



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

6th May 2021
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Pharmacovigilance Risk Assessment Committee (PRAC)

Signal assessment report on Embolic and Thrombotic events (SMQ) with COVID-19 Vaccine Janssen (Ad26.COV2-S [recombinant])

EPITT no:19689

Confirmation assessment report	3 rd April 2021
Adoption of first PRAC Recommendation	9 th April 2021
Submission of responses by MAH	15 th April 2021
Preliminary assessment report	19 th April 2021
Deadline for comments	19 th April 2021 (8pm CET)
Updated Rapporteur assessment	20 th April 2021 (9am)
Adoption of 2 nd PRAC recommendation	20 th April 2021
Submission of responses by MAH	22 nd April 2021
Rapporteur assessment	30 th April 2021
Deadline for comments	30 th April 2021 (8pm CET)
Updated Rapporteur assessment report	3 rd May 2021
Adoption of 3 rd PRAC recommendation	06 th May 2021



Administrative information

Active substance(s) (invented name)	COVID-19 Vaccine (Ad26.COVS-S [recombinant]) – COVID-19 Vaccine Janssen suspension for injection (Other viral vaccines)
Strength(s)	All
Pharmaceutical form(s)	All
Route(s) of administration	All
Indication(s)	COVID-19 Vaccine Janssen is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older
Marketing authorisation holder(s)	Janssen-Cilag International NV
Authorisation procedure	
<input checked="" type="checkbox"/>	Centralised
<input type="checkbox"/>	Mutual recognition or decentralised
<input type="checkbox"/>	National
Adverse event/reaction:¹	Embolic and Thrombotic events (SMQ)
Signal validated by:	EMA
PRAC Rapporteur appointed for the assessment of the signal:	Ulla Wändel Liminga, SE

¹ Please use MedDRA terminology whenever possible

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1. Background

Covid-19 Vaccine Janssen (also referred to as Ad26.COVS.2.S) is a monovalent, recombinant, replication incompetent adenovirus type 26 (Ad26) vectored vaccine encoding the severe acute respiratory syndrome coronavirus 2 (SARS CoV2) spike (S) protein.

On the 27th Feb 2021, the US FDA issued an emergency use authorisation for Covid-19 Janssen vaccine. Vaccination with Covid-19 Janssen vaccine in the US has commenced.

It received a conditional marketing authorisation (CMA) throughout the EU on the 11th March 2021 for the active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals aged 18 years and older. As of this date, initiation of vaccination within the EU with Covid-19 Janssen, has not commenced.

“Venous thromboembolism” has been included as an important potential risk in the list of safety concerns in the risk management plan for Covid-19 Janssen vaccine. This was due to a numerical imbalance observed in the pivotal phase 3 trial (VAC31518COV.3001) regarding venous thromboembolic events. At time of approval, data up to 22 January 2021 had been provided, and this numerical imbalance corresponded to 11 subjects in the vaccine group (n=21,895) vs. 4 in the placebo group. In the vaccine group, there were: 6 DVT type events, 4 pulmonary embolism, 1 transverse sinus thrombosis (including 6 SAEs & 1 non-serious related AE; 8 events occurred within 28 days following vaccination). In the placebo group (n=21,888), there were: 2 DVT events, 1 pulmonary embolism, 1 thrombosed haemorrhoid (including 1 related SAE & 1 none-related SAE, all within 28 days of vaccination).

Based on an overview of thromboembolic events submitted by the MAH to the EMA on the 29th March, with a cut off of 17 March 2021, the following summary was provided:

Table 1: Thrombotic and Thromboembolic Events in Study COV3001¹

<i>Full Analysis Set</i>	Ad26.COVS.2.S N=21,895 n	Placebo N=21,888 n
Total participants with any event (percentage)	29 (0.1)	22 (0.1)
Venous thromboembolic events		
Deep vein thrombosis	11 ²	3
Pulmonary embolism	7	3 ³
Cerebral sinus thrombosis	1	1
Retinal vein thrombosis	1	0
Thrombophlebitis	1	1
Venous stent occlusion	0	1
Thrombosed haemorrhoid	0	1
Total participants with venous events	21	9
Arterial thromboembolic events		
Cerebrovascular events	6 ⁴	9
Cardiovascular events	3	4
Arterial stent occlusion	0	1 ⁵
Total participants with arterial events	8	14

¹ Data until March 17th, 2021
² Includes one event reported as 'venous thrombosis limb' and one event reported as 'embolism venous'
³ One patient reported both deep vein thrombosis and pulmonary embolism as separate terms
⁴ Two events reported in 1 participant
⁵ One participant reported 2 events of stent occlusion (1 venous, 1 arterial)

On the 12th March 2021, a signal of Embolic and Thrombotic events was confirmed for VAXZEVRIA/COVID-19 AstraZeneca vaccine, another adenoviral vectored vaccine. Following further evaluation, the focus of the signal has been on atypical coagulopathies characterised by thrombosis, often in unusual location, together with thrombocytopenia. At this point in time the signal is currently ongoing.

2. Initial evidence

2.1. Signal validation

To date, three reports have been received by EMA concerning events of thrombosis co-reported with thrombocytopenia in association with Covid-19 Janssen vaccine. Of the 3 reports, one originates from the pivotal phase 3 trial (VAC31518COV.3001) and two concern spontaneous reports from the US. Of the three reports, 2 concern female patients (age ranges 38-48 & 52-62 years) while one concerns a male patient (18-28 years). Of the 3 reports, one is fatal. Time to onset included 11 days (n=2) and 19 days (n=1). Thrombotic events reported included transverse sinus thrombosis, cerebral venous sinus thrombosis and bilateral iliac and femoral deep vein thromboses. Although thrombocytopenia was reported in one case, platelet counts were not provided. In the remaining two cases, platelet counts were specified as 64,000 (units not specified) and 15,000 (units not specified).

The case narratives are presented below.

-Spontaneous

Case 1:

This serious case concerns a fatal report regarding a female patient aged between 38-48. Other illnesses at the time of vaccination and up to one-month prior included depression. Concomitant medications included fluoxetine. The adverse event started 7 days after vaccination.

Diagnosis included cortical vein thrombosis, massive intracerebral haemorrhage with tentorial herniation and thrombocytopenia (value not specified).

One week after receiving the Janssen Covid-19 vaccine, the patient developed gradually worsening headache. The patient presented to the hospital with dry heaving, sudden worsening of headache and left-sided weakness. Evaluation with head computed tomography (CT) revealed a large right temporoparietal intraparenchymal haemorrhage with 1.3cm midline shift. She was intubated for worsening mental status. On evaluation, upon arrival in the medical centre, she was noted to exhibit extensor posturing. Repeat imaging revealed worsening midline shift to 1.6cm. CT angiography showed cortical vein thrombosis involving the right transverse and sigmoid sinus with tentorial herniation. The patient developed brain herniation. Brain death was subsequently pronounced.

CT angiography (CTA) of the head: the supraclinoid internal carotid arteries (ICAs) are patent bilaterally. The right middle cerebral artery (MCA) is elevated by the large right hemispheric haematoma. There is no occlusion or significant stenosis involving the right MCA. The left MCA and bilateral anterior cerebral arteries (ACAs) are within normal limits. The intracranial vertebral arteries, left posterior inferior cerebellar artery (PICA), basilar artery and both posterior cerebral arteries (PCAs) are patent. There is no aneurysm or arteriovenous malformation (AVM). The evaluation of the venous

structures is limited on this CTA but there is no opacification of the right transverse and sigmoid sinuses suggestive of dural sinus thrombosis.

Large right hemispheric haematoma is demonstrated with significant right-to-left midline shift measuring approximately 16mm. Effacement of the right lateral ventricle and dilation of the left lateral ventricle. Right-sided transtentorial herniation is noted.

Impression: suspect right transverse and sigmoid sinus dural sinus thrombosis. This can be confirmed with CTV (i.e. CT cerebral venography) if clinically necessary. No evidence of aneurysm or AVM to account for the right hemispheric intraparenchymal haematoma. Significant right-to-left and downward transtentorial herniation is noted.

Case 2:

This serious case concerns a female patient aged between 52-62 years. Other illnesses at the time of vaccination and up to one-month prior include diarrhoea.

Concomitant medication included (levodopa/carbidopa), (formoterol/budesonide), (clonazepam), (citalopram), (lemborexant), (icosapent), (diclofenac), (sumatriptan), (ropinirole), (quetiapine), Celecoxib, Albuterol inhaler, Omeprazole, (levothyroxine), (hydrocodone), low dose aspirin. The report notes that the patient had allergies to tetracycline and vortioxetine.

The adverse event started 11 days after vaccination. The patient had 5 days of bruising and left leg swelling prior to presenting to the emergency department. She was found to have an extensive, occlusive deep vein thrombosis (DVT) of the left lower extremity as well as thrombocytopenia of 15,000 (units not specified).

That evening she had an inferior vena cava (IVC) filter placed. The next day, the patient began to have paraesthesia's and discoloration of the right lower extremity. Ultrasound showed high-grade occlusion of the right proximal, superficial femoral artery. The patient was pre-treated with platelets. In addition to the right superficial femoral artery (SFA) there is also thrombotic occlusion of the bilateral iliacs. The patient had bilateral thrombectomy and bilateral common iliac stent placement. The following day she developed gross haematuria. At the time of the report, the patient had not recovered from the event.

Clinical trial case

Case 3:

This case concerns a subject aged between 18-28, with no significant past medical history who was hospitalised with life threatening sinus venous transverse thrombosis and secondary cerebral haemorrhage, on day 19 day following vaccination with Ad26.COVID-19. Concomitant medications included naproxen and ibuprofen. The subject was administered Ad26.COVID-19 in the upper left arm. Afterwards, the subject reported mild fatigue, nausea, headache (moderate) and myalgia along with a fever (body temperature: 38.2 deg C, 101 deg F). Most of the symptoms resolved by the third day with the exception of the headache which eventually resolved the following day.

On day 9 the subject reported feeling unwell with viral-like symptoms of headache, fatigue, nausea, constipation, weakness, abdominal pain, sore throat, myalgias, chills, shaking and fever (body temperature: 38.4 deg C). At that time, he took ibuprofen (dose and times not reported). That same day his oxygen saturation via pulse oximetry was 94%. The next day, he began with rhinorrhoea, faintness and nasal congestions and body temperature increased to 39.2 deg C.

On Day 11, he reported continued fatigue, weakness, rhinorrhoea, myalgia, faintness, abdominal pain, nausea and headache. He denied any other neurological symptoms. His symptoms met the protocol

prescribed trigger for obtaining nasal swabs for Covid-19 and swabs were collected all of which were reported negative. Upon clinical examination, he had a fever (38.4 deg C), oxygen saturation 98% and blood pressure 98/64mmHg. The subject's symptoms gradually improved without treatment and all symptoms except for the headache had resolved over the next 7 days. The subject reported that the headache improved but never completely resolved.

On day 19, he experienced visual disturbances and was observed to pass out with subsequent tonic-clonic seizures. Upon hospitalisation, laboratory tests included: platelet count was 64,000 (unit and reference range not provided), prothrombin time (PT): 17.7, international normalised ratio (INR): 1.46, fibrinogen: 154, white blood cell count: 12.4, haemoglobin: 12.7 and haematocrit: 36.1 (units and normal ranges were not provided).

A SARS-CoV-2 PCR (nasal swab) test was not performed as he reported two recent negative tests. Computed tomography (CT) scan without contrast showed right posterior lobe haematoma approximately 5ml in size. CT scan with contrast performed 2 hours later showed an enlarged prior right posterior lobe haematoma with peripheral oedema. A CT angiography and magnetic resonance image (MRI) showed a cerebral haemorrhage (right temporal occipital haematoma). The investigator added that the acute parenchymal haemorrhage in the right posterior temporal lobe, measured 2.0 x 2.4cm in diameter and estimated volume was 5ml. There was no midline shift. There was no evidence of hydrocephalus and no skull fracture identified. There was no acute sinusitis or mastoiditis.

On day 20, platelet count was $60 \times 10^3/\text{mL}$ at 01.13 hours and $113 \times 10^3/\text{mL}$ at 17.55 hours, prothrombin time was 15.7 seconds (NR: 11.5-15) and INR was 1.29 (NR: 0.80-1.20). On day 21, peripheral blood smear showed neutrophilic leucocytosis, no blasts were identified. Red blood cell count and morphology were within normal limits and thrombocytopenia with rare large platelet forms were seen.

During the hospitalisation, a venogram showed a clot in the cerebral transverse sinus. The subject was given a diagnosis of severe transverse sinus venous thrombosis and underwent a thrombectomy on day 22. The interventional radiologist who performed the thrombectomy reported that the subject had significant stenosis in his right sigmoid sinus and thus placing him at high risk for thrombosis. At that time an angioplasty was also performed on the stenosed sinus and treatment with acetylsalicylic acid was initiated.

On day 23, the subject developed nausea and dizziness when standing. His headache continued to worsen in intensity and a repeat venogram was performed which showed the presence of a new clot in the transverse sinus resulting in recurrent occlusion of the right transverse sinus with no flow identified in the sigmoid sinus or jugular bulb. The subject then underwent a second thrombectomy with venoplasty and was started on a low molecular weight heparin for 24 hours as well as intravenous (IV) tissue plasminogen (tPA) and heparin drips. MRI ruled out arterio-venous malformation and aneurysm. Laboratory testing showed that methylenetetrahydrofolate reductase mutation test and Beta 2 glycoprotein 1 antibodies (IgG and IgM) were negative. Lupus anticoagulant was negative and lactate dehydrogenase was 304 unit/L (NR: 135-225).

On day 24, repeat venogram showed that the transverse sinus was free of thrombus with brisk venous flow. All catheters were removed, tPA was discontinued and heparin was continued with a plan to begin apixaban.

Of note, the interventional radiologist reported observing rapid thrombus formation during the two thrombectomy procedures that is consistent with a hypercoagulable state clinically. He also stated that the transverse sinus thrombosis most likely occurred days before the subject's clinical presentation

with a seizure, and that the seizure was a consequence of a secondary bleed caused by the elevated venous pressure from the venous flow obstruction. He further reported that the subject's apparent hypercoagulable clinically (based on observation that blood appeared to be re-clotting before his eyes during the thrombectomy) is similar to what he has seen with hypercoagulable COVID-19 patients. Another SARS-CoV2 PCR test was negative, activated partial thromboplastin time (APTT) was 136.9 seconds (critical) at 17.36 hours (NR: 23.5-37.5), fibrinogen was 274mg/dl (NR: 200 -450), phospholipid IgG and IgM antibodies were negative.

On day 25, CT of the brain revealed right temporo-occipital haematoma which appeared slightly more prominent than on the previous scan. Epstein Barr-virus (EBV) IgG was positive and EBV IgM was negative, EBNA antibody positive, APTT was 57.0 seconds (high) at 01.09 hours, 118.8 seconds (critical) at 08.42 hours and 30.3 seconds at 16.22 hours. SARS-CoV2 test was negative.

Multiple laboratory tests were performed during the hospitalization.

Seven days after initial hospitalization and 26 days post vaccination, the subject was discharged from the hospital on apixaban, butalbital/acetaminophen/caffeine, levetiracetam, tramadol, acetaminophen and aspirin to the care of the investigator. Discharge diagnosis included non-traumatic intracerebral haemorrhage, transverse sinus thrombosis, seizure, thrombocytopenia (possibly naproxen induced), acute headache, nausea with vomiting and constipation. At discharge, he had sore throat, problem swallowing and speaking and slight headache but no neurologic deficit. According to the investigator his symptoms were improving. With ongoing soreness and difficulty swallowing he had lost 15 pounds during the hospitalization. At discharge, laboratory data included white blood cell count $9.2 \times 10^3/\text{mcl}$, haemoglobin 9.9g/fl (low), haematocrit 27.3% (low) and platelet count $204 \times 10^3/\text{mcl}$. It was reported that individualized dose optimization technique was used for procedures performed. The subject was evaluated by the investigator on day 29. On examination he appeared weak and mildly febrile (37.8 degrees C) with normal blood pressure. Posterior oropharynx showed mild erythema, no exudate and minimal oedema peripherally. The uvula appeared normal without oedema or erythema. Heart and lung exam were normal. No lymphadenopathy on head and neck exam. No rash. Pallor noted. This was followed by a low-grade fever (99.4-99.6 degrees F) for 2-3 days. He had gained a couple of pounds but continued to have a persistent mild, intermittent headache. A barium swallow test (report not provided) did not show any findings that explained his swallowing problems. The assessment showed, there was no functional reasons for swallowing and speech issues, and it was due to muscle fatigue. The subject was seen by a neurologist (report not provided). The subject was seen by a speech therapist and he had been drinking fluids with no issues and some issues still existed with the solid food. The fatigue was getting better and there was no fever.

MAH's Expert consultation within the clinical trial

1. Academic experts in infectious disease, haematology and neurology were consulted by the company. They concurred with the diagnosis of transverse sinus thrombosis with reactive cerebral haemorrhage. Individually each consultant concluded that the event resulted from a combination of factors including: 1. An anatomic abnormality of cerebral transverse sinus stenosis that predisposes the subject to thrombosis;
2. A pre-existing or secondary hypercoagulable state;
3. An infectious event which started on day 9 that triggered inflammation and induced a hypercoagulable state or worsened a pre-existing hypercoagulable state;

Although a specific infection has not been identified, and Covid-19 infection was effectively ruled out with multiple negative PCR tests, the consultants all concurred that the viral-like symptoms likely

represented an infection that triggered a cascade resulting in the event of transverse sinus thrombosis. The consultants also provided recommendations for continued infectious disease and haematology work up.

The consultants also individually concluded that there is no evidence of the study vaccine causing this event of cerebral sinus thrombosis with reactive haemorrhage.

Investigator causality assessment: The events of transverse sinus thrombosis and cerebral haemorrhage were not related to Ad26. Cov2.

Company causality assessment: The events of transverse sinus thrombosis and cerebral haemorrhage were not related to Ad26. Cov2.

Source of Information

Reports from the US Vaccine Adverse Event Reporting System (VAERS) and also pivotal phase III trial, VAC31518COV.3001: A randomised, double-blind, placebo-controlled phase 3 study to assess the efficacy and safety of Ad26. COV2.S for the prevention of SARS-CoV2 mediated Covid-19 in adults aged 18 years and older.

Signal validator conclusion

To date, three reports have been received by EMA of thrombosis co-reported with thrombocytopenia in association with Covid-19 Janssen vaccine. While the data at this stage is preliminary, it is considered that further evaluation is warranted given that "venous thromboembolism" is listed as an important potential risk within the summary of safety concerns of the RMP and that a signal of Embolic and Thrombotic events is currently ongoing for VAXZEVRIA/COVID-19 AstraZeneca vaccine. However, it should be emphasised that a precautionary approach is being adopted.

2.2. Signal confirmation

In light of the important potential risk in the RMP for Covid-19 Vaccine Janssen of VTE, as well as the raised concern regarding events of thrombosis in combination with thrombocytopenia in association with another Covid-19 adenovirus vector vaccine, the MAH was, on 26 March 2021, asked the following:

Study VAC31518COV3001

- *For the cases of thrombosis reported in this clinical trial, following review of narratives summarised in a document on AESI, it is noted in no laboratory data are available. Please provide all available data for all cases of thrombosis as well as bleeding reported in the clinical trial, and it is of particular importance to obtain any measurements of complete blood count including platelets.*
- *Please provide summaries of thrombocyte levels in subjects in the study, and for subjects with thrombocytopenia, please provide case narratives.*

Current post marketing experience

- *Please provide an estimate on the current post marketing use*
- *Please provide a cumulative review of cases of thrombosis in combination with thrombocytopenia reported in the post marketing setting.*

On 29 March, the MAH provided a short response which included case narratives for all thrombotic events, but not for the bleeding events.

Due to inconsistencies in the response such as it was stated that there was no case in study VAC31518COV3001 of thrombosis in combination with thrombocytopenia, while it was evident from the case narrative (see description above), that the man developing transverse sinus thrombosis also had thrombocytopenia.

As a follow up to that, MAH was agreed to provide additional information from an ongoing review of the individual case reports of thrombotic and thromboembolic events for concurrent occurrence of thrombocytopenia.

On 31 March, the MAH provided the following:

The following methodology was used to assess if reports of thrombotic or thromboembolic events also included thrombocytopenia.

Janssen's Global Medical Safety (GMS) Database was first searched using the below search criteria and identified 132 reports:

- SMQ Hematopoietic cytopenias
- SMQ Haemorrhages
- SMQ Embolic and thrombotic events

Text string search of the case reports showed, 15 of 132 cases had platelet counts reported (some had actual lab values, and some had statements that just said "platelet counts normal" with no actual lab values specified). Of these:

- 8 of 15 reports had platelet counts in normal range
- 7 of 15 had platelet counts that were low

Of the 7 reports with low platelet counts, 1 was a spontaneous report and 6 were from trials (3 placebo/2 active/1 blinded).

Of the 4 cases that had low platelet counts reported on active (2), blinded (1), or spontaneous (1), only one case reported a thromboembolic event along with confirmed thrombocytopenia as summarized below.

Clinical trial case on active (see detailed narrative description above): a male subject between the ages of 18-28 experienced transverse sinus thrombosis resulting in cerebral haemorrhage on Day 19 after receiving a single dose of blinded study vaccine (Day 1) for prevention of SARS-CoV-2 virus infection. After experiencing flu-like illness starting Day 9, the subject was hospitalized on Day 19 following a tonic-clonic seizure. Upon hospitalization, his platelet count was 64,000 with a nadir of 60k. Upon discharge his platelet count was normal at 334.

The remaining 3 case summaries are provided below for completeness:

Spontaneous case: a female between the ages of 65-75 with COPD, smoker experienced "low platelet count" 5 days after receiving vaccine. Platelet count was reported as 138k (LL Normal is 150k). No symptoms/other events reported.

Clinical trial case blinded: A female between the ages of 63-73 hospitalized for Pancytopenia and determined to have Acute Myeloid Leukaemia (AML) 135 days after first vaccine dose and 6 days after second dose. She had a grade 3 platelet count of 26k.

Clinical trial case on active: An obese male between the ages of 65-75, who experienced COVID-19, Acute kidney injury, embolism venous and Hypoxia. On 35 days post vaccination he had the acute kidney injury, venous embolism, and hypoxia. The platelet count in this participant was not verifiable as it was reported as "11.7" with no normal range or units.

MAH Conclusion:

The review of cases of thrombotic or thromboembolic events and low platelets revealed that there is only one case report that has both a thrombotic or thromboembolic event and low platelets as described above.

