty that the true value would be between 7 and 33 events.

References

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Annex 1: EMA Product information wording

SPC: Section 4.4: Thrombocytopenia and coagulation disorders

A combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with Vaxzevria. 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.

Patient information leaflet: Section 2 Warnings and Precautions

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 Vaxzevria. 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. As with any vaccine, the 2-dose vaccination course of Vaxzevria may not fully protect all those who receive it. It is not known how long you will be protected for. Currently there are limited data on the efficacy of Vaxzevria in individuals aged 55 and older