On 2 April 2021; the MAH submitted the following summary regarding thrombotic and thromboembolic events from spontaneous reporting irrespective of thrombocytopenia: .

A search of Janssen's Global Medical Safety (GMS) Database was performed on 31 March 2021 for completed spontaneous cases using the Standardised MedDRA Query (SMQ) of Embolic and thrombotic events.

The search identified 13 serious spontaneous case reports (0 non-serious case reports) with the following 14 events from the SMQ:

- 2 Pulmonary embolism (PE);
- 1 Deep vein thrombosis (DVT) (this patient also experienced a Pulmonary embolism);
- 3 Myocardial infarction (MI);
- 5 Cerebrovascular accident (CVA);
- 1 Hemiparesis;
- 1 Hemiplegia;
- 1 Blindness transient;

Case specifics are detailed in Table 1 below and CIOMS forms were provided.

Pulmonary embolism: Both cases were reported from health care providers. For the 2 cases, one case had a risk factor of family history of PE and DVT; the other had minimal information to make a meaningful medical assessment.

Deep Vein Thrombosis: One of the above Pulmonary embolism cases also reported an associated DVT; the patient had risk factors of family history of PE and DVT.

Myocardial infarction: All 3 cases were reported from non-health care providers. Two of the 3 cases had diagnostics that were negative for myocardial infarction. The third case had a fatal outcome with insufficient information (no diagnostics reported) to make a meaningful medical assessment.

Cerebrovascular accident: All 5 cases were reported from non-health care providers. Two had minimal information reported. Two provided risk factors for stroke, including age in the 80s. One fatal case has an autopsy pending to provide a final diagnosis with cause of death.

Hemiparesis: This case was reported from a non-health care provider who described left sided weakness on the side of injection. There was no diagnosis of CVA, and the subject quickly recovered on the same day.

Hemiplegia: This case was reported from a non-health care provider who described "mild hemiplegia" [sic] at injection site with "sore arm" and "injection site stinging". No suggestion/diagnosis of CVA was made.

Blindness transient: This case was reported from a non-health care provider. No diagnosis of CVA was made. No medical care was sought, and the patient recovered.

MAH Conclusion: The search of the Global Medical Safety Database resulted in cases with limited information. Only one of the cases had a confirmed diagnosis reported from a physician who described a single patient with DVT/PE with known risk factors. No other cases had medically confirmed diagnoses. Based on the currently available information and/or lack of diagnostic evidence for the reported events, no conclusions can be reached from this dataset.

Table 1: case details

Gender	Age (years)	Latency (days)	Preferred Term	Outcome	MAH Comment
male	46-56	Unspecified	Pulmonary embolism; Deep vein thrombosis	unspecified	Report from a physician. Risk factor of family history of DVT and PE.
female	unspecified	3	Pulmonary embolism	unspecified	Report from pharmacist. Female of unknown age reported pulmonary embolism 3 days after vaccination.
female	43-53	Unspecified	Myocardial infarction	Fatal	Report from non-health care provider. 43-53 yo female died of "heart attack" an unknown time period after vaccination. Unknown if autopsy performed.
female	unspecified	1	Myocardial infarction	unspecified	Report from non-health care provider. Hospitalized with "heart attack symptoms" 1 day after vaccination. All diagnostic tests came back normal.
male	unspecified	7 hours	Myocardial infarction; Pyrexia	Recovered	Patient reported on himself. All diagnostics were normal as per patient report, including EKG, CAT scan, Nuclear stress test, and Transesophageal echo. Symptoms included fever. Confounded by history of aortic valve repair, and an unspecified heart disorder.
female	unspecified	Unspecified	Cerebrovascular accident; Blindness	unspecified	Report from non-health care provider. Female of unknown age reported stroke and blindness unknown time period after vaccination.
female	unspecified	Unspecified	Cerebrovascular accident; Blindness	unspecified	Report from non-health care provider.
male	77-87	10 hours	Cerebrovascular accident	Recovered	Report from non-health care provider. Risk Factors: Age of 77-87 and male sex.
female	80-90	1	Cerebrovascular accident	Not recovered	Report from non-health care provider. Risk Factors: History of prior stroke; age 80-90.

Gender	Age (years)	Latency (days)	Preferred Term	Outcome	MAH Comment
female	56-66	2	Cerebrovascular accident; Fatigue; Malaise	Fatal	Report from non-health care provider. Risk Factors: age of 56-66; hypertension; family history of stroke and hypertension An autopsy is pending.
female	25-35	Same day	Hemiparesis; Pain; Musculoskeletal stiffness; Chest pain; Pyrexia; Injection site pain	Recovered	Report from non-health care provider. Experienced non-serious events of stiffness, chest pain, fever, and soreness at injection site along with the left side of body weakness likely related to reactogenicity. There was no diagnosis of stroke, and the subject quickly recovered on the same day.
female	unspecified	Unspecified	Hemiplegia; Injection site pain; Pain in extremity	unspecified	Report from non-health care provider. Report of "mild hemiplegia" and injection site stinging and sore arm both of which resolved.
female	80-90	Same day/3 days	Blindness transient; Deafness; Chills	Recovered	Report from non-health care provider. 80-90-year-old with vision loss x1 hour on day of vaccine, then hearing loss 3 days later. Vision loss resolved, outcome of hearing loss not reported.

MAH's Estimated post marketing exposure:

According to the CDC (<https://covid.cdc.gov/covid-data-tracker/#vaccinations>), 3,215,657 doses of the Janssen COVID-19 vaccine were administered as of March 31, 2021.

PRAC Rapporteur comment:

At the approval of the CMA on 11 March 2021, "Venous thromboembolism" was included as important potential risk in the RMP, due to a numerical imbalance of venous thromboembolism observed in the main clinical study, VAC31518COV3001.

On 12 March 2021, a signal procedure regarding thrombotic and embolic events was started for another adenovirus vector Covid-19 vaccine, which is currently ongoing. During the assessment of this signal, very rare cases showing a combination of thrombosis and thrombocytopenia, and in some cases accompanied by bleeding, have gained particular attention.

For the Covid-19 Vaccine Janssen, we are currently aware of three cases with such unusual characteristics. This includes one case with concomitant thrombosis and thrombocytopenia in study VAC31518COV3001 and two post-marketing cases with concomitant thrombosis and thrombocytopenia, which have been reported from the US market. Of the three reports, 2 concern female patients while one concerns a male patient. Of the 3 reports, one is fatal. Time to onset included 11 days (n=2) and 19 days (n=1). Thrombotic events reported included transverse sinus thrombosis, cerebral venous sinus thrombosis and bilateral iliac and femoral deep vein thromboses. Although thrombocytopenia was reported in one case, platelet counts were not provided. In the remaining two cases, platelet counts were specified as 64,000 (units not specified) and 15,000 (units not specified). For further details of these cases, see above.

Some preliminary information has also been received from the MAH during the last days of March / first days of April; namely in short:

- The post marketing exposure is estimated to approximately 3.2 million doses by 31 March.
- A review of the MAH safety data base regarding thrombotic and thromboembolic events from spontaneous reporting irrespective of thrombocytopenia, resulted in identification of 13 serious spontaneous case reports (0 non-serious case reports). For many of this limited information was available. None described a combination of thrombocytopenia.
- The review of cases of thrombotic or thromboembolic events and low platelets revealed that there is only one case report that has both a thrombotic or thromboembolic event and low platelets.

Taken together, there are currently three cases of thrombosis together with thrombocytopenia within the clinical trial and post marketing data base, having occurred within 2 -3 weeks after vaccination with Covid-19 vaccine Janssen. For the two post marketing cases, information is relatively limited. Nevertheless, taking into account that VTE is an important potential risk in the RMP, and these in total three reports, it is considered warranted to further review thrombotic and embolic events SMQ within a signal prompt procedure.

Given that there are three cases of this unusual clinical picture, it may be considered warranted to already as a first step update the product information with a short description of the observed cases as well as advice to prescribers and vaccinated individuals.

2.3. Proposed recommendation

The MAH should address the following:

1. The cumulative post-marketing exposure divided by age groups if available.
2. Presentation of retrieved laboratory values on complete blood count including platelets for cases with venous or arterial thrombosis in all clinical studies with the Covid-19 vaccine Janssen.
3. Presentation of retrieved laboratory values on complete blood count including platelets for cases with bleeding in all clinical studies with the Covid-19 vaccine Janssen.
4. A cumulative review of cases observed in clinical studies with the Covid-19 vaccine Janssen; in clinical studies with other vaccines using the same Ad26 platform as well as post-marketing cases occurring within a month after vaccination reporting
 - a. Thrombosis (any);
 - b. thrombosis (any) and concomitant thrombocytopenia/low platelet count;
 - c. thrombocytopenia/low platelet count regardless of symptoms ;

The presentation should include concomitant disease and medications, COVID-19-testing, time to onset, clinical course and outcome and diagnostic work-up, as available.

5. Discussion on potential causal relationship between vaccination with Covid-19 vaccine Janssen and the events of thrombosis and thrombocytopenia, addressing possible mechanisms. This

should include any support from non-clinical data and address any potential role of the adenoviral gene transfer vector.

6. The MAH view on whether the current data warrant for *further* updates of the product information as well as if there is a need for additional risk minimisation measures. *[to be adapted depending on proposed option below]*.
7. The MAH is asked to address how this issue can be further studied both in the non-clinical and clinical setting.

Regarding the next steps and timelines; there are different options such as:

- During the PRAC April Meeting, agree a short warning statement (SmPC section 4.4, and section 2 of the package leaflet) describing the observed cases, and include advice to prescribers and vaccinated individuals. Adopt the above questions and continue the signal procedure, possibly by further conclusions at the PRAC meeting in May. A draft wording for section 4.4 is given below.
- Adopt the above questions during the PRAC meeting in April, and ask the MAH to respond promptly, to allow for further PRAC discussion on approximately 15 April or at PRAC ORGAM on 22 April with the aim to agree preliminary conclusions, including potential label updates.

Draft proposal for section 4.4

Thrombocytopenia and coagulation disorders

A combination of thrombosis and thrombocytopenia has been observed very rarely following vaccination with COVID-19 Vaccine Janssen. This includes thrombosis at unusual sites such as cerebral venous sinus thrombosis, and fatal outcome. The majority of these cases occurred within the first two to three weeks following vaccination.

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.

Package leaflet – to be updated accordingly.

2.4. Comments from other PRAC members

Please find here below comments from a member state regarding this signal assessment report on Embolic and Thrombotic events (SMQ) in association with COVID-19 Janssen Vaccine (Ad26.COV2-S [recombinant]) (EPITT 19689).

In order to have the same level of information in the Signal assessment report on embolic and thrombotic events (SMQ) with COVID-19 Vaccine, Janssen could be asked to provide the same scientific reflections/discussions on the non-clinical data as those asked for Vaxzevria. This would allow to study the mechanistic aspect in a more extensive way.

Proposal for new pre-clinical studies after assessment of the possible mechanistic explanations The MAH should address the following:

[...]

5. Discussion on potential causal relationship between vaccination with Covid-19 vaccine Janssen and the events of thrombosis and thrombocytopenia, addressing possible mechanisms. This should include

any support from non-clinical data and address any potential role of the adenoviral gene transfer vector.

- The MAH should propose a study to test in-vitro expression of the S protein of Janssen vaccine (these are already available for the other already authorised SARS-CoV-2 vaccines with a different S protein without showing concerns).

- The MAH should consider to perform in-vitro study to test the interaction of the Janssen vaccine with blood components (i.e. thrombocytes, erythrocytes, leucocytes etc., coagulation factors, natural IgM antibodies) both in the presence and absence of pre-existing immunity to recombinant, replication-incompetent adenovirus type 26 (Ad26) vector.

- The MAH should consider collecting more extensive non-clinical data namely but not limited to animal models. The MAH should provide further animal data namely on Ad26 vector. The potential effects of Ad26 vector to human should also be addressed.

- The MAH should propose further studies to elucidate the role of the spike antigen in these events specifically whether the Spike protein is antigenic (i.e. taking the role of heparin and binding with platelet factor 4).

- The MAH should propose any further non-clinical studies aimed at elucidating the mechanism that trigger platelet activation and subsequent thrombotic effects.

PRAC rapporteur comments; these comments have been taken into account in the updated LoQ.

Late breaking information submitted to EMA

Within the context of the oral explanation that was provided by Janssen-Cilag International NV to the PRAC on the 7th April 2021, the MAH referred to a case of cerebral thrombosis. Of note, the MAH specified that the case was subject to limited information and that at that point it had not yet been adjudicated as to whether the cerebral thrombosis concerned arterial or venous thrombosis. They also specified that no information regarding platelet count had been received.

On the 8th of April, the MAH sent a CIOMS form concerning the case in question.

A description of the case is provided below:

Case concerns a female patient between the ages of 18-28 from the which was received from a pharmacist. The patient had no known allergies, was a non-smoker, was not on any concomitant medications including combined oral contraceptives, had no medical history or familial history of clotting disorders. Sixteen days after vaccination she developed headache, vomiting and mental status changes. Her family noted she was "staring" or "spacey". She was brought to the hospital where MRI and CT scan of the brain revealed sagittal sinus thrombosis and haemorrhage. She was admitted to ICU. Platelet count on presentation was 18,000 (units not specified), fibrinogen was noted to be low and fibrin D-dimer was elevated. Platelet count remains at 22,000 to 24,000. Sixteen days after vaccination, the patient developed seizures, was intubated, sedated and placed on unspecified anti-epileptic drugs (AEDs). She was treated according to the "British Guidelines", was given a platelet transfusion in advance of thrombectomy and was anticoagulated (specific agent not provided). Following platelet transfusion and thrombectomy, the patient's platelet count rose to 160,000, fibrinogen normalised, and both remained stable for 1-2 days. Treatment with un-specified AEDs was continued. The patient remained intubated and sedated and thus her mental and neurologic status was not re-evaluated. At the time of the report it was noted that the patient had recovered from thrombocytopenia, but the outcome of sagittal sinus thrombosis, cerebral haemorrhage and seizures was not reported.

PRAC rapporteur comments; this is another case with an unusual clinical picture of a serious sagittal sinus thrombosis, in combination with thrombocytopenia, occurring in a healthy young woman, about 2 weeks after vaccination. This case strengthens the current signal in need of further prompt in depth review.

2.5. Adopted PRAC recommendation

Having considered the available evidence from both spontaneous reports and clinical trials, the PRAC has agreed that at this stage, there is insufficient evidence to warrant an update to the product information. Nevertheless, there are a number of issues in relation to thrombotic and embolic events that need further review, and therefore the signal procedure should proceed.

The MAH for COVID-19 Vaccine Janssen (Janssen-Cilag International NV) is therefore requested to submit, , responses to the following list of questions:

- The cumulative post-marketing exposure, stratified by age, if feasible.
- Presentation of retrieved laboratory values on complete blood counts including, but not limited to, platelets, anti-platelet factor 4 antibodies, fibrinogen, ADAMTS13, anti-phospholipid antibodies and D-dimer, for cases with venous or arterial thrombosis in all clinical studies with the Covid-19 vaccine Janssen.
- Presentation of retrieved laboratory values on complete blood counts including, but not limited to platelets, anti-platelet factor 4 antibodies for cases of haemorrhage in all clinical studies with the Covid-19 vaccine Janssen.
- A detailed cumulative review of cases observed in clinical studies with i) the Covid-19 vaccine Janssen; ii) other vaccines using the same Ad26 platform; as well as of iii) cases originating from the post-marketing setting of
 - a. thrombosis (any);
 - b. thrombosis (any) and concomitant thrombocytopenia/low platelet count;
 - c. thrombocytopenia/low platelet count regardless of symptoms;

The presentation should include all available information regarding concomitant disease and medications, COVID-19 testing, time to onset, clinical course and outcome and diagnostic work-up, as available. Full case narratives should also be provided.

- Observed to expected analyses of cases of
 - a. Cerebral venous thrombosis without thrombocytopenia (i.e. using all relevant PTs such as cerebral venous thrombosis, superior sagittal sinus thrombosis, transverse sinus thrombosis, aseptic cavernous sinus thrombosis, cerebral venous thrombosis and also events of cerebral thrombosis that are adjudicated to be related to venous thrombosis), also stratified by age bands (i.e. 10 years) should be provided. Background rates for events of CVST without thrombocytopenia should be used within the analysis.
 - b. Cerebral venous thrombosis with thrombocytopenia (i.e. using all relevant PTs such as cerebral venous thrombosis, superior sagittal sinus thrombosis, transverse sinus thrombosis, aseptic cavernous sinus thrombosis, cerebral venous thrombosis and also events of cerebral thrombosis that are adjudicated to be related to venous thrombosis), also stratified by age bands (i.e.10 years), should be provided. Background rates for CVST with thrombocytopenia should be used within the analysis.
- Discussion on potential causal relationship between vaccination with Covid-19 vaccine Janssen and the events of thrombosis and thrombocytopenia, addressing possible pathophysiological mechanism, including potential for platelet activation. This should include all relevant non-clinical data and clinical data and address any potential role of the adenoviral gene transfer vector.

- The MAH is asked to discuss how, beyond the already agreed studies in the PhV plan, the important potential risk *venous thromboembolism*, including the potential occurrence of the combination of thrombosis and thrombocytopenia can be further studied. Ways of gaining further mechanistic data, both non-clinical and clinical, regarding potential interactions of the Covid-19 vaccine Janssen and the coagulation system should specifically be addressed; and the following commented:
- Study the in-vitro expression of the spike protein of the Janssen Covid-19 vaccine, and the relative proportions of the spike protein expressed in the pre-fusion and post-fusion state after administration of the vaccine.
- Study the interaction of the Janssen Covid-19 vaccine with blood components such as thrombocytes, erythrocytes, leucocytes etc., as well as coagulation factors, natural IgM antibodies; both in the presence and absence of pre-existing immunity to recombinant, replication-incompetent adenovirus type 26 (Ad26) vector.
- Discuss how additional non-clinical as well as human studies can provide further data regarding potential effects of the i) Ad26 vector; ii) the spike protein on the coagulation system, including potential triggers of platelet activation and subsequent thrombotic effects. This should include addressing whether the Ad26 vector may activate platelets via interaction with the cell adhesion molecule CAR (i.e. coxsackie and adenovirus receptors), or affect the structure of PF4.
- For on-going clinical studies, should cases of thrombocytopenia and/or thrombosis occur, a thorough laboratory testing should be performed including, but not limited to: complete blood count incl platelets, haemolysis parameters, D-dimer, fibrinogen, PTT, PT/INR, antiphospholipid antibodies and anti-PF4 antibodies.
- Considering the findings of the review, the MAH should discuss the need for amendment to the Product Information and/or Risk management plan, for the latter, including, but not limited to, the list of safety concerns and studies specified within the pharmacovigilance plan.

The PRAC will perform the assessment within a 30-day timeframe.

3. Additional evidence

3.1. Assessment of additional data

On 15 April 2021, the MAH submitted responses to Question 1-8 outlined above. Furthermore, on 15 April 2021, the PRAC Rapporteur has received EudraVigilance data and analyses from the EMA. The latter was updated on 17 April 2021.

The PRAC Rapporteur assessment to be sent to the PRAC on 19 April 2021, is the first step in the further evaluation of this signal. As agreed with the EMA on 15 April 2021, the aim of this first step is to review of cases of unusual thrombosis in combination with thrombocytopenia, and taking experience gained from a recently finalised signal evaluation², and based on that, evaluate the need for updates of

² https://www.ema.europa.eu/en/documents/prac-recommendation/signal-assessment-report-embolic-thrombotic-events-smq-covid-19-vaccine-chadox1-s-recombinant_en.pdf

the product information, as well as the need for additional risk minimisation measures. For the AR to be sent out on 19 April, 17 April 2021 is the cut-off for new data.

A more in-depth evaluation of any mechanistic aspects, as well as of the pharmacovigilance plan, and thereby the responses to Q7, will be undertaken in the second step of the assessment of the MAH responses. In addition, review of laboratory results from clinical studies and post-marketing on conditions not predominantly related to the combination of thrombosis and thrombocytopenia will be assessed in more depth in the second step as well.

A timeline for that second step is to be finally agreed, but tentatively planned for the PRAC meeting in May 2021.

3.1.1. MAH response as of 15th April 2021

The safety databases (A) used to identify reports of thrombotic or thromboembolic events with concurrent thrombocytopenia, the search criteria used (B), and laboratory results (C) were:

Safety Databases:

Ad26.COV2.S Clinical Database. This contains safety data (including both nonserious adverse events [AEs] and serious adverse events [SAEs]) from all ongoing and completed COVID-19 vaccine Janssen Ad26.COV2.S Phase 1, Phase 2 and Phase 3 clinical studies, including VAC31518COV1001, hereby referred to as COV1001; VAC31518COV1002, hereby referred to as COV1002; VAC31518COV2001, hereby referred to as COV2001; VAC31518COV3001, hereby referred to as COV3001, and VAC31518COV3009, hereby referred to as COV3009.

Ad26 Platform Clinical Database. The MAH's clinical AdVac® integrated safety database report (V6.0, version of 28 March 2021, cut-off date 31 December 2020) describes integrated safety data from 32 completed clinical studies using Ad26-based vaccines: Ad26.ZEBOV (Ebola program; 10 studies), Ad26.ENVA.01, Ad26.Mos.HIV, and Ad26.Mos4.HIV (human immunodeficiency virus [HIV] program; 8 studies), Ad26.CS.01 (malaria program; 1 study), Ad26.RSV.FA2 and Ad26.RSV.preF (respiratory syncytial virus [RSV] program; 10 studies), and Ad26.Filo (filovirus program; 1 study), and Ad26.HPV16 and Ad26.HPV18 (human papillomavirus [HPV] program; 1 study).

Global Medical Safety Database. This contains all reports of SAEs from Ad26.COV2.S clinical studies conducted by Janssen, as well as spontaneous post-marketing reports of both nonserious AEs and SAEs:

Study VAC31518COV3012, hereby referred to as COV3012 Sisonke open-label single-arm Phase 3b implementation study to monitor the effectiveness of the single-dose Ad26.COV2.S COVID-19 vaccine among health care workers in South Africa. This is a collaborative study, sponsored by the South African Medical Research Council (SAMRC). SAEs only will be captured.

SAEs reported in collaborative studies and vaccination programs conducted with Ad26.ZEBOV (Ebola program; 10 studies) for which SAEs are followed in the GMS database. SAEs reported in these studies and programs will only appear in the GMS Database. These include VAC52150EBL1005, EBL1007, EBL2004, EBL2006, EBL2007, EBL2008, EBL2009, EBL3008, EBL3010 and EBL4002.

The following trials/programs are conducted as a collaborative non-Janssen sponsored initiative:

EBL1005: Phase 1 Randomized, open-label trial conducted in healthy adults (18 to 50 years of age) to assess the safety and reactogenicity of 2-dose vaccine regimens. Sponsor: Oxford University

EBL1007: Phase 1 Randomized, uncontrolled, double-blind trial conducted in healthy adults (18 to 45 years of age) to assess the safety and reactogenicity of 2-dose vaccine regimens and third vaccination. Sponsor: National Institute of Allergy and Infectious Diseases (NIAID)

EBL1008: A Systems Biology Phase 1 Evaluation of the Safety, Reactogenicity, and Immunogenicity of Chimpanzee Adenovirus Type 3- vectored Ebolavirus Zaire (ChAd3-EBO-Z) and Modified Vaccinia Ankara- vectored Multivalent Filovirus (MVA-BN®-Filo) Vaccine Candidates. Sponsor: NIAID

EBL2004: Phase 2 Randomized, placebo controlled, double-blind trial conducted in healthy adults (≥ 18 years), adolescents (12 to 17 years of age), and children in 2 age groups (1 to 11 years of age). To assess the safety and reactogenicity of 2-dose vaccine regimens; To compare the 2-dose vaccine regimen with the matched placebo regimen for antibody response 3 months after randomization (approximately 28 days after Dose 2 vaccination). Sponsor: NIAID.

EBL2006: Phase 2 Open-label trial in participants who received investigational Ebola vaccines (ChAd3-EBO-Z, MVA-BN-Filo, MVA-EBO-Z, or Ad26.ZEBOV) administered in previous studies led by the Oxford Vaccine Center (EBL1001, EBL1004, and EBL1005). To assess the persistence of humoral and cellular immunity against EBOV glycoprotein with or without a booster dose of Ad26.ZEBOV administered 2 to 5 years after adenoviral and MVA-vectored Ebola vaccine schedules. Sponsor: Oxford University

EBL2007: Phase 2 Open-Label trial conducted in health care providers in the Democratic Republic of the Congo who are at risk of exposure to Ebola in the event of a future Ebola outbreak; To assess the immunogenicity and safety of a prophylactic vaccination by administration of the heterologous vaccine regimen. In addition, after randomization (1:1) a booster of Ad26.ZEBOV will be offered at respectively 1 year or 2 years after the first dose. Sponsor: University of Antwerp/University of Kinshasa.

EBL2008: Phase 2 Open-label trial conducted in participants previously enrolled in the EBL2006 study led by IRESSEF and UOXF investigators. To assess humoral and cellular immunity against EBOV glycoprotein at 1 year following a late booster dose of Ad26.ZEBOV administered 3 to 4 years after receiving heterologous Dose 1 or Dose 2 of ChAd3- EBO-Z /MVA-EBO-Z administered at Day 1 and Day 8. Sponsor: Oxford University

EBL2009: Phase 2 Non-randomized, uncontrolled, open-label trial in adult health care or frontline workers to characterize the humoral immune response to the Ebola surface glycoprotein (GP) and the persistence of antibodies after IM administration of a 2-dose vaccine regimen. Sponsor: The London School of Hygiene & Tropical Medicine and Uganda Virus Research Institute.

EBL3008: Ongoing Phase 3 open-label trial conducted in nonrandomized Adults (≥ 18 years of age) and children (≥ 1 year of age) to assess the 2-dose regimen for effectiveness and safety in the Democratic Republic of Congo during the ongoing Ebola outbreak. Sponsor: The London School of Hygiene & Tropical Medicine

EBL3010: Ongoing Phase 3 trial in healthy pregnant women (≥ 18 years of age) in Rwanda to assess the 2-dose regimen for safety, reactogenicity and immunogenicity. Partner: Emory University and Rwanda Institution

EBL4002: Ongoing open-label collaborative trial: Rwandan government-led Ebola vaccination campaign under conditional approval) UMURINZI. Ebola Vaccine Program Campaign in Rwanda. Sponsor: Ministry of Health, Rwanda.

It is important to note that as many of the clinical studies are currently ongoing, the clinical database and the GMS database have not been fully reconciled, hence the number of SAEs reported may differ

depending on the source. Whereas a search of the clinical database will provide information on both cases of nonserious AEs and SAEs, the GMS database will only contain reports of SAEs.

Post-marketing safety assessment of AEs spontaneously reported have well-known limitations that often preclude an accurate and meaningful medical assessment, including: insufficient case detail such as clinical course/laboratory data/ diagnostics, lack of medical accuracy due to non-health care provider reporters (e.g., consumers/patients), and an inability to follow-up secondary to multiple factors such as contact details or reluctance by reporters to provide authorization or contacting the health care provider. Data obtained from the Food and Drug Administration (FDA) and CDC’s co-managed US national Vaccine Adverse Events Reporting System (VAERS), which is the principal source of spontaneously reported AEs, has an unspecified delay in data entry from time of receipt by the FDA, which in turn delays visualization by the company. Case details can only be obtained following Freedom of Information Act request by the company and have an undefined time period before being released).

Search Criteria

A comprehensive search was performed on the Janssen's Global Medical Safety (GMS) Database and the Janssen Clinical Databases for adverse events of interest using the following Standardised MedDRA Query (SMQ) version 23.1 broad search terms, where applicable (the clinical database and the GMS database have not been fully reconciled, hence the number of SAEs reported may differ depending on the source. Whereas a search of the clinical database will provide information on both cases of nonserious adverse events (AEs) and serious adverse events (SAEs), the GMS database will only contain serious events (SAEs):

Question 2	Embolic and thrombotic events (SMQ)
Question 3	Haemorrhages (SMQ)
Question 4	
A) Thrombotic	A) Embolic and Thrombotic events (SMQ)
B) Thrombotic & Thrombocytopenia	B) Embolic and Thrombotic events (SMQ) and High Level Term Thrombocytopenias or Haematopoietic cytopenias (SMQ)
C) Thrombocytopenia	C) High Level Term Thrombocytopenias or Haematopoietic cytopenias (SMQ)

The search was performed on the following clinical trials databases, containing both serious adverse events (SAEs) and non-serious adverse events (AEs):

The data lock points (DLP) used for the searches performed in the different databases were the following: COV1001 (DLP 01 April 2021); COV1002 (DLP 31 March 2021) – Data are blinded; COV2001 (DLP 17 March 2021) – Data are blinded; COV3001 (DLP 24 March 2021); COV3009 (DLP 01 April 2021) – Data are blinded; The Ad26 Platform Clinical Database (AdVac report, Version 6.0, DLP 31 December 2020). The post-marketing reports for Ad26.COVS had a DLP 09 April 2021. EBL1007, EBL2004, EBL2006, EBL2008, EBL2007, EBL2009, EBL3008, EBL3010 and EBL4002 (DLP 09 April 2021).

Laboratory Results

In the clinical trials, analysis of blood count, including platelets was not routinely performed, except in the phase 1 studies COV1001 (only abnormality flag, no actual values) and COV1002 where baseline and post-vaccination samples were collected for Laboratory assessments. Protocols do specify that abnormal laboratory values, when available, are reported as unsolicited adverse events (AEs). Overall, in most cases of venous or arterial thrombosis (reported as AE or SAE) complete blood count including platelets is not be available. The MAH has contacted the study sites to retrieve possible individual laboratory data from source document. Analysis of the available data showed limited reports of thrombocytopenia and other coagulopathies.

To address the important potential risk of venous thromboembolism data generated in COV2001 will be used to assess potential vaccine-induced anti phospholipid syndrome and potential vaccine-induced activation of coagulation in adults aged 18 to ≤ 55 years and adults aged ≥ 65 years. Protocol required haematology laboratory assessments include Lupus anticoagulants, Anti- $\beta 2$ glycoprotein, Anti cardiolipin and D-dimer. Results of the ongoing study COV2001 are expected to become available at the end of April 2021.

PRAC Rapporteur assessment comment

The background data on safety databases, the search criteria used, and laboratory results are noted.

QUESTION 1

The Cumulative post-marketing exposure, stratified by age, if feasible.

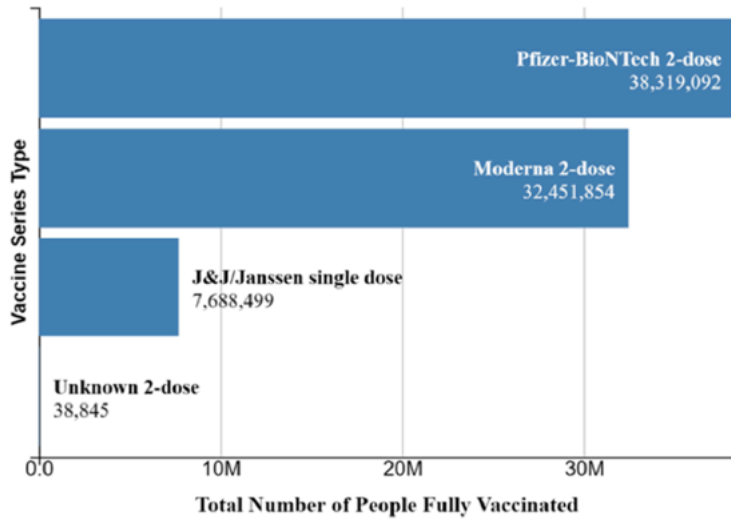
Janssen cumulative (US) post-marketing exposure according to the Center of Disease Control (CDC) as of the 15 April 2021, is a total of 7,688,499 doses of the COVID-19 vaccine Janssen. As of 12 April 2021 (of a total of 6,453,740 doses), it is estimated, that approximately 66.5.% of recipients of the Janssen COVID-19 vaccine were in the 18 to 59 -year age group and approximately 33.5% of recipients were in the ≥ 60 -year age group. Age group percentages are derived from the exposure numbers published daily by the CDC at <https://covid.cdc.gov/coviddata-tracker/#vaccination-demographic>.

The percentages are based on:

Calculation of post-marketing exposure, stratified by age, according to the CDC is based on the overall age group percentages across all COVID-19 vaccines authorized for us in the US, and therefore may not represent the best current estimate of the actual age by distribution for the COVID-19 vaccine Janssen.

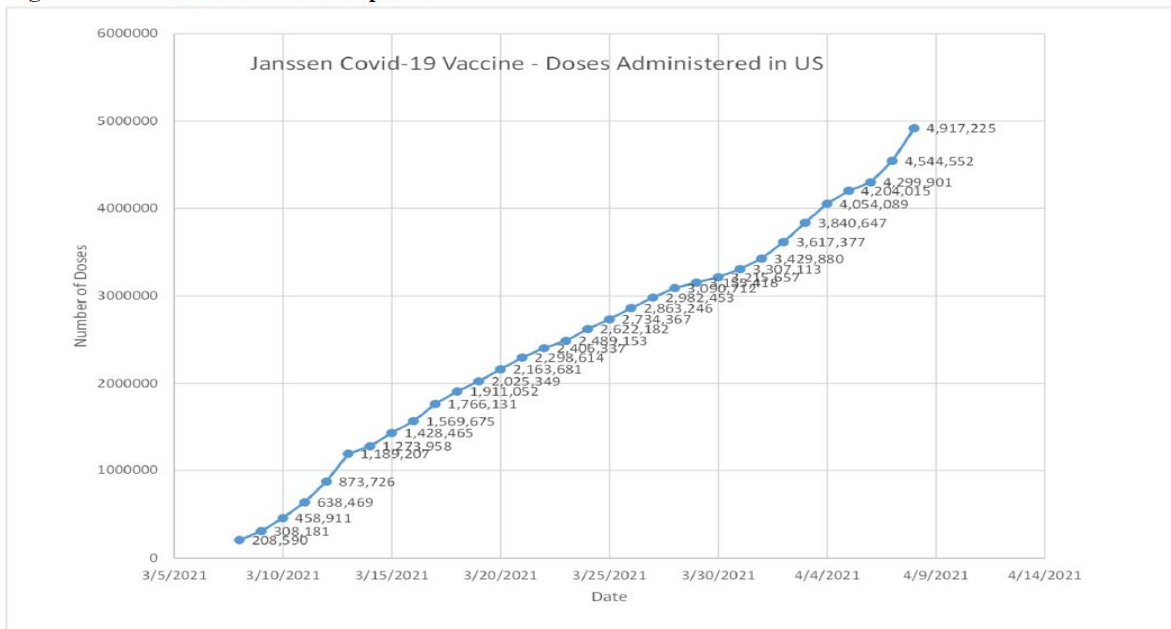
COVID-19 vaccine Janssen received Emergency Use Authorization (EUA) for use in the US on 27 February 2021, and vaccination of the US population initiated on 08 March 2021. As of 13 April 2021, a total of approximately 2,489,153 individuals are within the 21-day post vaccination period. The company estimates that more than 100,000 individuals were being vaccinated each day in the US with COVID-19 vaccine Janssen immediately prior to the pause initiated on 13 April 2021. As of 12 April 2021: Janssen has 6 post-authorization cases of CVST (4 of 6 with low platelets, 2 unknown) with 6.8 million individuals vaccinated.

Number of People Fully Vaccinated in the U.S. by COVID-19 Vaccine Series Type



from <https://covid.cdc.gov/covid-data-tracker/#vaccinations> – 15 April 2021

Figure 1: Vaccinations to date per CDC



The clinical study exposure is detailed in Table 1 below:

Table 1: Clinical Trial Exposure Data for Ad26.COV2.S

Clinical Trials Ad26.COV2.S	DLP(cut-off-date)	Blinding status	Ad26 5e10	Ad26 1e11	Placebo	Blinded	Total
COV1001	01 April 2021	Unblinded (Cohort 1 and 3) Blinded (Cohort 2a/b)	323	319	163	271	1076
COV1002	21 March 2021	Blinded				250	250
COV2001	17 March 2021	Blinded				595	595
COV3001	24 March 2021	Unblinded	21895		21888		43783
COV3009	01 April 2021	Blinded				24421	24421
Subtotal		Subtotal	22218	319	22051	25537	70125
COV3012	30 March 2021	Open-label	263878				263878
Total estimated clinical exposure#			286096	319	22051	25537	334003

Abbreviations: DLP = Data Lock Point; N = number; NA = not applicable

* Note: Clinical studies COV1002, COV2001 and COV3009 as well as Cohorts 2a/b of Study COV1001 are blinded so number receiving Ad26.COV2.S is an estimate based on randomization ratio.

Total estimated exposure from the clinical trial databases for Ad26.COV2.S. This does not include post-marketing exposure, ongoing blinded Ad26 clinical trials which have not been integrated or collaborative studies.

Studies: COV1001 = VAC31518COV1001; COV1002 = VAC31518COV1002; COV2001 = VAC31518COV2001; COV3001 = VAC31518COV3001; and COV3009 = VAC31518COV3009

Study COV3012 is the VAC31518COV3012 Sisonke open-label single-arm Phase 3b program to monitor the effectiveness of a single dose Ad26.COV2.S vaccine among health care workers in South Africa. No electronic case report forms (eCRFs) are available for this trial.

Table 2: Clinical trial exposure data Ad26 Platform (excluding COVID-19)

Dataset	DLP (cut-off-date)	Blinding Status	Ad26 vaccine Recipients (N)
Adenoviral Vaccine Safety Database V6.0 ¹ <ul style="list-style-type: none"> Pooled data from 32 completed and ongoing unblinded clinical studies¹ Ebola, HIV, Malaria, RSV, Filovirus, and Zikavirus Ad26-based vaccine programs 	31 Dec 2020	Unblinded	8,826*
Data from 12 ongoing blinded studies ² <ul style="list-style-type: none"> Ebola, HIV, and RSV, Ad26-based vaccine programs 	21 Dec 2020	Blinded	2,250
Total number of participants (31 December 2021)			11,076

¹ For some studies, the long-term extension or follow-up period is still ongoing.

² Number is approximate, based on study randomization ratio

*Ad26 Platform: as of cut-off-date of 30 Dec 2020: Total of 8826 participants administered an Ad26 based vaccine, and 4075 participants received placebo = overall Total of 12701 participants

Table 3: Clinical Trial Exposure Data for Ad26.ZEBOV Collaborative Clinical Trials and Vaccination Programs

Clinical study	Completed / Ongoing - DLP	Ad26 vaccine Recipient (N)
EBL1005	Completed	32
EBL1007	Completed enrolment	48
EBL2004	Completed enrolment	1,571
EBL2006	Completed enrolment	28
EBL2007	Completed enrolment	700
EBL2008	Completed enrolment	28
EBL2009	Completed enrolment	800
EBL3008	Ongoing 7 April 2021	20,247
EBL3010	Ongoing 7 April 2021	215*
EBL4002	Ongoing 8 April 2021	191,343
Total estimated exposure		215,012

Abbreviations: DLP = Data Lock Point; N = number

* 215 participants randomized and vaccinated while being pregnant

Table 3 relates to the Ad26 platform exposure data from all completed and ongoing clinical trials using Ad26-based vaccines excluding COVID-19 (see Table 1 for COVID-19). The table relates to the Ad26 platform exposure data for the Janssen Collaborative Ebola studies, including the Ebola vaccination campaign in Democratic Republic of the Congo (DRC-EB-001 / VAC52150EBL3008) and Rwandan government-led Ebola vaccination campaign under conditional approval (UMURINZI / VAC52150EBL4002) with cut-off dates for individual studies/programs provided, as listed in the GMS safety database.

PRAC Rapporteur assessment comment

Regarding cumulative (US) post-marketing exposure, the MAH refers to the Center of Disease Control (CDC), which reports a total of 7,688,499 doses of the COVID-19 vaccine Janssen being used as of 15 April 2021.

As of 12 April 2021 (of a total of 6,453,740 doses), it is estimated, that approximately 66.5% of recipients of the Janssen COVID-19 vaccine were in the 18 to 59 -year age group and approximately 33.5% of recipients were in the ≥ 60 -year age group. However, this estimation appears based on use of all vaccines, and is therefore uncertain.

The MAH has also specified the approximate number of individuals being within the 21-day post vaccination period as of 13 April; namely 2,489,153 individuals. Although not entirely clear what is meant, review of the cumulative presentation above, this exact number of subjects appear to have been vaccinated more than three weeks ago, and thus possibly having past the main risk window for this unusual clinical event.

By end of March 2021, the clinical study exposure is estimated to about 286 000 subjects with the Covid-19 Vaccine Janssen, and more than 200 000 individuals with the Ad26 platform. However, it should be noted that the vast majority of these data for the Covid-19 vaccine Janssen have not yet been assessed by EMA. In the evaluation supporting the CMA on 11 March 2021, approximately 27,200 vaccinated subjects had been assessed in clinical studies for death and SAEs ³, and is thus the most relevant clinical study safety database.

QUESTION 2.

Presentation of retrieved laboratory values on complete blood counts including, but not limited to, platelets, anti-platelet factor 4 antibodies, fibrinogen, ADAMTS13, anti-phospholipid antibodies and D-dimer, for cases with venous or arterial thrombosis in all clinical studies with the Covid-19 vaccine Janssen.

In the clinical studies (COV1001, COV1002, COV2001, COV3001, COV3009), under the SMQ term "Embolic and thrombotic events", the following events have been reported: 33 cases were reported among 22,218 (0.1%) participants that received Ad26COV2.S vaccine at the 5x10¹⁰ vp dose level. 1 case was reported among 319 (0.3%) participants that received Ad26COV2.S vaccine at 1x10¹¹ vp dose level. 26 cases were reported among 22,051 (0.1%) participants that received placebo. 18 cases were reported among 25,537 (0.1%) participants that are blinded to treatment. Refer to Table 4 below for further details. Among those cases, the number of cases of venous or arterial thrombosis have been retrieved from the clinical trials and are summarized in Table 5.

³ EPAR for [COVID-19 Vaccine Janssen, INN-Ad26.CO2-S, recombinant \(europa.eu\)](https://www.ema.europa.eu/en/medicines/human/EPAR/covid-19-vaccine-janssen/INN-Ad26.CO2-S_recombinant(europa.eu))

**Table 4: Ad26.COV2.S Clinical Studies: Number of Subjects with AEs of Interest by SMQ term
“Embotic and Thrombotic events; Full Analysis Set**

Study	SMQ term	N	Ad26.COV2.S (5x10 ¹⁰)	N	Ad26.COV2.S (1x10 ¹¹)	N	Placebo	N	Blinded
COV1001	Embotic and thrombotic events	323	1 (0.3%)	319	1 (0.3%)	163	0 (0.0%)	271	0 (0.0%)
COV1002	Embotic and thrombotic events	-		-		-		250	1 (0.4%)
COV2001	Embotic and thrombotic events			-				595	2 (0.3%)
COV3001	Embotic and thrombotic events	21895	32 (0.1%)	-		21888	26 (0.1%)	-	
COV3009	Embotic and thrombotic events	-		-		-		24421	15 (0.1%)
Total		22895	33 (0.1%)	319	1 (0.3%)	22051	26 (0.1%)	25537	18 (0.1%)

For each study (COV1001, COV1002, COV2001, COV3001, COV3009) the number of subjects with an AE of Interest System Organ Class and Preferred Term are presented in the Subject Listings within the Appendices. Table 5 provides the number of cases of embolic and thrombotic events of interest. As already reported for the COV3001 clinical study results (the main efficacy trial), there is a numerical imbalance for DVT cases with the Ad26COV2.S vaccine (10 cases in the Ad26 5x10¹⁰ recipients, 1 case in Ad26 1x10¹¹ recipient, 2 cases that are still blinded and 3 cases in the placebo arm). For CVST, there was no imbalance in terms of cases reported in the clinical trials. Nevertheless, as stated in answer to Question 8, venous thromboembolism (VTE) is considered an Important Potential Risk for the EU-RMP, and relevant events for VTE have been identified and are monitored as Adverse Events of Special Interest (AESI). Please refer also to Question 4 for further description of thrombosis events.

**Table 5: Ad26.COV2.S Clinical Studies: Number of Subjects with selected AEs of Interest by SMQ term
Embotic and Thrombotic events; Full Analysis Set.**

SOC by Preferred Term	Ad26.COV2.S 5x10 ¹⁰ (study)	Ad26.COV2.S 1x10 ¹¹ (study)	Placebo (study)	Blinded (study)
Deep vein thrombosis	10 (COV3001)	1 (COV1001)	3(COV3001)	2 (COV3009)
Cerebral thrombosis				1 (COV1002)
Cerebral venous sinus thrombosis			1 (COV3001)	
Haemorrhoids thrombosed	0		1 (COV3001)	
Retinal vein thrombosis	1 (COV3001)			
Transverse sinus thrombosis	1 (COV3001)*	0		
Peripheral artery thrombosis				1 (3009)
Venous thrombosis limb	1 (COV3001)			
Full analysis set	22895	319	22051	25537
Total number (%)	13 (0.1%)	0	5 (<0.1%)	4 (<0.1%)

Abbreviations: SOC=System Organ Class

MeDRA version 23.1

*Further details on the case of Venous Transverse Sinus Thrombosis and Cerebral Hemorrhage reported following administration of Ad26.COV2.S in COV3001.

In most cases of venous or arterial thrombosis (reported as AE or SAE) complete blood count including platelets is not available. The MAH has contacted the study sites to retrieve possibly individual laboratory data from source document. For arterial and venous thrombosis cases, available data are presented and no conclusion can be drawn from the limited available information. Finally, for studies

COV1001 and COV1002 complete blood counts, including platelets was performed at baseline and post-vaccination timepoints. For both studies, only normal or abnormality status are collected for pre and post vaccination timepoints. The results are available for study COV1001 and described below.

Analysis of the laboratory assessments performed in the COV1001 clinical study revealed that there were no trends/abnormalities observed in platelet numbers as compared to placebo at Day 8 (7 days post-dose 1) or at Day 57 and Day 64 (post-dose 2). Similar there was no trend/abnormalities in levels of activated partial thromboplastin time or in prothrombin time (Table 4). It should be noted that these reported laboratory values are not reported as consequence of an adverse event but are used to see trends when comparing pre and post-vaccination timepoints. Overall, there is no impact of the vaccine on platelet counts: there was no notable change in platelets counts observed at the post vaccination timepoints.

Table 6: Laboratory results for subject in clinical trials COV1001, COV1002, COV2001, COV3001 for subjects with vein and arterial thrombotic events

Study	Vaccine/ Placebo	Risk period	Age (years)/ Gender/ Race	System Organ Class	Serious/ relatedness	PCR positive	AE onset/ end date	Labs
1001	Ad26.COV2S 1x10 ¹¹	> 28	65-75/ M/	Embolic and thrombotic events /Vascular disorders / Deep vein thrombosis / DEEP VEIN THROMBOSIS	No NR		52	
1002	Blind		58-68/ M/	Embolic and thrombotic events /Nervous system disorders / Cerebral thrombosis / CEREBRAL THROMBOSIS	Yes NR		105 post-dose 2 (161 post-dose 1)	CIOMS form
3001		0-28	50-60/ M/	Vascular disorders /Deep vein thrombosis /DEEP VEIN THROMBOSIS IN LOWER LEFT LEG				Pending
3001		0-28	33-43/ M/	Vascular disorders /Deep vein thrombosis /RIGHT LEG DEEP VEIN THROMBOSIS			DVT & PE: -ongoing	PLT= 257 (RR 140-420) PT normal INR=1.12 PT normal INR=1 aPTT 31.4 (H) (RR 22.4- 29.3) PLT=251 (RR 140-420) D-dimer 5.55 (H) (RR 0-0.5 mg/L)
3001		0-28	37-47/ M/	Vascular disorders /Deep vein thrombosis /DEEP VEIN THROMBOSIS				The PI directly informed me it was a placebo participant and thought it didn't make sense to check the relevant labs.
3001		0-28	83-93/ M /	Vascular disorders /Deep vein thrombosis /DEEP VEIN THROMBOSIS IN HEMORAL VEIN		No		PT/INR = normal = 11.3 sec/1.1 APTT = normal = 23 sec Normal CBC = normal platelets = 204 x10 ³ /uL (RR 140-400), the WBC was elevated to 11.59 x10 ³ /uL, with slight increase in IMM GRAN ABSOLUTE = 0.07 x10 ³ /uL and MONOCYTE ABSOLUTE COUNT = 1.24 x10 ³ /uL, and with low Mean Cell Hemoglobin Concentration 31.3 g/dL CMP = all normal Lactic acid = 0.8 mmol/L D-dimer and fibrinogen were not evaluated Follow up CBC CBC is unremarkable, normal Platelets = 197 x10 ³ /uL
3001		0-28	35-45/ M/	Vascular disorders /Deep vein thrombosis /DEEP VEIN THROMBOSIS				Pending
3001		0-28	18-28/ M/	Nervous system disorders /Transverse sinus thrombosis /TRANSVERSE SINUS VENOUS THROMBOSIS				CIOMS form

Study	Vaccine/ Placebo	Risk period	Age (years)/ Gender/ Race	System Organ Class	Serious/ relatedness	PCR positive	AE onset/ end date	Labs
3001		0-28	56-66 /M/ Race	Vascular disorders/Deep vein thrombosis /DEEP VEIN THROMBOSIS		No	(from RAVE)	(this seems to be the admission date, as per the attached medical records) PLT 141 (L) (RR not known) PT 24.6 (H) INR 2.1 (H) See attachment for full details.
3001		0-28	45-55/ M/ Race	Vascular disorders/Deep vein thrombosis /DEEP VEIN THROMBOSIS				Pending
3009	Blinded		54-64 M	Embotic and thrombotic events Vascular disorders Peripheral artery thrombosis THROMBOSIS ARTERIO FEMORALIS SUPERFICIALIS				No local lab results for the platelets and coagulation parameters were obtained
3009	Blinded		65-75 F	Embotic and thrombotic events Nervous system disorders Cerebrovascular accident THROMBO- VASCULAR CVA RIGHT				No local lab results for the platelets and coagulation parameters were obtained
3009	Blinded		46-56 F	Embotic and thrombotic events Respiratory, thoracic and mediastinal disorders Pulmonary embolism SUSPICION OF PULMONARY THROMBOEMBOLISM				Platelets was 203x10E3/ml (normal 150-370), D-dimer 350 ng/ml (normal 0-500); PT 10.6 sec; INR 1.0; Fibrinogen 660 mg/dl (normal 150 –450); antibiotic was initiated with cephalin
3009	Blinded		31-41 F	Embotic and thrombotic events Vascular disorders Deep vein thrombosis DEEP VEIN THROMBOSIS				Pending
3009	Blinded		78-88 M	Embotic and thrombotic events Respiratory, thoracic and mediastinal disorders Pulmonary embolism PULMONARY EMBOLISM				Pending
3009	Blinded		46-56 M	Embotic and thrombotic events Vascular disorders Deep vein thrombosis DEEP VEIN THROMBOSIS				Pending
3009	Blinded		46-56 M	Embotic and thrombotic events Respiratory, thoracic and mediastinal disorders Pulmonary embolism PULMONARY EMBOLISM				The Study Coordinator said that since the subject only went to the ER and the event was an AE, they had not requested medical records and do not have the local lab results for the platelets and coagulation parameters (PT/PTT, bleeding time etc.). The study coordinator has requested the records right after her conversation with the CRA and will send us any updated information once received.
3009	Blinded		72-82 M	Embotic and thrombotic events Respiratory, thoracic and mediastinal disorders Pulmonary embolism PULMONARY EMBOLISM				Pending

PRAC Rapporteur assessment comment

There are some issues with regards to the presentation of data that hamper further assessment of the cases with venous or arterial thrombosis in the clinical studies with the Covid-19 vaccine Janssen.

In Table 5 above, there were 13 subjects with thromboembolic AEs of interest in the Ad26COV2.S vaccine group, including various venous thromboses and peripheral artery thrombosis in study 3001; apparently, there were 19 additional cases reporting embolic and thrombotic events in the Ad26COV2.S group in study 3001 based on Table 4; for completeness, the MAH should summarize the main reasons for not including the additional cases among AEs of interest (**RSI**). Also, only 8 cases with thromboembolic events are included in Table 6, and there is one case apparently missing from the summary in Table 5 (according to table 6, there is one case report of a 65-75 year-old female with cerebrovascular accident, with no lab results).

In table 6, laboratory results for 18 subjects in the clinical trials with vein and arterial thrombotic events are presented: for the majority of cases, however, no such data are available. For 2 cases, there is no summary of relevant laboratory data but only a reference to appended CIOMS forms. In four additional subjects, laboratory values are reported. Notably, for any patient diagnosed with any thromboembolic event, collection of lab tests including platelets is expected. It is unclear if the cases in table 6 pertain to those who received the Ad26COV2.S vaccine only (for all cases in study 3001, these data are not included in this table although that study has been unblinded).

For 3 of the 4 cases with laboratory values reported, platelet counts were normal. However, there is one additional case with concomitant thrombosis and thrombocytopenia in Table 6: a male between the ages of 56-66 who presented with thrombocytopenia (platelet levels 141) 15 days after vaccination; he was hospitalised 21 days after vaccination with deep vein thrombosis. Based on additional values, it is possible that this patient was treated with a vitamin K antagonist (INR was 2.1) unless he had severe co-morbidities such as liver failure (which could potentially also cause thrombocytopenia) or severe dietary vitamin K insufficiency. No CIOMS-report has been provided; based on the very short narrative of this case, reported co-morbidities included obesity and depression, and he received the Ad26COV2.S vaccine (i.e. not placebo). There are no lab tests at all in the narrative for this case, however, it is stated that the patient was treated with rivaroxaban following his DVT; since rivaroxaban would not be used in patients with severe liver failure, the INR value is assumed to be related to anticoagulant therapy at the time of his thrombosis.

This case should obviously have been presented within the case reports of concomitant thrombosis and thrombocytopenia in the clinical trials, regardless of concomitant disease and treatment. Such case reports have been requested several times from the MAH. Notably, should this case pertain to venous thrombosis with thrombocytopenia in a patient treated with therapeutic anticoagulation, this is remarkable and should likely have prompted further medical attention; lab values should likely be available. In table 6, the MAH refers to an attachment which has not been found. Full details on this case including complete CIOMS report should be provided (**immediate RSI**).

Questions were raised regarding laboratory results from clinical studies and from post-marketing data, regarding e.g. thrombocytopenia. Further data presentation is asked for to allow final assessment of whether thrombocytopenia without thrombosis or bleeding, may be caused by the Covid-19 vaccine Janssen (**RSI**).

QUESTION 3

Presentation of retrieved laboratory values on complete blood counts including, but not limited to platelets, anti-platelet factor 4 antibodies for cases of haemorrhage in all clinical studies with the Covid-19 vaccine Janssen.

In the clinical trials (COV1001, COV1002, COV2001, COV3001, COV3009), under the SMQ term “Haemorrhages”, the following events have been reported: 36 cases were reported among 22,218 (0.2%) participants that received Ad26COV2.S vaccine at the 5x10¹⁰ vp dose level. 9 cases were reported among 319 (2.8%) participants that received Ad26COV2.S vaccine at 1x10¹¹ vp dose level. 53 cases were reported among 22,051 (0.2%) participants that received placebo. 35 cases were reported among 25,537 (0.1%) participants that are blinded to treatment. Among those cases, the cases of interest (Cerebral haemorrhage, Haematemesis, Haematochezia, Haematuria, Haemoptysis, Haemorrhoidal haemorrhage, Subarachnoid haemorrhage) have been retrieved from the clinical trials and are summarized in Table 7. Further information on all haemorrhage cases is provided in the Appendices. From this, it can be concluded that there are no imbalances in number of haemorrhage cases when comparing vaccine versus placebo group.

Table 7: Number of Subjects with AEs of Interest by SMQ term “Haemorrhages”; Full Analysis Set

Study	SMQ term	N	Ad26.COV2.S (5x10 ¹⁰)	N	Ad26.COV2.S (1x10 ¹¹)	N	Placebo	N	Blinded
COV1001	Haemorrhages	323	6 (1.9%)	319	9 (2.8%)	163	3 (1.8%)	271	2 (0.7%)
COV1002	Haemorrhages							250	1 (0.4%)
COV2001	Haemorrhages							595	10 (1.7%)
COV3001	Haemorrhages	21895	30 (0.1%)			21888	2 (0.2%)		
COV3009	Haemorrhages							24421	30 (0.1%)
Total N (%)		22218	36 (0.2%)	319	9 (2.8%)	22051	53 (0.2%)	25121	35 (0.1%)

Table 8: Number of Subjects with selected AEs of Interest by SMQ term “Haemorrhages”; Full Analysis Set

Study	SOC by Preferred Term	N	Ad26.COV2.S (5x10 ¹⁰)	N	Ad26.COV2.S (1x10 ¹¹)	N	Placebo	N	Blinded
COV3001	Cerebral haemorrhage	21895	1 (<0.1%)			21888	1 (<0.1%)		
COV3001	Haematemesis	21895	0			21888	1 (<0.1%)		
COV3001	Haematochezia	21895	0			21888	3 (<0.1%)		
COV1001	Haematuria	323	0	319	0	163	1 (0.6%)	271	1 (0.4%)
COV3001	Haematuria	21895	2 (<0.1%)			21888	2 (<0.1%)		
COV3009	Haematuria							24421	2 (<0.1%)
COV1001	Haemoptysis	323	0	319	0	163	0	271	1 (0.4%)
COV3001	Haemoptysis	21895	0			21888	1 (<0.1%)		
COV3009	Haemoptysis							24421	1 (<0.1%)
COV3009	Haemorrhoidal haemorrhage							24421	1 (<0.1%)
COV3001	Subarachnoid haemorrhage	21895	0			21888	1 (<0.1%)		

SOC = System Organ Class
MedDRA version 23.1

Laboratory values for cases of hemorrhagic (i.e., bleeding) events reported for the COVID-19 vaccine Janssen in clinical trials:

Reviewing all AEs and SAEs cases that were reported in the clinical trials databases, limited data is available for blood laboratory results:

COV1001: Subject reported hemoptysis and hematuiria had no abnormal laboratory results. Subject (COV1001) that reported Vaginal hemorrhage (mild vaginal bleeding (spotting)) reported normal laboratory results.

COV1002: no event reported.

COV2001: 10 events reported: no laboratory data pertaining to blood counts

COV3001: for those cases reported, no laboratory data pertaining to blood counts have been reported except for the case described here below (study pause case)

Subject: male subject between the ages of 18-28 with cerebral hemorrhage (18 days postvaccination)

- lowest platelet count of 64,000/UI;

no other laboratory data has been reported in conjunction with hemorrhagic events

COV3009: no laboratory data has been reported in conjunction with hemorrhagic events. In addition, haemorrhage cases (SAEs) were also retrieved from the GMS safety database, to evaluate whether additional laboratory data was reported in the CIOMS forms. A total of 22 subject cases with 23 SAEs were reported in clinical studies. These are listed in Table 9 by preferred term (PT) and case count.

Only 9 SAEs haemorrhage cases (8 cases in COV3001 and 1 case in COV3009) included blood count laboratory data, of which only 3 cases were reported within 28 days of receipt of the vaccine. Of those cases for which complete laboratory blood count values were provided, only 2 cases exhibited thrombocytopenia:

COV3001: Subject 3, a male between the age of 18-28 with cerebral hemorrhage (18 days post-vaccination) - lowest platelet count of 64,000/uL. Further details on the case of CVST (Transverse Sinus Venous Thrombosis and Cerebral Hemorrhage) reported following administration of Ad26.COV2.S in COV3001 can be found in the programmed case narratives and attached CIOMS form.

COV3001: subject 4, a female between the ages of 18-28 with immune thrombocytopenia (76 days post-vaccination) - lowest platelet count of 6x10⁹/L

None of the cases with CBC information had baseline values prior to vaccination. Also, majority of the available CBC laboratory values did not have normal reference ranges precluding adequate medical assessment.

Table 9: Serious cases of hemorrhagic events reported in clinical trials with the COVID-19 vaccine

Preferred Term	Case Count
IMMUNE THROMBOCYTOPENIA	1
GASTROINTESTINAL HAEMORRHAGE	3
HAEMATEMESIS	1
LOWER GASTROINTESTINAL HAEMORRHAGE	1
OESOPHAGEAL VARICES HAEMORRHAGE	1
RETROPERITONEAL HAEMORRHAGE	1
UPPER GASTROINTESTINAL HAEMORRHAGE	2
ANASTOMOTIC ULCER HAEMORRHAGE	1
POST PROCEDURAL HAEMORRHAGE	1
HAEMOGLOBIN DECREASED	1
CEREBRAL HAEMORRHAGE	2
HAEMORRHAGE INTRACRANIAL	1
SPINAL CORD HAEMATOMA	1
SUBARACHNOID HAEMORRHAGE	1
HAEMATURIA	1
RENAL HAEMATOMA	1
HAEMORRHAGIC OVARIAN CYST	1
MENORRHAGIA	1
UTERINE HAEMORRHAGE	1
Totals	23

Information from the 9 cases of serious hemorrhagic events with the COVID-19 vaccine Janssen reported in clinical trials are presented in Table 10 below. Given the limited information available, no conclusions can be drawn at this time. Detailed information is provided for all cases observed in clinical trials with the COVID-19 vaccine Janssen.

Table 10: Cases of Serious Hemorrhagic Events with COVID-19 Vaccine Janssen, Reported in Clinical Trials, for which Complete Blood Counts are Available

Case type	Age	Gender	Bleeding Reported Adverse Event Preferred Term	Time to onset from vaccination date	Available laboratory values on complete blood count
study COV3001	75-85	Male	HEMOGLOBIN DECREASED	97 days	Hgb 7 in ER (narrative); Hgb of 8.6 is listed in the adverse event report; reference ranges not reported.
study COV3001	18-28	Male	CEREBRAL HAEMORRHAGE	18 DAYS	Platelet count on hospitalization 64,000, white blood cell count 124, haemoglobin 12.7 and haematocrit 36.1 (units and normal ranges were not provided) The next day platelet count was $60 \times 10^3/\mu\text{L}$, increased to 110×10^3 several hours later, no Hgb/Hct reported. Peripheral blood smear showed neutrophilic leucocytosis, no blasts were identified, red blood cell count and morphology were within normal limits and thrombocytopenia with rare large platelet forms were seen. WBC - $9.2 \times 10^3/\mu\text{L}$ at discharge, Plt $334 \times 10^3/\mu\text{L}$ after discharge, Hgb - 11 gm/dl after discharge
study	64-74	Male	GASTROINTESTINAL HEMORRHAGE	2 days	Haemoglobin was 7.2 (NR not provided).
study COV3001	65-75	Male	GASTROINTESTINAL HEMORRHAGE	13 days	Haemoglobin was 6.2 g/dl (NR: not reported)
study	58-68	Male	SUBARACHNOID HEMORRHAGE	34 days	Haematocrit was 37 (units unspecified), Haemoglobin was 13 (units unspecified), Lymphocytes was 602 (units unspecified), Mean corpuscular volume was 92 (units unspecified), Neutrophils was 6880 (units unspecified), Platelet count was 166000 (units unspecified),
study COV3001	43-53	Female	LOWER GASTROINTESTINAL HEMORRHAGE	19 days	CBC showed white blood cell count 7.5, haemoglobin 11.8, haematocrit 11.8, and platelet count 208 (unit and reference range were not provided). haemoglobin 9.2 on admission (units and reference range not provided).
study COV3001	18-28	Female	IMMUNE THROMBOCYTOPENIA	76 days	Platelet count was $6 \times 10^9/\text{L}$ (NR: 186 - 454), increasing to $223 \times 10^9/\text{L}$
study COV3001	18-28	Female	CEREBRAL HEMORRHAGE	64 days	WBC (reference range: 4100-10900) 6960/mm ³ , haemoglobin (reference range: 11.6-15.7) 13.9 g/dL, platelet count (referenced range: 140000-440000) 289000/mm ³ .
study COV3001	40-50	Female	ANASTOMOTIC ULCER HEMORRHAGE	40 days	Haematocrit (NR: not provided) 30.2 %, and Haemoglobin (NR: not provided) 10.5 g/dL. haematocrit 37.1 %, and haemoglobin 13.3 g/dL.

* Further details on the case of (CVST) Venous Transverse Sinus Thrombosis and Cerebral Haemorrhage reported following a administration of Ad26.COV2.S in COV3001 can be found in the attached CIOMS I form.

PRAC Rapporteur assessment comment

There is no imbalance for cases of haemorrhages in the clinical COVID-19 vaccine Janssen (in total 45 cases for participants that received Ad26COV2.S vaccine, 53 cases for placebo; however, for 35 additional cases, treatment remains blinded).

Data on laboratory values are missing for the majority of these cases. There are two cases with thrombocytopenia in study 3001; male subject between the ages of 18-28 with concomitant thrombosis and thrombocytopenia (further discussed below) and one female with immune thrombocytopenia 76 days post-vaccination.

Questions were raised regarding laboratory results from clinical studies and from post-marketing data, regarding e.g. thrombocytopenia. Further data presentation is asked for to allow final assessment of whether thrombocytopenia without thrombosis or bleeding, may be caused by the Covid-19 vaccine Janssen (RSI).

QUESTION 4

A detailed cumulative review of cases observed in clinical studies with i) the Covid-19 vaccine Janssen; ii) other vaccines using the same Ad26 platform; as well as of iii) cases originating from the post-marketing setting of

- a. thrombosis (any);**
- b. thrombosis (any) and concomitant thrombocytopenia/low platelet count;**
- c. thrombocytopenia/low platelet count regardless of symptoms**

The presentation should include all available information regarding concomitant disease and medications, COVID-19 testing, time to onset, clinical course and outcome and diagnostic work-up, as available. Full case narratives should also be provided.

MAH RESPONSE:

Note for the reviewer

The answer to this question has been structured in the following way:

- Section A, presents the thrombosis cases
- Section B, presents the thrombosis / thrombocytopenia case
- Section C, presents the thrombocytopenia cases

Each of these sections has 5 subcategories that present data derived from different sources

- A1, B1, C1 relate to the Covid vaccine trials (COV1001, COV1002, COV2001, COV3001 and COV3009): AEs and SAEs
- A2, B2, C2 relate to Covid vaccine trial COV3012: SAEs, as this is a collaborative study
- A3, B3, C3 relate to Ad26 platform vaccine trials (excluding Covid trials): AEs and SAEs
- A4, B4, C4 relate to Ad26 platform collaborative trials: SAEs
- A5, B5, C5 relate to Post-marketing cases
- Section D presents narratives for the cases of thrombosis / thrombocytopenia
- Section E provides a summary statement

For post-marketing cases, a cumulative review through 09 April 2021 of Janssen spontaneous cases with the COVID-19 vaccine Janssen in the Global Medical Safety Database was performed for events using the below search criteria of:

- a. SMQ: Embolic and thrombotic events
- b. SMQ: Embolic and thrombotic events SMQ AND (SMQ Haematopoietic thrombocytopenia OR SMQ Thrombocytopenias)
- c. SMQ: Haematopoietic thrombocytopenia OR Thrombocytopenias High Level Term (HLT)

For the clinical trials, please refer to the background section for search criteria and DLP of clinical databases.

Narratives for all known reported cases, as of 12 April 2021, of thrombosis and concomitant thrombocytopenia/low platelet count are provided below, followed by the detailed answers to the question.

Case Narratives of thrombosis (any) and concomitant thrombocytopenia/low platelet count

Of the 6 total cases contained in the GMS Safety Database, that had Cerebral venous sinus thrombosis (CVST), one was from a clinical trial (see below).

Case 1)

Clinical trial case on active treatment: a male subject between the ages of 18-28 experienced transverse sinus thrombosis with secondary cerebral haemorrhage on Day 19 after receiving a single dose of blinded study vaccine (Day 1) for prevention of SARS-CoV-2 virus infection. After experiencing flulike illness starting Day 9, the subject was hospitalized on Day 19 following a tonic-clonic seizure. Upon hospitalization, his platelet count was 64,000 with a nadir of 60,000. Upon discharge his platelet count was normal at 334. Of note, pre-vaccination his HEP-IND Thrombocytopenia PF4 Antibodies, IgG were negative, and post-vaccination, were elevated at 2.137 OD (reference interval ≤ 0.399).

The remaining 5 case summaries (all from spontaneous sources) are provided below:

Case 1):

A woman between the ages of 38-48 with a history of depression on concomitant fluoxetine, experienced a headache 1 week after vaccination and subsequent left sided weakness, dry heaves, worsening headache who developed "cortical vein thrombosis" involving the right transverse and sigmoid sinus, tentorial herniation, massive intracerebral haemorrhage, and thrombocytopenia (values not provided) resulting in death 12 days after vaccination.

Case 3):

A female between the ages of 18-28 who experienced a sagittal sinus thrombosis with cerebral haemorrhage 16 days following COVID-19 vaccine Ad26.COVS. Platelet count on presentation was 18,000 (units unspecified), fibrinogen was noted to be low (value not provided), fibrin D-dimer was elevated (specific levels not provided). The platelet counts remained 22,000 to 24,000. The patient developed seizures, was intubated, sedated, and placed on unspecified anti-epileptics. The patient was treated using the "British guidelines", was given a platelet transfusion in preparation for thrombectomy, and was anticoagulated (specific agents not provided). Following thrombectomy, the patient's platelet count rose to 160,000, fibrinogen normalized (value not provided), and both remained stable for 1-2 days. Treatment with unspecified antiepileptics was continued. The patient remained intubated and sedated, and thus her mental and neurologic status was not re-evaluated. She has not yet recovered. Additional information has been requested.

Case 4):

This spontaneous report was received from physician via literature article: Gundabolu K, Kallam A, Muir K, Thrombotic Thrombocytopenia Following Ad26.COVS Vaccination, New England Journal of Medicine, and describes a woman between the ages of 41-51 who developed splanchnic vein thrombosis, cerebral venous sinus thrombosis (CVST), hepatic vein thrombosis, splenic vein thrombosis, anaemia, DIC, haemorrhagic stroke, and thrombocytopenia (platelet nadir of 13,000) 14 days following administration of Ad26.COVS vaccine. Initial presentation also included hypofibrinogenemia and markedly elevated D-dimer. Anti-PF4/heparin antibody ELISA testing was

strongly positive. The CVST progressed while on treatment with heparin (before vaccination status was known), with secondary haemorrhagic stroke.

Anticoagulation was switched to argatroban, and platelet count increased following treatment with intravenous immunoglobulin.

Case 6):

A female between the ages of 19-29 who experienced portal vein thrombosis, pulmonary embolism and cavernous sinus thrombosis one week after vaccination. Platelet count was 120,000, D-dimer was elevated (value not reported), and fibrinogen was normal. The subject was initially treated with heparin; antibodies to platelet factor 4 (PF4) were later noted to be positive at 3.0 (reference range not provided). Heparin was stopped and intravenous immunoglobulin (IVIG) was initiated, at which point the platelet count had already increased. The subject is recovering. COVID-19 testing was reported to be negative..

Case 7):

A 31-41 year old female was vaccinated with the Janssen COVID-19 vaccine Ad26.COVID.S. It was noted that the patient was "experiencing headaches 1 week ago" and had aphasia later in the week. CT of the head without contrast on showed parenchymal haemorrhage and persistent hyperdensity in the left transverse sinus, consistent with known venous sinus thrombosis being treated for the venous sinus thrombosis with heparin. No platelet counts were mentioned in the report.

One additional spontaneous case of thrombosis (Deep Vein Thrombosis) also had a reported thrombocytopenia and is summarized below:

This serious case concerns a female patient from between the ages of 52-62.

Concomitant medication included (levodopa/carbidopa), (formoterol/budesonide), (clonazepam), (citalopram), (lemborexant), (icosapent), (diclofenac), (sumatriptan), (ropinirole), (quetiapine), Celecoxib, Albuterol inhaler, Omeprazole, (levothyroxine), (hydrocodone), low dose aspirin. The report notes that the patient had allergies to tetracycline and vortioxetine.

The adverse event started on day 11. The patient had 5 days of bruising and left leg swelling prior to presenting. She was found to have an extensive, occlusive deep vein thrombosis (DVT) of the left lower extremity as well as thrombocytopenia of 15,000 (units not specified). She had an inferior vena cava (IVC) filter placed. The next day, the patient began to have paraesthesia's and discoloration of the right lower extremity. Ultrasound showed high-grade occlusion of the right proximal, superficial femoral artery. The patient was pre-treated with platelets. In addition to the right superficial femoral artery (SFA) there is also thrombotic occlusion of the bilateral iliacs. The patient had bilateral thrombectomy and bilateral common iliac stent placement. The following day she developed gross haematuria. At the time of the report, the patient had not recovered from the event.

Late Breaking Information:

The MAH was informed by the US FDA of an additional case of a case of CVST involving a female patient between the ages of 21-31.

MAH Summary:

As of 14 April 2021, there have been 6 reported cases of CVST from spontaneous sources. Of these, 5 reported thrombocytopenia; 2 reported Anti-PF4 positive antibodies (both of these patients were

treated with heparin prior to the lab testing); and 2 reported D-dimer elevation. In addition, there was 1 other case of thrombosis in combination with low platelet count from a spontaneous source.

PRAC Rapporteur assessment comment

For the clinical trial case of CVST and thrombocytopenia, there have been several different CIOMS reports provided; one in which thrombocytopenia was not mentioned and lab values of platelet levels were omitted; one in which the platelet levels with thrombocytopenia as well as the result of the peripheral blood smear showing thrombocytopenia and the discharge diagnosis of thrombocytopenia were included; and finally one in which also anti-PF 4 antibodies are included (negative before vaccination; strongly positive during hospitalisation and remaining positive more than one month after discharge). The test dates for the anti-PF 4-antibodies (September 2020, October 2020 and December 2020, respectively) indicate that these results have been previously available to the investigator. The MAH should clarify when these tests were actually performed, and when they became aware of the results (**RSI**).

The cases with concomitant thrombosis and thrombocytopenia are further discussed in section 3.1.2 below.

Thrombosis (any)

A.1 Clinical trials with the COVID-19 vaccine Janssen:

The search identified a total of 27 non-serious cases (AEs) in subjects aged between 38 and 90 years old. Out of the 27 AEs, 13 were associated with the Ad26.COV2.S, 8 with the placebo and 6 AEs are still blinded. The AEs related to Ad26.COV2.S and blinded group included deep vein thrombosis (N =10), monoplegia (N=1), pulmonary embolism (N =3), thrombophlebitis (N=2), transient ischaemic attack (N=1) and venous thrombosis limb (N=1). Time to onset after vaccination varies between 2 and 98 days. In 7 out of the 13 cases from the Ad26.COV2.S group the event occurred within the first 28 days. Only one case in the Ad26.COV2.S was reported as related: a male, between the ages of 45-55 reported DVT 27 days post vaccination.

The search identified a total of 55 serious adverse events (SAEs) in 14 female subjects aged between 24 and 80 years-old and 14 males aged between 25 and 85 years-old. Out of the 55 SAEs, 22 were associated with the Ad26.COV2.S, 19 with the placebo and 14 SAEs are still blinded. The events reported in the Ad26.COV2.S and blinded group included pulmonary embolism (N=9), cerebrovascular accident (N=5), deep vein thrombosis (N=3), acute myocardial infarction and myocardial infarction (N=7), transient ischaemic attack (N=3), Ischemic stroke (N=2) and 1 case of each for cerebral infarction, cerebral thrombosis, embolism venous, hemiparesis, retinal vein thrombosis, transverse sinus thrombosis, and peripheral artery thrombosis. Time to onset after vaccination varies between 3 and 108 days. In 6 out of the 22 cases from the Ad26.COV2.S group the event occurred within the first 28 days. From the 19 placebo cases, the events reported included acute myocardial infarction and myocardial infarction (N=6), cerebrovascular accident (N=3), deep vein thrombosis (N=2), pulmonary embolism (N=2), Transient ischaemic attack (N=2), and 1 case of each for cerebral infarction, cerebral venous sinus thrombosis, carotid artery occlusion, and paraparesis. The investigator causality was not related for 54 out of the 55 SAEs and related for 1 event of deep vein thrombosis in the placebo group.

Further details on the cases reported in the Janssen Ad26.COV2.S COVID-19 clinical trials (unblinded and blinded cases) can be found in the detailed programmed case narratives.

PRAC Rapporteur assessment comment

From the clinical studies, there was a total of 27 non-serious and 55 serious adverse events of thromboembolism in subjects aged between 24 and 90 years old.

Out of the 27 non-serious AEs, 13 were associated with the Ad26.COVID.S, 8 with the placebo and 6 AEs are still blinded. In 7 out of the 13 cases from the Ad26.COVID.S group the event occurred within the first 28 days.

Out of the 55 serious AEs, 22 were associated with the Ad26.COVID.S, 19 with the placebo and 14 SAEs are still blinded. In 6 out of the 22 cases from the Ad26.COVID.S group the event occurred within the first 28 days.

It is expected that laboratory results for the cases with thromboembolism in the clinical studies are presented with the next Response to **RSI**.

A.2 COVID3012 SISONKE:

A separate review of cases from clinical trial COV3012 Sisonke (Together):

OPEN LABEL TRIAL Open-label, single-arm Phase 3b implementation study to monitor the effectiveness of the single-dose Ad26.COVID.S COVID-19 vaccine Janssen among health care workers in South Africa was performed as this is a collaborative study with the South Africa Health Authority, and the serious cases are sent directly to Janssen for entry into the Global Medical Safety Database. The cumulative review through 09 April 2021 in the Global Medical Safety Database was performed There are 3 cases with PTs reported in the SMQ: Embolic and thrombotic events.

Recently Received Information: Per the monthly "4-Weekly* Abridged COVID-19 Interim Progress Report Form For Clinical Trials" received by the MAH on 12 April 2021 from the South African Health Products Regulatory Authority (SAHPRA) , there was 1 additional case of a CVA reported to the Health Authority, but not yet received by the MAH).

Of the 3 cases contained in the GMS Safety Database, 1 case reported Cerebrovascular accident (CVA) 1 case reported Retinal vein occlusion and Retinal haemorrhage and 1 case reported Pulmonary embolism with Cor pulmonale. Of note, there has been a second case of Pulmonary embolism recently received by the MAH from SAHPRA.

One case concerns a female aged between 29-39 who was hospitalized for CVA 8 days post vaccination. After vaccination the subject experienced moderate (unspecified) reactogenicity and returned back to work. Her first symptoms 8 days after vaccine administration were slurred speech, dizziness and collapse, and she was brought to the hospital. Upon arrival she developed a seizure followed by left sided weakness. Electrocardiogram showed sinus tachycardia, chest x-ray was normal, and COVID-19 PCR test was negative. Results of magnetic resonance imaging (MRI) and echocardiogram are pending. The subject is receiving speech therapy and physiotherapy and improving remarkably. The event is resolving.

Another case concerns a female subject aged between 58-68 with a history of diabetes who experienced left retinal vein occlusion and macular haemorrhage 10 days after vaccine administration. After vaccination, the subject was "lethargic, sleepy, and flushed". The next day she complained of myalgia, stiff neck, and took acetaminophen. She felt well for a week and on day 8 post vaccination experienced blurring of vision in the left eye and noted deterioration of vision with progression of

blurring, which had worsened significantly by the next day. On day 10 post vaccination, she was examined by an ophthalmologist and noted to have blocked vessels, haemorrhage, and oedema of one eye. The patient has a history of elevated triglycerides with the highest noted at 2.0 mmol/L (Normal - NR: 0.4 - 1.6) in 2017. More recent labs from 13 days after vaccination showed normal erythrocyte sedimentation rate (ESR) and C-reactive protein. Haemoglobin, white blood cell count, and platelet counts were 13.4 g/dL (NL: 12.1-16 .3), $6.54 \times 10^9/L$ (NL: 3.92 - 9.88), and $290 \times 10^9/L$ (NL: 150-450) respectively. Triglycerides were 1.4 mmol/L, and Hgb A1C was 5.8% (NL: 4.0-6.0). The patient's estimated glomerular filtration rate (eGFR) was 58 ml/min (NL: >90) and has been in the range of 63 to 69 since 2018. Outcome of the events were not reported.

A third case concerns a female subject aged between 57-67 who was hospitalized 17 days after vaccine administration for pulmonary embolism and cor pulmonale. Concomitant medications included an unspecified statin and fluoxetine. The subject developed sudden shortness of breath and mottled skin on legs; she was taken to a hospital and was admitted to the intensive care unit. Results of diagnostic tests included elevated D-dimer; computerized tomogram pulmonary angiogram showed multiple bilateral pulmonary emboli and cor pulmonale; echocardiogram showed dilated right ventricle and atrium, severe tricuspid incompetence, hypokinetic intraventricular septum but no thrombi. Magnetic resonance imaging of the spine showed scattered sclerotic areas. There was no finding of deep vein thrombosis. No platelet counts or CBC were provided. The subject was discharged after 5 days and is recovering.

Another case concerns a female aged between 55-65 who experienced pulmonary embolus (fatal). The event occurred 23 days after vaccination COVID-19 vaccine Ad26.COVS2 was administered intramuscularly for the prevention of symptomatic SARS-CoV-2 virus infection. It was reported that she was overweight with a number of co-morbidities.

On an unspecified date, the subject's SARS-CoV-2 polymerase chain reaction (PCR) test was negative. 23 days post vaccination, the subject experienced pulmonary embolus (fatal). Her body build was normal. Nutritional status was good. External body examination: body examination revealed no visible injuries. Main findings: pulmonary thrombus of the pulmonary truncus with congestion and oedema of the lungs. The rest of the organs and structures were all within normal limits with no injuries noted. Cause of death reported as natural causes: pulmonary embolus. Investigator's causality assessment: The event of pulmonary embolus was not related to the study vaccine.

Another case concerns a female aged between 38-48 who experienced a CVA less than 24 hours after vaccination. Further case details are pending.

MAH Conclusion: There were 5 cases of embolism/thrombosis from clinical trial VAC31518COV3012. A single case which reported haemorrhage in the eye had normal thrombocytes; in the 2 other cases without bleeding thrombocyte counts were not provided. COVID-19 was ruled out in one case. Two cases of pulmonary embolism were confounded by a preceding distant travel and co-morbidities.

Of the 5 cases, for 1 case the causality to vaccine was considered unclassifiable, 1 case had indeterminate causal association and 1 case was considered inconsistent with the causal association to immunization per the WHO causality classification for adverse events following immunization. The remaining 2 cases have not yet been assessed by the company

PRAC Rapporteur assessment comment

In the open-label, single-arm Phase 3b implementation study to monitor the effectiveness of the single-dose Ad26.COVS2 COVID-19 vaccine Janssen among health care workers in South Africa, only serious cases have been provided.

For the case with cerebrovascular accident (CVA), this concerns a female aged between 29-39 with CVA 8 days following vaccination. COVID-19 PCR test was negative; no additional laboratory test has been provided.

For the case with retinal vein occlusion and macular haemorrhage, this concerns a female aged between 58-68 with a history of diabetes who presented with blurred vision 8 days post vaccination. Laboratory tests revealed normal platelet levels.

For the first case with pulmonary embolism, this concerns a female aged between 57-67 who was hospitalized 17 days after vaccination, having travelled long distance the day before, and was diagnosed with pulmonary embolism. No platelet counts have been provided.

For the second case with pulmonary embolism, this was diagnosed post-mortem in a female aged between 56-66, 23 days after vaccination. There is one additional case of CVA within 24 hours of vaccination in a female aged between 38-48; no further details have been provided.

Based on the above, there are currently no case reports of concomitant thrombosis and thrombocytopenia. Additional information regarding platelet levels should be attempted to be provided for the cases with CVA and the first case of pulmonary embolism (**RSI**).

Ad26 Platform Data

A search for reported cases of thromboembolic events using the search terms embolic and thrombotic of the AdVac platform safety database revealed the following cases (cut-off 31 December 2020).

Table 11 includes all AEs identified, based on the embolic and thrombotic events search criteria in studies integrated in the AdVac Safety Database V6.0. A total of 8,826 participants in 32 studies were vaccinated with at least one dose of an Ad26-based vaccine (hereafter also referred to as "Ad26 recipients") and 4,075 participants received placebo.

In total, 18 subjects (0.2%) in the Ad26 vector-based vaccination group and 25 subjects (0.6%) in the placebo group reported at least one embolic or thrombotic event following vaccination.

Table 11: Number of Subjects with Unsolicited Adverse Events of Special Interest by SOC and PT; By Vaccination Group; Full Analysis Set

	Vaccination Group	
	Ad26 (N=8826)	Placebo* (N=4075)
Entire study	8826	4075
Embolic and thrombotic events	18 (0.2%)	25 (0.6%)
Narrow	18 (0.2%)	25 (0.6%)
Cerebrovascular accident	6 (0.1%)	4 (0.1%)
Deep vein thrombosis	2 (<0.1%)	1 (<0.1%)
Myocardial infarction	2 (<0.1%)	6 (0.1%)
Pulmonary embolism	2 (<0.1%)	2 (<0.1%)
Thrombophlebitis	2 (<0.1%)	0
Acute myocardial infarction	1 (<0.1%)	2 (<0.1%)
Carotid artery occlusion	1 (<0.1%)	0
Portal vein thrombosis	1 (<0.1%)	0
Transient ischaemic attack	1 (<0.1%)	5 (0.1%)
Lacunar infarction	0	1 (<0.1%)
Peripheral arterial occlusive disease	0	1 (<0.1%)
Thrombosis	0	2 (<0.1%)
Vertebral artery occlusion	0	1 (<0.1%)

Note: Percentages of subjects are based on N

Only AEs starting at or after the vaccination are tabulated

For the Special Interest Category, the total number of subjects with at least one event in the Special Interest Category is given

Studies included: HIV-V-A004 IPCAVD001 IPCAVD003 IPCAVD004 MALVA001 VAC18192RSV1001 VAC18192RSV1003 VAC18193RSV1003 VAC18193RSV1004 VAC18193RSV1005 VAC18193RSV2001 VAC18193RSV2002 VAC18193RSV2003 VAC18193RSV2005 VAC18194RSV2001 VAC26911ZIK1001 VAC52150EBL1001 VAC52150EBL1002 VAC52150EBL1003 VAC52150EBL1004 VAC52150EBL2001 VAC52150EBL2002 VAC52150EBL2003 VAC52150EBL3001 VAC52150EBL3002 VAC52150EBL3003 VAC69120FLV1001 VAC81623HPV1002 VAC89220HPX1002 VAC89220HPX2003 VAC89220HPX2004 VAC89220HTX1001

*Placebo control for all studies

Adverse events are coded using MedDRA Version 23.1.

Safety laboratory values (platelet counts ^a) were only available for five subjects for which thromboembolic events were reported. No abnormal platelet counts were reported postvaccination, with the exception of one subject that had low platelet counts at screening (114,000 cell/mm³).

a *Laboratory parameter searches for abnormalities were as follow: Activated Partial Thromboplastin Time, Platelets

Ad26.ZEBOV (Ebola) Collaborative Clinical Trials and Vaccination Programs

The search identified 9 cases in subjects between 30 and 71 years old. A total of 6 out of the 9 cases are still blinded. The time to onset after first dose vaccination varies between 44 and 297 days. In one case associated with exposure during pregnancy the time to onset was not reported. The reported events reported included: Cerebrovascular accidents (CVA, 6 cases including one fatal case), ischemic stroke (1 fatal case), acute myocardial infarction and coronary artery disease and atherosclerosis (1 fatal case), deep vein thrombosis (1 pregnancy case). All these cases were reported prior to the outbreak of the COVID-19 pandemic and therefore results of COVID-19 testing is not available. Platelet counts were available in one case of CVA reported in a female subject aged between 64-74, 207 days after vaccination. At the time of the event the subject had a normal platelet count reported as "Mean platelet volume (NR: 8.3 - 12.1) 7.6 fL, Platelet count (NR: 156 - 342) 311 x10⁹/L, Platelet-large cell ratio (NR: 25.30 - 53.80) 36.2%"

In all the cases reported, the causality of the vaccine is unlikely because of long time to onset after vaccination and the significant medical history or underlying conditions such as hypertension, elderly

age, underlying infections causing disseminated intravascular coagulation with fatal outcome, or underlying pregnancy.

PRAC Rapporteur assessment comment

No cases with concomitant thrombosis and thrombocytopenia have been identified in the Ad26 platform data or the Ad26ZEBOV (Ebola) collaborative clinical trials and vaccination program.

There was no increase in thromboembolic events in the Ad26 platform data: 8,826 participants in 32 studies who were vaccinated with at least one dose of an Ad26-based vaccine and 4,075 participants received placebo; 18 subjects (0.2%) in the Ad26 vector-based vaccination group and 25 subjects (0.6%) in the placebo group reported at least one embolic or thrombotic event following vaccination.

Spontaneously reported cases with COVID-19 vaccine Janssen (post-marketing) – SMQ Embolic and Thrombotic events

There are 27 spontaneous cases which report preferred terms (PTs) meeting the search criteria of SMQ: Embolic and thrombotic events.

Of the 27 cases, 5 cases reported events of interest, reporting central venous sinus thrombosis or significant peripheral thrombosis. Six cases were reported by Health Care Professionals and 21 were non-medically confirmed cases. Two cases reported COVID-19 test results, with 1 positive result and 1 negative result. The narrative of 2 cases suggests that thrombotic diagnoses were ruled out: one case involved a woman of unspecified age who was hospitalized with “heart attack symptoms” one day after vaccine administration and all tests on her heart “came back good.” Another case involved an adult man with a history of “born in” heart condition who thought he was having a heart attack the same day as vaccine, and underwent “EKG, MRI, Nuclear stress test, CAT scan and Transoesophageal ECHO, all of which came back ok” in addition to “countless tests, blood screens, monitoring and consultation[s].” 22 of the 27 cases reported an event latency from vaccine; all of these occurred less than 28 days (range 0-19 days; mean 6.2 days) after vaccine administration.

There was one case of disseminated intravascular coagulation (DIC) with “exacerbation of idiopathic capillary leak syndrome (ICLS)” in a 61-71year-old female with limited information provided.

PRAC Rapporteur assessment comment

There were 27 post-marketing case reports of thromboembolism; based on the narratives, thrombotic disease was ruled out in two of these. 22 of 27 cases occurred with a latency from vaccination but within 28 days after vaccine administration. No laboratory tests have been provided in this section; five of the cases are included in the EudraVigilance case reports in section 3.1.2. Laboratory tests are expected with the next Responses to **RSI**.

The case of capillary leak syndrome is noted, and this condition should be followed up in monthly safety summary reports (**RSI**).

Thrombosis (any) and Concomitant Thrombocytopenia/low platelet count;

B.1. Clinical trials with the COVID-19 vaccine Janssen

A Clinical Trial search for Thromboembolic events revealed a single case from study COV3001 where thromboembolism in combination with thrombocytopenia was observed. Venous Transverse Sinus Thrombosis and Cerebral Haemorrhage was reported following administration of Ad26.COVID-19-S. This participant was tested negative 28 days post vaccination for SARS-CoV-2 infection, based on SARS-CoV-2 nucleocapsid antibody serology, as measured by ELISA and Meso Scale Discovery assays. SARS-

CoV-2 neutralizing antibody titers elicited by Ad26.COVS.S vaccine (IC50 of 66) 29 days post vaccination were in the range of titers observed in participants that received Ad26.COVS.S at a dose level of 5x10¹⁰vp (N=10, IC50 of 117 with a 95% confidence interval of 18 - 449) in COV1001 cohort 1b, as measured by psVNA. The neutralizing antibody titers against the vector were not evaluated.

Additional Heparin-Induced Thrombocytopenia (HIT) PF4 antibody IgG test results were received by the Company on April 12th, 2021 and were not yet included in the CIOMS I form:

- Day 1, pre-vaccination (21 Sep 2020): 0.246 (negative)
- Day 29 (22 Oct 2020): 2.137 (positive)
- Day 71 (01 Dec 2020): 1.451 (positive)

B.3 Ad26 Platform Data,

No case of Thrombosis (any) and Concomitant Thrombocytopenia/low platelet count were reported.

B.4 Ad26.ZEBOV (Ebola) Collaborative Clinical Trials and Vaccination Programs

No serious cases of thromboembolic events with concomitant thrombocytopenia were reported. Safety laboratory values (including platelet counts) were only available for five subjects that reported an embolic or thrombotic event. None of the subjects reported thrombocytopenia/low platelet counts post-vaccination, with the exception of one subject that reported a low platelet counts at screening (114,000 cell/mm³) and thrombophlebitis on the day of vaccination (grade 1, mild; duration 6 days). The platelet count was back to normal range at the day of vaccination (214,000 cell/mm³).

B.5 Spontaneously reported cases with COVID-19 vaccine Janssen (post-marketing) - SMQ: Embolic and thrombotic events SMQ AND SMQ Haematopoietic thrombocytopenia OR SMQ Thrombocytopenia

Five cases reported thrombosis with thrombocytopenia reported thrombocytopenia, but platelet count was not reported, with platelet count of 18,000, 3 of these cases also reported elevated D-dimer. Two cases included a positive PF4/polyanion ELISA of 3.0 (no reference range provided) and 3.179 Optical Density units (upper range of normal is below or equal to 0.399), respectively.

PRAC Rapporteur assessment comment

In the clinical studies with the COVID-19 vaccine Janssen, one case with concomitant thrombosis (CVST) and thrombocytopenia was reported; this case was discussed with the signal confirmation above and is further discussed in section 3.1.2 below.

As discussed in the assessment of Q2 above, there appears to be one additional case with concomitant thrombosis and thrombocytopenia in study 3001 (a male aged between 56-66 with DVT and thrombocytopenia). It is unclear why the MAH has not included this subject in the presentation of case reports as requested; full details on this case including CIOMS report is expected (**immediate RSI**).

For the Ad26 platform data and the Ebola collaborative clinical trials, no cases with concomitant thrombosis and thrombocytopenia were reported.

C) Thrombocytopenia/low platelet count regardless of symptoms

C.1 Clinical trials with the COVID-19 vaccine Janssen

The search identified a total of 18 non-serious cases (AEs) of any haematological abnormalities in subjects aged between 19 and 76 years old. Out of the 18 AEs, 12 were associated with the Ad26.COVS.S, 1 with the placebo and 6 AEs are still blinded. The AEs reported as related to

Ad26.COVID.S and blinded group included leukopenia (N=1) neutropenia (N=1), leukopenia (N=1), neutrophil count decreased (N=1), low haemoglobin (N=1) and anaemia (N=1). For these related cases, time to onset after vaccination varies between 6 and 76 days and 4 cases occurred within the first 28 days.

The search identified a total of 7 serious adverse events (SAEs) in 4 female subjects aged between 25 and -65 years old and 3 male subjects between 51 and 68 years old. Out of the 7 SAEs, 2 were associated with the Ad26.COVID.S vaccine, 4 were associated with the placebo and 1 SAE is still blinded. The events reported included anaemia reported in the Ad26.COVID.S group (N=2) ,the blinded group (N=1) and in the placebo group (N=1) . One case of Immune thrombocytopenia and 3 cases of anaemia were reported in the placebo group. Time to onset reported for anaemia was 1 day (blinded case), 21 days and 72 days in the Ad26.COVID.S group. Time to onset in the placebo group varied between 36 and 107 days. The investigator causality was not related for all the 8 SAEs.

Further details on the cases reported in the Ad26.COVID.S COVID-19 clinical trials Janssen (unblinded and blinded cases) can be found in the detailed programmed case narratives. The following events were reported for the COVID-19 clinical trials (Table 12). There are no events reported in COV1002 and COV2001.

Table 12: COVID-19 vaccine Janssen clinical trials: Cases of Thrombocytopenia/low platelet count regardless of symptoms

SMQ term / Preferred term	Study	N	Ad26 5e10	N	Ad26 1e11	N	Placebo	N	Blinded
Thrombocytopenias									
Immune thrombocytopenia	3001	21895	0			21888	1 (<0.1%)		
Thrombocytopenia	1001	323	0	319	1 (0.3%)	163	0	271	1 (0.4%)
Haematopoietic cytopenias									
Anaemia	3001	21895	7 (<0.1%)			21888	4 (<0.1%)		
	3009							22558	3 (<0.1%)
Blood disorder	3009							22558	1 (<0.1%)
Haematopoietic cytopenias	1001	323	0	319	3 (0.9%)	163	0	271	2 (0.7%)
	3001	21895	9 (<0.1%)			21888	4 (<0.1%)		
	3009							22558	4 (<0.1%)
Haemoglobin decreased	1001	323	0	319	1 (0.3%)	163	0	271	1 (0.4%)
Leukopenia	1001	323	0	319	1 (0.3%)	163	0	271	0
	3001	21895	1 (<0.1%)			21888	0		
Neutropenia	1001	323	0	319	1 (0.3%)	163	0	271	0
Neutrophil count decreased	1001	323	0	319	1 (0.3%)	163	0	271	0
Thrombocytopenia	1001	323	0	319	1 (0.3%)	163	0	271	1 (0.4%)
White blood cell count decreased	3001	21895	1 (<0.1%)			21888	0		

PRAC Rapporteur assessment comment

Overall, based on Table 12, there were 27 cases of haematopoietic cytopenia/thrombocytopenia in the COVID-19 vaccine Janssen clinical trials in patients who received the vaccine; 9 in the placebo groups and for 13 cases, treatment is still blinded.

The figures in the MAH text in this section are not congruent with Table 12; it is unclear if this relates to the cases in Table 12 not being reported as AEs or SAEs. It is however noted that there was an

imbalance also in non-serious AEs of any haematological abnormalities in the clinical trials with the COVID-19 vaccine Janssen, with 12 AEs reported in the Ad26.COV2.S group, 1 in the placebo group and for 6 AEs, treatment is still blinded. For serious AEs of haematological abnormalities, there were 2 in the Ad26.COV2.S group, 4 in the placebo group and for 1 SAE, treatment remains blinded. Anaemia was the most frequent of these SAEs.

Overall, the majority of cases appear to pertain to 'haematopoietic cytopenias' without further specification, for which also an imbalance is noted (in total 12 cases in the Ad26.vaccine groups, 4 in the placebo groups, and 2 in whom treatment is blinded).

One case in the placebo group was reported with Immune thrombocytopenia in study 3001, and there was one case of thrombocytopenia in the vaccine group in this section (however, as discussed above, there was also one case with concomitant thrombocytopenia and CVST in study 3001).

The MAH should clarify the cases of 'haematopoietic cytopenias' in the clinical trials with COVID-19 vaccine Janssen and whether any of these were thrombocytopenic (**RSI**).

C.2 COV3012: SISONKE

No cases of Thrombocytopenia/low platelet count regardless of symptoms were reported at the time of this report.

C.3 Ad26 Platform Data,

A summary tabulation of the worst laboratory toxicity grades within 28 days following study vaccination for selected laboratory safety parameters of all studies that are integrated in the AdVac Safety Database V6.0. is provided in Table 13. Most laboratory toxicities were transient (including Grade 3 events) and returned to normal range upon repeat testing. The frequency of graded laboratory toxicities was also similar in both the Ad26 vaccine and placebo groups. Platelet count decrease was observed following 70 out of 4,105 Ad26 doses (1.7%) and 7 out of 719 placebo doses (1.0%). None of the platelet count decrease cases post vaccination were concomitant with an embolic or thrombotic event. In total, 18 cases of Grade 3* platelet count decrease cases were reported within 28 days following Ad26 vaccination (mostly at 8-day post-vaccination visit).

Except one case for which the safety laboratory assessment was not repeated, all grade 3 platelet count decrease cases were back to normal range upon retesting in the days following the grade 3 event. One case of persistent grade 3 (31,000 cells/mm³) thrombocytopenia was reported 8 days following vaccination for a female subject aged between 54-64 in study VAC18193RSV1004 following vaccination with Ad26.RSV.preF. The event persisted for 40 days upon returning to normal range. The subject remained asymptomatic during the event and had normal physical exams (no bruising or petechiae reported).

Table 13: Tabulation of Worst Laboratory Toxicity Grades Within 28 Days Following Study Vaccination; All Participants; FAS

	Vaccination Group	
	Ad26 (N=8826)	Placebo (N=4075)
Activated Partial Thromboplastin Time	673	95
Grade 1	14 (2.1%)	2 (2.1%)
Hemoglobin*	396	24
Grade 1	1 (0.3%)	4 (16.7%)
Grade 2	3 (0.8%)	1 (4.2%)
Grade 3	1 (0.3%)	0
Hemoglobin Change from Baseline**	3091	587
Grade 1	1792 (58.0%)	304 (51.8%)
Grade 2	105 (3.4%)	18 (3.1%)
Grade 3	47 (1.5%)	12 (2.0%)
Neutrophils/ Neutrophils, segmented	3340	715
Grade 1	125 (3.7%)	40 (5.6%)
Grade 2	74 (2.2%)	9 (1.3%)
Grade 3	45 (1.3%)	16 (2.2%)
Platelets Decreased	4105	719
Grade 1	26 (0.6%)	2 (0.3%)
Grade 2	26 (0.6%)	4 (0.6%)
Grade 3	18 (0.4%)	1 (0.1%)
Prothrombin Intl. Normalized Ratio	118	24
Grade 1	1 (0.8%)	0
Grade 2	1 (0.8%)	0
Prothrombin Time	611	82
Grade 1	5 (0.8%)	1 (1.2%)
Grade 2	3 (0.5%)	1 (1.2%)
Grade 3	3 (0.5%)	1 (1.2%)
White Blood Cell Count Decreased	3712	695
Grade 1	117 (3.2%)	24 (3.5%)
Grade 2	14 (0.4%)	2 (0.3%)
White Blood Cell Count Increased	3053	582
Grade 1	24 (0.8%)	6 (1.0%)
Grade 2	2 (0.1%)	0

* Grading based on absolute hemoglobin values. Note: For children < 12 years only

** Grading based on hemoglobin change from baseline. Note: For adults and children ≥12 years only

Adapted from [TSFLAB01AT.RTF] [ADVAC\CLINSAFSUM\DBR_SCS_2021\RE_SCS_2021\PROD\TSFLAB01-A-TABLES.SAS] 12APR2021, 10:08

PRAC Rapporteur assessment comment

There is an imbalance in platelet count decrease in the Ad26 platform data. Platelet count decrease was observed following 70 out of 4,105 Ad26 doses (1.7%) and 7 out of 719 placebo doses (1.0%). None of the platelet count decrease cases post vaccination were concomitant with an embolic or thrombotic event. In total, 18 cases of Grade 3* platelet count decrease cases were reported within 28 days following Ad26 vaccination (mostly at 8-day post-vaccination visit) and 1 case in the placebo groups.

All grade 3 platelet count decrease cases that were re-tested (all but one) went back to normal range upon retesting in the days following the grade 3 event. One case of persistent grade 3 (31,000 cells/mm³) thrombocytopenia was reported 8 days following vaccination for a female subject aged between 54-64 in study VAC18193RSV1004 following vaccination with Ad26.RSV.preF. The event persisted for 40 days upon returning to normal range. The subject remained asymptomatic during the event and had normal physical exams (no bruising or petechiae reported). This event is considered of interest; for a comparison, HIT (heparin-induced thrombocytopenia) can present with thrombocytopenia without other symptoms. These data need to be considered for further review regarding thrombocytopenia.

C.4 Ad26.ZEBOV (Ebola) Collaborative Clinical Trials and Vaccination Programs

No serious cases thrombocytopenia were reported.

C.5 Spontaneously reported cases with COVID-19 vaccine Janssen (post-marketing) -SMQ Haematopoietic thrombocytopenia OR Thrombocytopenias HLT

There were 7 total spontaneous cases of thrombocytopenia. Of these, 6 were serious and 5 were detailed above in response 4. There was one non-serious case of thrombocytopenia that was not associated with thrombosis; this case reported a decreased platelet count in a female aged between 65-75 with a platelet count of 138 (NR: 150-450). The one late breaking serious case of platelet count decreased is described below.

There was a late-breaking case also included in the above counts of platelet count decreased an unknown time after vaccine. This case involved a female of unspecified age with an unspecified autoimmune disease, who had quarterly blood tests and was hospitalized due to a decreased platelet count (value not reported). She was discharged after a week with "weekly test checks." Additional information has been requested.

Narratives

Programmed case narratives are provided in all Ad26.COVID.S COVID-19 vaccine clinical trials with the exception of COV3012 which is an open-label collaborative study).

Information from serious cases observed from the AdVac platform are reported in the GMS safety database and therefore, available in the COIMS.

More detailed information for spontaneous cases and cases observed in the open-label collaborative COV1012 clinical trial are available in the CIOMS.

EMA Response Late Breaking Information

The data presented by the MAH in this response document have a data lock of 12 April 2021 or earlier, as further specified in the different sections of the responses provided.

To assure transparency with respect to additional information available to the MAH at the time of issue of this document, the MAH would like to add the following elements in this section with late breaking information.

On 12 April 2021, the MAH was informed of an event of sagittal vein thrombosis, right lower extremity DVT and thrombocytopenia. On 15 April 2021, further information was provided to the MAH under the Freedom of Information Act. The case is currently processed in the global safety database and further follow-up attempts will be made.

Available case details:

A female aged between 21-31 with no reported medical history received JNJ vaccine on and complained of a "viral syndrome" including fevers, rigors, muscle pain and shortness of breath an unspecified time after the vaccine. She received azithromycin as treatment. Fever persisted for 1 day after her emergency room visit, and she continued to "feel badly". The following day, she awakened with severe Right>Left jaw pain, posterior headache with standing, pain in cartilage from the tip of nose, and shortness of breath. Shortness of breath resolved 12 days after the vaccination. Headaches persisted as did jaw pain, and pain behind the eyes. On 11 days after vaccination, she noted increasing bruising and periorbital petechiae. She sought help from her primary care provider who noted bilateral leg swelling (R>L). Labs and a Doppler ultrasound were performed but results are not yet available. She had a syncopal spell and was taken to emergency room where she received a diagnosis of sagittal vein thrombosis, right lower extremity deep vein thrombosis and thrombocytopenia. Her platelet count was 125k, smear review: no clumping, no schistocytes. Hypercoagulation panel ordered as well as ANA, Anti PF4/HIT (pending). CT and MRI head with Dural sinus thrombosis. Duplex US of RLE thrombosis. She was stabilized and as to yet recovered.

Advisory Committee on Immunization Practices (ACIP) in the USA

On 14 April 2021, a meeting was organized by the CDC / Advisory Committee on Immunization Practices (ACIP) where the reports of CVSTs with thrombocytopenia after COVID-19 vaccine Janssen reported in the US since the start of the vaccination program were presented. As CDC and FDA have access to more detailed information than the MAH, we herewith include the link to ACIP website for further details on the presentation made during that meeting
<https://www.cdc.gov/vaccines/acip/meetings/slides-2021-04.html>.

MAH Summary

Review of all clinical trial data with Janssen Ad26.COVID.S vaccine identified one report of cerebral venous sinus thrombosis with thrombocytopenia in a 18-28 year old male. Review of clinical trial and spontaneous reports with Ad26 platform, not including the Janssen Ad26.COVID.S vaccine, identified events of thrombocytopenia or platelet decreased with a higher incidence in the Ad26 treatment arm compared to placebo. None of the subjects with thrombocytopenia or decreased platelets count reported a concomitant embolic or thrombotic event. The thrombocytopenia or platelet decreased events were transient, occurred 7 days post vaccination and resolved by the date of the next laboratory assessment,

Review of MAH safety database for events reported from collaborative study in South Africa (SISONKE, 3012) identified three cases of interest: 1 of Cerebrovascular accident, 1 of retinal vein occlusion and Retinal haemorrhage and 1 of Pulmonary embolism (PE) with Cor pulmonale. One additional report of CVA and one of PE have been included in the monthly report dated 12 April. None of the above reports included thrombocytopenia, it should be noted that MAH is not sponsor of the study and limited information is provided in the monthly reports, Spontaneous reports from MAHs safety database included 6 reports of cerebral venous sinus thrombosis 5 with thrombocytopenia. Most occurred within 16 days of vaccination and all 6 were in women aged between 18 and 48.

The number of thrombotic events with thrombocytopenia are low and there is insufficient data to conclude a definitive causal association with the Ad26.COVID.S vaccine at present. However, given the seriousness of the events, further monitoring and characterization are planned as described in the subsequent sections of this response.

PRAC Rapporteur comment (totality of Q4):

For thrombosis (any), there was an imbalance noted for venous thrombosis with the initial assessment of the clinical trial data; the RMP includes thromboembolism as an important potential risk; there is currently no mentioning of thrombosis in the product information. It is noted that there was no increase in thromboembolic events in the Ad26 platform data; however, there is an imbalance in decreased platelet levels based on that platform data (see below).

Based on the data provided with this answer, information remains insufficient to assess how many cases in the clinical studies with thrombosis (n=35 in the Ad26.COVID.S groups, 20 who remain blinded) who had concomitant thrombocytopenia. As discussed in Q2 above, lab tests have not yet been provided for the majority of these subjects; in only three of the cases with thrombosis, a normal platelet count has been provided. One clinical study case is well documented (18-28 year old male), in whom three different CIOMS reports have been submitted with varying information; it is clear, however, that this previously healthy individual with no pre-existing anti-PF4-antibodies was hospitalized with CVST with haemorrhage and thrombocytopenia following vaccination with COVID-19 vaccine Janssen, with positive anti-PF4-antibodies after vaccination. One additional clinical trial case

with deep vein thrombosis and thrombocytopenia is noted in Q2, further data are requested (**immediate RSI**).

For the open-label clinical study with COVID-19 Vaccine Janssen in South Africa, there were five cases of thromboembolism that occurred between less than 24 hours and 23 days after vaccination. Normal platelet counts have been provided for only one of these; for one case, pulmonary embolism was diagnosed postmortem and is thus not expected to provide further laboratory testing; for the remaining three cases, platelet levels are expected with the Responses to the next **RSI**.

For the Ad26 platform data and the Ebola collaborative clinical trials, no cases with concomitant thrombosis and thrombocytopenia were reported

For thrombocytopenia, no imbalance is apparent with the data as presented for the clinical COVID-19 vaccine Janssen studies; however, there is an imbalance in haematopoietic cytopenias: in total 12 cases in the Ad26.vaccine groups, 4 in the placebo groups, and 2 in whom treatment remains blinded. A more precise diagnosis of these cases is requested (**RSI**). Also, in the Ad26 platform data, there is an imbalance in platelet count decrease, which was observed following 70 out of 4,105 Ad26 doses (1.7%) and 7 out of 719 placebo doses (1.0%). None of these were associated with a thromboembolic event.

The MAH concludes that the number of thrombotic events with thrombocytopenia are low and there is insufficient data to conclude a definitive causal association with the Ad26.COVID.S vaccine. This is not supported. The PRAC Rapporteur considers that a causal association is sufficiently supported based on the following:

-The observed cases with CVST and concomitant thrombocytopenia represent clinical entities that are extremely rare in an overall population. Although CVST is well-known to occur predominantly in younger females, often related to hormonal factors such as pregnancy, puerperium or estrogen-containing medications, concomitant thrombocytopenia is not part of any usual clinical picture for CVST.

-The findings of positive anti-PF4-antibodies in several cases, in one case with documented non-existing anti-PF4-antibodies before vaccination, suggest that the clinical picture is likely due to these antibodies. A similarity with HIT (heparin-induced thrombocytopenia) is evident based on the clinical picture; however, there is no known exposure to heparin before the events of thrombosis and thrombocytopenia in any of the reported cases, and in one case, a screening test for anti-PF4/heparin antibodies by latex-enhanced immunoassay was negative whereas results of a PF4/polyanion ELISA were strongly positive.

-In the majority of the cases, there was no apparent risk factor for CVST or other thrombosis or for thrombocytopenia. For a picture of thrombotic thrombocytopenia with positive anti-PF4-antibodies, this is similar to "spontaneous HIT" which is characterized by a similar clinical and laboratory picture in patients without exposure to heparin; however, some trigger is warranted in such cases (such as surgery, infectious disease etc). The only common trigger in these cases is the vaccination with the Ad26.COVID.S vaccine.

-The timing of events is congruent for all of the cases, with symptoms of thrombosis and/or thrombocytopenia occurring within three weeks from the vaccination. This is also in line with what is known for HIT type II and spontaneous HIT as well as for the thrombotic thrombocytopenia related to another adenoviral vector COVID-19 vaccine.

-Extensive work-up excluding other potential causes of thrombosis and/or thrombocytopenia has been provided for two of the cases. This includes antiphospholipid antibodies, homocysteine, Factor VIII, antithrombin, protein C, protein S, Factor V Leiden, prothrombin gene mutation, hepatitis/HIV, ADAMTS 13, PNH and JAK2. The only abnormality that could explain the clinical picture in these cases was positive anti-PF4-antibodies.

-Although the absolute number of cases is low, there is one well characterized case in the clinical trials (and one potential case for which details are unknown, see Q2). However, it remains unknown how many cases with thrombosis and concomitant thrombocytopenia that occurred in the clinical trials with the Ad26.COVS.S vaccine. An imbalance was noted with regards to venous thromboembolism in the initial assessment of these studies, with more cases in the vaccine vs the placebo group. However, platelet levels have not been provided for more than very few of these cases. Further, the post-marketing exposure to COVID-19 vaccine Janssen has increased rapidly within recent weeks and thus, the numbers at risk for having developed these symptoms does not correspond to actual doses given (see also Q1).

Based on the above, the PRAC Rapporteur considers that 'thrombotic thrombocytopenia' should be included in the product information section 4.4 and 4.8.

QUESTION 5

Observed to expected analyses of cases of

- a. Cerebral venous thrombosis without thrombocytopenia (i.e. using all relevant PTs such as cerebral venous thrombosis, superior sagittal sinus thrombosis, transverse sinus thrombosis, aseptic cavernous sinus thrombosis, cerebral venous thrombosis and also events of cerebral thrombosis that are adjudicated to be related to venous thrombosis), also stratified by age bands (i.e. 10 years) should be provided. Background rates for events of CVST without thrombocytopenia should be used within the analysis.**
- b. Cerebral venous thrombosis with thrombocytopenia (i.e. using all relevant PTs such as cerebral venous thrombosis, superior sagittal sinus thrombosis, transverse sinus thrombosis, aseptic cavernous sinus thrombosis, cerebral venous thrombosis and also events of cerebral thrombosis that are adjudicated to be related to venous thrombosis), also stratified by age bands (i.e. 10 years), should be provided. Background rates for CVST with thrombocytopenia should be used within the analysis.**

MAH RESPONSE:

Incidence of Cerebral sinus venous thrombosis

Cerebral venous sinus thrombosis is a rare phenomenon that can be seen with some frequency in young patients. CVST is a multifactorial condition with gender-related specific causes, with a wide clinical presentation, the leading causes differ between developed and developing countries, converting CVST in a condition characterized by a highly variable clinical spectra, difficult diagnosis, variable etiologies and prognosis that requires fine medical skills and a high suspicious index. This disease can affect the cerebral venous drainage and related anatomical structure. The symptoms may appear in relation to increased intracranial pressure imitating a pseudotumor cerebri. Prognosis depends on the early detection and appropriate treatment. Correcting the cause, generally the complications can be prevented (Alvis-Miranda 2013).

As in any thrombotic process, risk factors are associated with the classical Virchow triad of thrombogenesis: hypercoagulability, vessel wall damage and blood stasis. It may be associated with inherited and acquired risks factors; however, this categorization is fairly artificial, because they have additive effects and CVST is multifactorial. By far, in developed countries, the most frequently associated factor is congenital thrombophilia.

Inherited prothrombotic risk factors include homocysteinemia, factor V Leiden homozygous mutation, G20210A prothrombin gene and Methylene- Tetra-Hydro-Folate-Reductase 677TT mutations, protein C and S and anti-thrombin III deficiency, and positive anti-cardiolipin or antiphospholipid antibodies.

Acquired risks factors include all the usual causes of VTE and additionally causes such as brain tumors, head trauma, central nervous system infections (bacterial meningitis, cerebral malaria, intracranial hypotension, any local head infection, extracerebral neoplasia's, dural fistulas, hematological conditions, nephrotic syndrome, systemic vasculitis, medicaments (cisplatin, methotrexate, and steroids), neurological surgery, lumbar puncture, pregnancy, and puerperium (Alvis-Miranda 2013).

Cerebral venous thrombosis has an annual incidence estimated to be 3 to 4 cases per million. The frequency of peripartum and post-partum cerebral venous thrombosis is about 12 cases per 100,000 deliveries in pregnant women, which is only slightly lower than that of peripartum and postpartum arterial stroke. More recently, there has been a significant female predominance among young adults, with the majority of cases (70% to 80%) being in women of childbearing age, but not among children or elderly persons (Tadi 2020).

Observed to expected analyses of cases of CVST with and without thrombocytopenia by age are provided in Table 14, Table 15, and Table 16.

Table 14: OE Analysis CVST with Thrombocytopenia

CVST with Thrombocytopenia (ages 18, 26, 45, 48, 59; all Female)								
Age Group	Sex	Observed	O/E Point Estimate	O/E Lower Bound	O/E Upper Bound	IR Point Estimate	IR Upper bound	IR Lower Bound
18 - 34	M	0	0	0	0			
18 - 34	F	2	29.7	8.48	N/A	0.2	0.7	0
35 - 54	M	0	0	0	0			
35 - 54	F	2	35.15	7.03	N/A	0.1	0.5	0
55 - 64	M	0	0	0	0			
55 - 64	F	1	12.61	0.25	N/A	0.2	10	0
65 - 74	M	0	0	0	0			
65 - 74	F	0	0	0	0			
75 - 84	M	0	0	0	0			
75 - 84	F	0	0	0	0			
85+	M	0	0	0	0			
85+	F	0	0	0	0			
TOTAL OBSERVED		5						
Incidence Rates: /100,000 PYs								

O/E: Observed to expected; IR: Incidence Rate; M: Male; F :Female. Incidence rates are expressed per 100,000 person-years.

Table 15: OE Analysis CVST without Thrombocytopenia

CVST without Thrombocytopenia (age 38; Female)								
Age Group	Sex	Observed	O/E Point Estimate	O/E Lower Bound	O/E Upper Bound	IR Point Estimate	IR Upper bound	IR Lower Bound
18 - 34	M	0	0	0	0			
18 - 34	F	0	0	0	0			
35 - 54	M	0	0	0	0			
35 - 54	F	1	1.17	0.10	17.58	1.5	18.3	0.1
55 - 64	M	0	0	0	0			
55 - 64	F	0	0	0	0			
65 - 74	M	0	0	0	0			
65 - 74	F	0	0	0	0			
75 - 84	M	0	0	0	0			
75 - 84	F	0	0	0	0			
85+	M	0	0	0	0			
85+	F	0	0	0	0			
TOTAL OBSERVED		1						

O/E: Observed to expected; IR: Incidence Rate; M: Male; F :Female. Incidence rates are expressed per 100,000 person-years.

Table 16: OE Analysis Addendum

CVST with Thrombocytopenia (18, 26, 45, 48, 59; F)								
Age Group	Sex	Observed	O/E Point Estimate	O/E Lower Bound	O/E Upper Bound	IR Point Estimate	IR Upper bound	IR Lower bound
ALL	M	0	0	0	0			
ALL	F	5	14.4	1.15	N/A	0.2	2.5	0
CVST without Thrombocytopenia (38; F)								
ALL	M	0	0	0	0			
ALL	F	1	0.44	0.03	5.74	1.3	18.4	0.11
CVST (18, 26, 38, 45, 48, 59; Female)								
ALL	M	0	0	0	0			
ALL	F	6	2.46	0.17	34.5	1.4	19.9	0.1
Incidence Rates: /100,000 PYs								
M percentage		0.452399371						
F percentage		0.547600629						
Total vaccinations as of 15 March 21: 1,428,465								
Total vaccinations as of 12 April 21: 6,859,877								

The MAH has also provided the following supplementary contextual information to support question 5:

Cerebral venous sinus thrombosis (CVST) has an annual incidence estimated to be two to five cases per million (Capecchi, 2018). These data are aligned with the publicly available data from the ACCESS project (ENCePP Home Page). Two other studies found higher incidence rates than previously reported with annual rates ranging between 13.2 to 15.7 cases per million (Countinho, 2012; Devasagayam, 2016). The frequency of peripartum and post-partum cerebral venous thrombosis is about 12 cases per

100,000 deliveries in pregnant women, which is only slightly lower than that of peripartum and postpartum arterial stroke. More recently, there has been a significant female predominance among young adults, with the majority of cases (70% to 80%) being in women of childbearing age, but not among children or elderly persons (Tadi, 2020).

Observed to expected analyses of cases of CVST with and without thrombocytopenia by age and sex are provided in Table 14 and Table 15, and Table 16 provides overall Observed to expected analysis.

Given the absence of publicly available background incidence rates on CVST with and without thrombocytopenia, the Janssen's team estimated incidence rates of CVST with and without thrombocytopenia using existing databases for which Janssen has a license. The rates were generated using US claims and electronic medical databases. Incident cases of CVST were identified using pre-defined algorithms, the co-occurrence of CVST and thrombocytopenia was defined as a diagnosis of thrombocytopenia or low platelet measurement within 42 days prior to CVST and 14 days after CVST index date. The incidence of CVST overall was 1.4/100,000 person-years in females which is in the higher range of published data (see Table 16).

PRAC Rapporteur comment:

The MAH has provided Observed/Expected (O/E) analysis by age and sex for events of cerebral venous sinus thrombosis (CVST) with and without thrombocytopenia. Given the absence of publicly available background incidence rates on CVST with and without thrombocytopenia, the MAH has estimated incidence rates of CVST with and without thrombocytopenia using existing databases for which MAH has a license. The co-occurrence of CVST and thrombocytopenia was defined as a diagnosis of thrombocytopenia or low platelet measurement within 42 days prior to CVST and 14 days after CVST index date. The incidence of CVST overall was 1.4/100,000 person-years in females which is in the higher range of published data. The incidence of CVST with thrombocytopenia is unknown but is considered to be very rare.

The MAH has not explained which cut-off date for post-marketing data that was used in the analysis, which needs further clarification. In addition, it needs to be clarified what time frame that was used to calculate the expected rate of these rare events of CVST in combination with thrombocytopenia (**RSI**).

CVST without thrombocytopenia

O/E analysis provided by MAH 16th of April 2021 based on the available post-marketing data:

Table 15 illustrate the O/E analysis of CVST without thrombocytopenia stratified by age and sex. One event has been reported (female aged 31-41 years), however, lab data regarding thrombocytes has not been provided for this case and it is therefore not known if the CVST was accompanied with thrombocytopenia or not. A slightly increased O/E point estimate (1.2) for the subgroup female 35-54 years was presented based on this case, but since it is not known if this case was associated with thrombocytopenia or not, and given the very limited data, the value of the analysis is limited.

CVST with thrombocytopenia

O/E analysis provided by MAH 16th of April 2021 based on the available post-marketing data:

Table 14 illustrate the O/E analysis of CVST with thrombocytopenia stratified by age and sex. Within this O/E analysis, five events of CVST in combination with thrombocytopenia has been included by the MAH. Even though the numbers of cases reported are limited, the OE ratios are clearly greater than one in women for the different age ranges assessed, as well as for the total numbers, which suggests a signal of an excess of risk. Furthermore, the O/E lower bounds for the two younger age ranges are clearly above one.

It is noted that the analysis does not include a male aged between 18-28 from the phase III study that was reported with CVST and thrombocytopenia, in addition, at female subject aged between 52-62 included in this analysis had thrombosis located to the legs but not CVST. The O/E analysis for both male aged 18-34 years and female aged 55-64 years old in table 14 and 15 is therefore incorrect. Revised, and updated analyses are requested **(RSI)**.

The O/E analysis (CVST with thrombocytopenia) based on sex (table 16) showed an increased risk compared to expected for female (O/E point estimate 14.4) whereas the corresponding analysis for men showed an O/E point estimate of 0. Based on what is described above, revised, and updated analyses are requested **(RSI)**.

Conclusion

The O/E analysis is based on very limited data since CVST in combination with thrombocytopenia is an extremely rare medical condition, and reported cases so far are few. Despite the use of some incorrect data, the provided O/E analysis shows a clear signal of increased risk for CVST with thrombocytopenia in female subjects aged <64 years compared to what can be expected in this population.

QUESTION 6

Discussion on potential causal relationship between vaccination with Covid-19 vaccine Janssen and the events of thrombosis and thrombocytopenia, addressing possible pathophysiological mechanism, including potential for platelet activation. This should include all relevant non-clinical data and clinical data and address any potential role of the adenoviral gene transfer vector.

MAH RESPONSE:

There are currently no data that suggest an obvious causal relationship or pathophysiological mechanism specifically linking vaccination with Janssens COVID-19 vaccine and the events of thrombosis and thrombocytopenia.

While one could speculate around the role of cytokines, that are elicited by Ad26.COVS.2.S, in the activation of platelets and release of PF4, the subsequent steps that lead to PF4 immunogenicity and PF4 antibody production are not known. In addition, while the induction of cytokines by vaccination and viral infections is a general phenomenon, CVST in the presence of thrombocytopenia is extremely rare. Indeed, based on the observations that the incidence of CVST following vaccination with the Janssen vaccine is at a rate predicted for the non-vaccinated population and that these CVST events are associated with thrombocytopenia it is interesting to speculate that the inflammation and postulated hypercoagulability in some vaccinated individuals is a trigger rather than a cause of CVST in individuals with predisposition to CVST. The one subject in our clinical trials that developed CVST had low platelets, hyper-coagulability and tested positive for PF4 antibodies. This patient also had pre-existing narrowing of the sigmoid sinus which was a predisposing factor for CVST. We are currently exploring potential underlying mechanisms for a relation between induction of PF4 antibodies and vaccination, for instance by analyzing the ability of (parts of) the Ad26 vector, the spike protein, or residual host cell protein and or host cell DNA in the vaccine, to form an immunogenic complex with PF4, eliciting PF4 antibodies. This may be further stimulated by Ad26 induced innate immunity. Investigation of potential pre-dispositioning for what is called 'vaccine-induced immuno

thrombocytopenia' (HLA, polymorphisms in PF4, Fcγ receptors, etc) and/or CSVT (genetic, anatomical) will be done in collaboration with experts in the field.

Nonclinical safety data

An assessment of the potential risk for thromboembolic events or coagulopathies based on nonclinical GLP safety data available for Ad26.COV2.S as well as other Ad26-based vaccines is provided in the next sections. Overall, these data do not indicate any adverse vaccine-related effect suggestive of an increased risk for thromboembolic events or coagulopathies associated with Ad26.COV2.S or the Ad26 platform.

Ad26.COV2.S

The nonclinical safety profile of Ad26.COV2.S was evaluated in a 4-week GLP-compliant intermittent repeated dose toxicity and local tolerance study in male and female New Zealand White (NZW) rabbits (study TOX14382). In this study, rabbits were injected intramuscularly (IM) with a control solution (0.9% sodium chloride) or 1×10^{11} vp Ad26.COV2.S on three occasions with a 14-day interval period (Days 1, 15, and 29; See study design in Table 17). The animals were followed up until 3 weeks after the third vaccination to assess the potential reversibility, persistence or delayed occurrence of any vaccine-related findings.

Table 17: Study Design of the GLP Repeat-Dose and Local Tolerance Toxicity Study With Ad26.COV2.S in NZW Rabbits

Group No.	Treatment	Dosage (vp)	Dose Volume	Dosing Days	Number of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Control (Saline)	0	1 mL	1, 15, 29 ^a	5	5	5	5
2	Ad26.COV2.S	1×10^{11}	1 mL	1, 15, 29 ^a	5	5	5	5

^a Injections are given in the right thigh (anterior) on Day 1, left thigh (anterior) on Day 15 and right thigh (posterior) on Day 29
vp: virus particles

Fibrinogen and CRP levels were measured before the first vaccination, Day 2 (CRP only), Day 3, Day 7, Day 15 (before injection), Day 16 (CRP only), Day 17, Day 21, Day 29 (before injection), Day 30 (CRP only), Day 31 (ie, 2 days after third vaccination, at necropsy), Day 35 (ie, during treatment-free period), and Day 50 (end of treatment-free period, at necropsy). Clinical pathology parameters (hematology, coagulation, and clinical chemistry) were determined before the first vaccination, 2 days after the first and third vaccination (ie, on Days 3 and 31, respectively) and 3 weeks after the third vaccination (Day 50; end of treatment-free period). Macroscopic (gross necropsy findings and organ weights) and microscopic pathology evaluations of a full tissue list were performed from animals sacrificed 2 days (i.e., Day 31) and 3 weeks after the third vaccination (i.e., Day 50).

The dose administered to the animals (1×10^{11} vp) is 2-fold above the clinical dose (5×10^{10} vp). Based on a 3 kg rabbit, this would yield a 33-fold margin versus a 50 kg human. In addition, the animals received three doses versus a single dose which is proposed for the emergency use of Ad26.COV2.S in humans. Further details of the study/design can be found in the report (Study TOX14382). Overall, Ad26.COV2.S was well tolerated by the animals and there were no adverse vaccine-related effects noted in the study. A more detailed assessment of potential risk for thromboembolic events or coagulopathies based on the nonclinical safety data available for Ad26.COV.2S is included below.

In TOX14382, IM administration of Ad26.COV2.S at 1x10¹¹ vp on 3 occasions (Days 1, 15, and 29) was associated with mild, transient increases in fibrinogen concentrations on Days 3, 17 and 31 in male and female animals (Text Table 12 in Section 7.8 of the report; Study TOX14382). These increases were partially reversed within one week following vaccine administration, ie, on Days 7, 21 and 35. On Days 15 and 29, thus 2 weeks following the 1st and the 2nd vaccine administration, respectively, the fibrinogen values were similar to pre-study / control group values. Also at the end of the recovery period (Day 50, ie, 3 weeks after the third vaccine administration), changes in fibrinogen concentrations were no longer observed. The maximum mean fold changes in the vaccine treated group versus the control group were 1.63x for male animals 2 days after the 3rd vaccine administration (i.e., on Day 31) and 1.85x for female animals 2 days after the 2nd vaccine administration (i.e., on Day 17).

Increases in fibrinogen values are not unique to Ad26 based vaccines and are seen in nonclinical safety studies with various vaccine- and adjuvant modalities or platforms (Baldrick 2016). In toxicity studies with vaccines, fibrinogen is used as a biomarker for inflammatory / acute phase responses following vaccination, together with other acute phase proteins such as C-reactive protein (CRP, depending on the nonclinical species used) (Green 2015; Destexhe 2013). The vaccine-induced increases in fibrinogen observed with Ad26.COV2.S in TOX14382 (i.e., up to approximately 1.63x / 1.85x), are similar as reported in rabbits with other vaccines or adjuvant systems (e.g., Destexhe 2013; Sheets, 2008), and are not deemed adverse. Other changes in coagulation or platelet parameters noted in TOX14382 were sporadic, transient and of minimal severity grades, eg; In vaccine-treated male animals a 12% decrease in platelets (ie, 354 x 10⁹/L versus 402 x 10⁹/L for control) was observed on Day 3, two days after the first vaccine administration, and a 7% reduction (ie, 6.8 sec versus 7.3 sec for control) of prothrombin time was observed on Day 31, two days after the third vaccine administration. Despite being statistically significant, these two changes were not considered vaccine-related based on their small magnitude and overlap of individual values on these single occasions with the range of control and/or baseline values in the study.

No histopathological changes suggestive of a thrombotic event / coagulopathy or its sequelae were seen in any of the tissues examined in TOX14382, and no local or systemic adverse effects of the Ad26.COV2.S vaccine were observed on full-tissue microscopic examination.

In addition, in efficacy and immunogenicity studies using nonhuman primates (NHP), and hamsters no pathological evidence of thromboembolic events or coagulopathies was observed in animals that were vaccinated with Ad26.COV2.S and subsequently challenged with the SARS-COV-2 virus. In these studies, histopathological evaluation of respiratory tract tissues did not reveal any evidence of thrombosis and other coagulopathies in the pulmonary vascular bed in vaccinated animals, including breakthrough cases.

Overall, these (GLP) nonclinical safety data for Ad26.COV2.S do not indicate any adverse vaccine-related effect suggestive of an increased risk for thromboembolic events or coagulopathies.

Ad26 vaccine platform

As described in the Nonclinical Overview (i.e., Module 2.4 of the cMA package), the MAH has significant nonclinical experience with other Ad26-vectored vaccines using various transgenes encoding for HIV, malaria, RSV, Zikavirus, Filovirus (Ebola virus, Marburg virus), influenza (Universal influenza) and HPV antigens. More than 10 GLP combined repeated dose toxicity and local tolerance studies have been performed in rabbits (and one study in rats) testing the nonclinical safety of these various Ad26-based vaccines. High-level (tabulated) summaries from these studies are provided in Supporting Information:

Overview of Supportive GLP Toxicology Studies Testing Ad26-vectored Vaccines in Rabbits or Rats After IM Injections.

The various Ad26-based vaccines in these studies were tested either alone, or in regimens/combinations with other vaccine modalities, including Ad35-based vaccines, Modified Vaccinia Virus Ankara (MVA)-based vaccines and/or (glyco)proteins with or without an aluminum phosphate adjuvant. The fold changes as indicated in the table are the maximum mean fold changes (irrespective of vaccine regimen, sampling time or sex) measured during the study, versus controls. In the available studies up to 5 sequential IM dose administrations have been tested at Ad26 vaccine levels up to 4×10^{11} vp (i.e., up to 8-fold above the full clinical dose currently used for Ad26.COVID-19), covering in life study phases up to 12 weeks (including recovery). Overall, the Ad26-based vaccines/regimens in these additional studies were well tolerated and no adverse vaccine-related effects were noted in any of the studies.

In line with the results described for Ad26.COVID-19 above, across these additional studies with Ad26-based vaccines a consistent vaccine-related acute phase response was observed, evidenced by transient increases in e.g., fibrinogen (up to 2.5-fold) and CRP (or α_2 -macroglobulin in rats; study TOX12276). The following changes in coagulation parameters were considered vaccine related, and hence retained in the respective report summaries; In few studies (e.g. TOX12014, TOX10931, TOX11260 and 1854-09764) a transient, minimally shorter prothrombin time (generally less than 10%) was reported versus controls. Similar minimal shortening of prothrombin time has been described for other adenoviral vaccines (Sheets 2008). Changes in activated partial thromboplastin time (APTT) were observed in TOX10931 (0.9x; male animals), and in study 1854-09764 (1.4x). In study 1854-09764 a reduction in platelet counts (0.65x) was observed in animals that received an Ad26-based vaccine following three preceding vaccinations with an Ad35-based vaccine. There were further miscellaneous changes observed in prothrombin time and/or platelets, as well as other clinical pathology parameters in other studies, which occasionally reached statistical significance. However, these changes were not considered vaccine-related, e.g., due to their sporadic pattern, small magnitude, lack of toxicological relevance, and/or relation to pre-treatment or control ranges.

Thus, vaccine-related changes in coagulation parameters and platelet counts were minor and not consistently observed across studies with other Ad26-based vaccines. In addition, similar to study TOX14382 with Ad26.COVID-19, there were no vaccine-related histopathological changes suggestive of a thrombotic event / coagulopathy or its sequelae in any of the available studies, which supports the conclusion that the minor changes in coagulation parameters as described above are not adverse. All vaccine-related histopathological changes observed in the additional studies with Ad26-based vaccines were consistent with an anticipated, non-adverse (local and systemic) immunologic response to vaccination.

Overall, the GLP nonclinical safety data from Ad26.COVID-19 and other Ad26-based vaccines summarized above do not indicate any adverse vaccine-related effect suggestive of an increased risk or a pathogenic mechanism of action for thromboembolic events or coagulopathies associated with Ad26.COVID-19 or the Ad26 platform.

PRAC Rapporteur comment:

Across the non-clinical studies with Ad26.COVID-19 and other Ad26-based vaccines there were no observations indicating an adverse vaccine-related effect on thrombosis and/or thrombocytopenia. The study findings were generally limited to mild and transient effects expected from a local and general inflammatory reaction subsequent to vaccination. Given the very low incidence of the thromboembolic

events or coagulopathies associated with Ad26.COV2.S, likely of multifactorial aetiology, it is not unexpected that no signals are observed in healthy animals.

Taken together, the non-clinical data with Ad26.COV2.S and other Ad26-based vaccines provide no further understanding on potential causal relationship between vaccination with Covid-19 vaccine Janssen and the events of thrombosis and thrombocytopenia.

Regarding clinical assessment of causality, see Q4 and 3.1.4 PRAC Rapporteur Discussion.

QUESTION 7

The MAH is asked to discuss how, beyond the already agreed studies in the PhV plan, the important potential risk venous thromboembolism, including the potential occurrence of the combination of thrombosis and thrombocytopenia can be further studied. Ways of gaining further mechanistic data, both non-clinical and clinical, regarding potential interactions of the Covid-19 vaccine Janssen and the coagulation system should specifically be addressed; and the following commented:

PRAC Rapporteur comment: This question will not be commented in the first step of this assessment.

QUESTION 8

Considering the findings of the review, the MAH should discuss the need for amendment to the Product Information and/or Risk management plan, for the latter, including, but not limited to, the list of safety concerns and studies specified within the pharmacovigilance plan.

MAH RESPONSE:

As described in the responses to the previous questions, the MAH conducted extensive review of available data across its different databases covering the Ad26.COV2.S and other Ad26-vectored clinical development programs, collaborative trials and vaccination programs, and the Ad26.COV2.S spontaneous reports. Very rare cases of thrombotic events with thrombocytopenia have been observed to date in individuals who received Ad26.COV2.S with no cases confirmed for other Ad26 vectored vaccines.

Review of the reported AEs showed that, as of 12 April 2021, the MAH has 6 post-authorization cases of Cerebral Venous Sinus Thrombosis (CVST) (4 of which are associated with low platelets, 2 unknown) with 6.8 Million individuals vaccinated with the Ad26.COV2.S vaccine. While the observed incidence rates of CVST with Ad26.COV2.S is generally consistent with what would be expected, the observed incidence rates of CVST with thrombocytopenia in women appears to higher than what would be expected (Table 9).

Given the very low incidence of cases observed following vaccination, there is currently insufficient data to conclude a causal association with the Ad26.COV2.S vaccine. Based on the current data, MAH believes the benefit - risk profile for Janssen Ad26.COV2.S vaccine is positive across the population for which it is currently authorized.

However, the MAH strongly supports making vaccinees aware of the signs and symptoms of this very rare event, as well as recommendations to health care professionals to ensure the early and correct diagnosis and treatment of the patients and reporting of the events.

Therefore, the MAH proposes to amend the Product Information to include information on these observed events, to guide healthcare providers, vaccine recipients and the general public regarding when to seek urgent medical attention and to guide healthcare providers so that they can promptly diagnose and treat people affected, in line with available guidelines.

In the current EU Risk Management Plan (RMP, version 1.4 dated 11 March 2021), Venous thromboembolism is considered an Important Potential Risk, and events of Deep vein thrombosis and Pulmonary embolism, together with Non-hemorrhagic stroke and Hemorrhagic stroke have been identified and are monitored as Adverse Events of Special Interest (AESI), in addition to events of Immune thrombocytopenia and Disseminated intravascular coagulation. The MAH will further update the Safety Concerns section in the RMP, to add further details on the events of thrombotic events associated with thrombocytopenia, update the PV Plan to include the implementation of processes for evaluating thromboembolic events in the clinical trials as described in Question 7 and to update the Risk Minimization Measures activities accordingly, including proposed changes to the Product Information. The MAH will continue to monitor these events and assess for additional activities as more data becomes available.

The following is proposed by the MAH regarding updates of the product information:

SmPC

Section 4.4

Coagulation disorders and thrombocytopenia

A combination of venous thrombosis and thrombocytopenia has been observed very rarely following vaccination with COVID-19 Vaccine Janssen. This includes cerebral venous sinus thrombosis and can lead to a fatal outcome. These cases occurred within the first three weeks following vaccination.

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 pain or swelling, or progressive 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.

Since management may be different than usual medical practice for blood clots, healthcare professionals should consult applicable guidance and/or consult specialists (e.g., haematologists) to diagnose and treat this condition.

Risk of bleeding with intramuscular administration

Package leaflet

Section 2

Blood disorders

A combination of blood clots and low levels of 'platelets' (cells that help blood to clot) in the blood has been observed very rarely following vaccination with COVID-19 Vaccine Janssen. This includes severe cases with blood clots and, possibly, bleeding, including in the brain, and can be fatal. These cases occurred within the first three weeks following vaccination.

Seek immediate medical attention and inform your health care provider that you have recently received COVID-19 Vaccine Janssen, if you experience severe or persistent headaches or blurred vision, unexplained skin bruising beyond the site of vaccination, develop shortness of breath, chest pain, leg pain or swelling, or progressive abdominal pain which appear a few days after vaccination.

PRAC Rapporteur comments

Proposed label updates

The PRAC Rapporteur agrees with the MAH that an update of section 4.4 of the SmPC, as well as of section 2 of the package leaflet, is warranted. However, the proposed wording needs revision (see below).

In the proposal from the MAH, there is a statement highlighting that management of this condition may differ from usual management of blood clots, and therefore refer HCPs to applicable guidance / specialists for diagnosis and treatment. This statement is fully supported for section 4.4 of the PI.

Furthermore, following evaluation of the currently available data, there is sufficient evidence to, with a reasonable possibility, conclude *thrombosis in combination with thrombocytopenia* being an adverse drug reaction of the Covid-19 vaccine Janssen. Therefore, update of section 4.8 is warranted.

Regarding the frequency for section 4.8, very rare (< 1/ 10 000) is proposed. This is based on one certain clinical study case, and one possible case, among a clinical safety database of approximately 27,200 vaccinated subjects, which were part of the safety assessment at approval, and who had been evaluated for death and SAEs⁴. Although the MAH refers to a total clinical study data base of approximately 280 000, the vast majority of these data has not been submitted to EMA for review, and is therefore not considered useful for this estimation of frequency.

The PRAC rapporteur's proposals are as follows; with comments made to the proposal of the MAH as also shown above.

Deletion – ~~strikethrough~~. Addition; double underline

Section 4.4

~~Coagulation disorders and~~ Thrombocytopenia and coagulation disorders

A combination of venous thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with COVID-19 Vaccine Janssen. This includes venous thrombosis at unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis concomitant with thrombocytopenia, and can lead to a fatal outcome has been reported. These cases occurred within the first three weeks following vaccination, and mostly in women under 60 years of age.

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

⁴ EPAR for [COVID-19 Vaccine Janssen, INN-Ad26.COV2-S, recombinant \(europa.eu\)](https://www.ema.europa.eu/en/medicines/humans/vaccines/COVID-19-Vaccine-Janssen)

bruising (petechia) beyond the site of vaccination after a few days, should seek prompt medical attention.

Since management may be different than usual medical practice for thromboembolic events if patients present with concomitant thrombocytopenia-blood clots, healthcare professionals should consult applicable guidance and/or consult specialists (e.g., haematologists, specialists in coagulation) to diagnose and treat this condition.

Risk of bleeding with intramuscular administration

Section 4.8

In the Table

SOC: Vascular disorders: Thrombosis in combination with thrombocytopenia*

* *Severe and very rare cases of thrombosis in combination with thrombocytopenia have been reported post-marketing. These included venous thrombosis such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis (see section 4.4).

Frequency: Very rare

Package leaflet

Section 2

[...]

As with any vaccine, vaccination with COVID-19 Vaccine Janssen may not fully protect all those who receive it. It is not known how long you will be protected.

Blood disorders

A combination of blood clots and low levels of 'platelets' (cells that help blood to clot) in the blood has been observed very rarely following vaccination with COVID-19 Vaccine Janssen. This includes severe cases with blood clots and, possibly, in unusual locations, such as the brain and liver, in some cases in combination with bleeding, including in the brain, and can be fatal. These cases occurred within the first three weeks following vaccination, and occurred mostly in women below 60 years of age. Fatal outcome has been reported.

Seek immediate medical attention and inform your health care provider that you have recently received COVID-19 Vaccine Janssen, if you experience severe or persistent headaches or blurred vision, unexplained skin bruising beyond the site of vaccination which appear a few days after vaccination, develop shortness of breath, chest pain, leg pain or swelling, or progressive persistent abdominal pain which appear a few days after vaccination. Inform your health care provider that you have recently received COVID-19 Vaccine Janssen.

Section 4

Very Rare (may affect up to 1 in 10.000 people) - blood clots often in unusual locations (e.g. brain, liver) in combination with low level of blood platelets

Risk management plan

As the MAH points out, the current EU RMP (v. 1.4 dated 11 March 2021), VTE is listed as an Important Potential Risk, and various relevant terms are monitored as AESI, in addition to events of Immune thrombocytopenia and Disseminated intravascular coagulation.

The MAH proposes to further update the Safety Concerns section in the RMP, to add further details on the events of thrombotic events associated with thrombocytopenia, and to update the PV Plan as described in Question 7, and to update the RMM in line with the actions taken for the PI.

Details on the RMP will not be addressed within this first step of assessment, and thus not further commented here.

3.1.2. Case reports from EudraVigilance/received through VAERS

1. This fatal case concerns a female aged between 38-48, described as Case 1 in section 2.1 above. *Summary: prior medical history including depression. 1 wk after vaccination developed headache and hemiparesis. CT revealed severe cerebral haemorrhage + CVST, leading to brain herniation and death. Thrombocytopenia also mentioned.*

Additional information: SARS-CoV-2 viral assay negative. PF4 heparin HIT ELISA antibody test was not done. Platelet nadir 12,000/mm³.

2. This case concerns a female aged between 52-62, described as Case 2 in section 2.1 above. No additional information compared to above. *Summary: Multiple co-morbidities, including COPD, coronary artery disease, hypertension, hypothyroidism and bipolar disorder. 11 days after the vaccination the patient had bruising and leg oedema, with a diagnose of severe thrombocytopenia (15) and extensive DVT. She had an IVC filter placed. The next day the patient developed arterial thrombosis as well (superficial femoral and iliac arteries) requiring thrombectomy + stent.*

3. This clinical trial case concerns a male aged between 18-28, described as Case 3 in section 2.1 above. *Summary: no significant prior medical history. Received vaccine and had inflammatory syndrome the same day (fever, myalgia, fatigue, nausea, headache) that improved within 3 days (except headache). 9 days after vaccination he had a similar inflammatory syndrome (plus abdominal pain, sore throat, chills and rhinorrhea) and the pt took ibuprofen. Repeated COVID tests were negative. Symptoms improved except headache. 18 days after vaccination the patient had seizures. CT scans confirmed cerebral haemorrhage + CVST (2 days later). He also had moderate thrombocytopenia (65).*

Follow-up adds additional test results: Anti PF4 antibodies were negative 0.246 (Day 1) and positive 2.137 (Day 29) and 1.451 (Day 71). On Day 155: Lyme disease test: high IgM (interpreted as negative), Lupus anticoagulant: normal, N-ELISA: negative. The patient received heparin which complicates interpretation of anti -PF4 antibody results. A more definitive causality requires confirmation of the PF4 test to determine if these antibodies are related to coagulopathy. However, based on recent publications including the Thrombotic Thrombocytopenia after ChAdOx1 nCov -19 Vaccination published in The New England Journal of Medicine on 09 April 2021 which suggests an evolving scientifically plausible relationship between immunization with certain COVID -19 vaccines and CVST with thrombocytopenia and platelet factor 4 (PF4) antibody, the case is considered possibly related by the MAH.

4. This case concerns a female aged between 18-28, summarised in Late breaking information above. *Summary: no previous medical history or family history of clotting disorders. Non-smoker, no concomitant medications. 16 days after vaccination, she developed headache, vomiting and mental*

status changes. MRI and CT scan revealed sagittal sinus thrombosis and haemorrhage; Platelet count on presentation was 18,000, fibrinogen was low and fibrin D-dimer was elevated. She developed seizures, was given a platelet transfusion in advance of thrombectomy and was anticoagulated (specific agent not provided), after which platelet count rose to 160,000 and fibrinogen was normalised. Further outcome unknown.

Additional information: SARS-CoV-2 viral assay negative. PF4 heparin HIT ELISA antibody positive (optical density 2.7).

5. Published Gundabolu K et al. *Thrombotic Thrombocytopenia Following Ad26.COVID-19 Vaccination, New England Journal of Medicine*. This concerns a woman aged between 41-51 with unremarkable past medical history who received COVID-19 VACCINE AD26.COVID-19 (date unknown). She developed malaise and abdominal pain 11 days following vaccination and presented to an emergency room 3 days later. Evaluation revealed mild anaemia and severe thrombocytopenia (platelet count, 13,000 per cubic millimetre). Peripheral blood smear confirmed marked reduction in platelet count with occasional schistocytes. Other laboratory evaluation showed hypofibrinogenemia (89 mg/dL), prolonged activated partial thromboplastin time (41 sec), and marked elevation in D-Dimer (117.5 mg/L), indicating disseminated intravascular coagulation. Nasopharyngeal swab tested negative for SARS-CoV2 by RT-PCR (polymerase chain reaction).

CT (computerised tomogram) imaging of abdomen/pelvis which showed extensive splanchnic vein thrombosis. The patient developed a new onset headache, and head CT revealed cerebral venous sinus thrombosis (CVST) involving right transverse/straight sinus. Initially, the hospital was not aware that the patient was recently vaccinated, and initiated treatment with unfractionated heparin. She developed progressive thrombosis with haemorrhagic stroke evident by MRI (magnetic resonance imaging)/MRV of brain while on heparin, with repeat CT angiography showed new thrombus involving right hepatic and splenic veins.

Upon further inquiry it was noted she had received the Ad26.COVID-19 vaccine 14 days before symptom onset. Screening test for anti-PF4/heparin antibodies by latex-enhanced immunoassay was negative; results of a PF4/polyanion ELISA were strongly positive (3.179 OD [optical density] units; upper limits of normal below or equal to 0.399). Heparin was switched to argatroban. The patient was also treated with intravenous immunoglobulin (1 gm/kg times 2 days). Her platelet count increase from 30,000 to 145,000 over 5 days. She remained critically ill at time of last report. The outcome of the mild anaemia, severe thrombocytopenia, disseminated intravascular coagulation, cerebral venous sinus thrombosis, haemorrhagic stroke, hepatic vein thrombosis, splenic vein thrombosis and splanchnic vein thrombosis was not reported.

Assessor's comment: additional laboratory tests were reported in the publication by Gundabolu et al, including antiphospholipid antibodies (lupus anticoagulant, cardiolipin, GpIb2 which were all not detected/not elevated), normal levels of homocysteine, Factor VIII, antithrombin, protein C, protein S. No mutation regarding Factor V Leiden R506Q or prothrombin G20210A. Hepatitis B and C as well as HIV testing was negative. Bilirubin was 0.5 (ref 0.2-1.3 mg/dL), LDH was 354 U/L (ref 100-250 U/L) and haptoglobin was 183 mg/dL (ref 30-200 mg/dL). ADAMTS 13 activity was normal. PNH antigen was not detected. Janus Kinase 2 gene mutation was not detected.

6. This case concerns a female aged between 19-29, reported to be overweight (weight/BMI unknown) but physically active. She has no history or family history of clotting disorder. She is not on any medication or birth control pills. The patient received 1 dose of covid-19 vaccine ad26.cov2.s (suspension for injection, route of admin not reported, batch number: Unknown) on an unspecified date. Approximately 1 week following vaccination, she developed a severe headache and visited the

emergency department. The patient was given paracetamol and antihistamine and sent home. The patient continued to have headaches. Approximately another week later, the patient developed abdominal discomfort and rapid heart rate and was seen in the hospital. Laboratory evaluation revealed platelet count of 120,000 (thrombocytopenia), elevated D-Dimer (level unknown) and normal fibrinogen (level unknown). Covid-19 infection was ruled out (exact test unknown). Diagnostic scans showed cerebral cavernous sinus thrombosis (coded to cerebral venous sinus thrombosis), portal vein thrombosis and pulmonary embolism. Initial treatment with heparin was stopped and IVIG administered after lab result showed positive antibodies to platelet factor 4 (level 3.0). Platelet count was reported to have started increasing prior to IVIG administration. The patient spent 1-1.5 weeks in the hospital and was released home on oral anticoagulants. The outcome of portal vein thrombosis, pulmonary embolism, cerebral venous sinus thrombosis, thrombocytopenia was recovering. Additional follow up information has been requested.

7. This case concerns a female aged between 31 -41. The patient's height, and weight were not reported. The patient received covid-19 vaccine ad26.cov2.s (suspension for injection, intramuscular) dose was not reported. No concomitant medications were reported. 19 days after vaccination the patient was "experiencing headaches 1 week ago", and also had aphasia later in the week. On day 16, the patient went to an outside hospital and was found to have intraparenchymal haemorrhage in addition to venous sinus thrombosis and developed intracerebral haematoma. On day 17, Computerized tomography (CT) of the head without contrast showed parenchymal haemorrhage and persistent hyperdensity in the left transverse sinus, consistent with known venous sinus thrombosis. Treatment medications (dates unspecified) included: heparin. The action taken with covid-19 vaccine ad26.cov2.s was not applicable. The outcome of the experiencing headaches 1 week ago, intracerebral haematoma and venous sinus thrombosis was not reported. The case will be assessed further when additional information is received.

Further information: thrombocytopenia (platelet nadir 69,000/mm³). PF4 heparin HIT ELISA antibody positive (optical density 1.2). SARS-CoV-2 viral assay negative.

8. This case concerns an adult male patient (greater than 50 years old). The patient's weight, height, and medical history were not reported. The patient received Covid-19 vaccine AD26.Cov2.S (suspension for injection, intramuscular, batch number was not reported) dose and site of vaccination were not reported, administered for prophylactic vaccination. No concomitant medications were reported. On an unspecified date in 2021, the patient experienced deep vein thrombosis (DVT), pulmonary embolism (PE), and kidney bleeding. The patient was admitted to the hospital and was treated with heparin as well as an inferior vena cava (IVC) filter (put in after he experienced bleeding from his kidney).

Laboratory data included: a negative COVID-19 virus test, and throughout hospitalization his platelet count (NR: not provided) was normal: 191,000 and 264,000 (units not provided). The patient's test came back positive for one copy of the Factor V Leiden mutation which predisposed him to blood clots.

At the time of this report, the patient was still hospitalized but doing well. The patient was recovering from DVT, pulmonary embolism, and kidney bleeding

9. This case concerns a female aged between 21-31 who received the covid-19 vaccine ad26.cov2.s. Prescriptions being taken at the time of vaccination was oral contraceptive pill. She presented with a "viral syndrome" including fevers, rigors, muscle pain and shortness of breath. Fever persisted for 1 day after ER visit, but she continued to feel badly. The following day, she was awakened with severe R>L jaw pain, post HA with standing, pain in the cartilage on the tip of her nose and shortness of breath. Shortness of breath resolved by day 12. HAS persisted as did jaw pain and pain behind her

eyes. On day 11 she noted increasing bruising and periorbital petechiae which continued through when she sought help from her PcP. She was noted to have bilateral leg swelling R>>L. She had labs and a Doppler US. She had a syncopal spell on and was brought to ER at where she was diagnosed with sagittal vein thrombosis, RLE DVT and thrombocytopenia. Medical tests and laboratory results related to the adverse event(s): Plt count 125K; Plt ct 34K, smear reviewed, no clumping, no schistocytes. Ordered hypercoag panel, ANA and Anti PF4/HIT (awaiting all results) CT and MRI of head with dural sinus thrombosis, Duplex US with RLE thrombosis. At the time of reporting, the patient had not recovered from the adverse events.

Additional information: platelet nadir 10,000/mm³. PF4 heparin HIT ELISA antibody positive (optical density 1.2). SARS-CoV-2 viral assay negative.

PRAC Rapporteur comment: updated

Out of the 9 cases found in EudraVigilance and received through VAERS, concomitant thrombosis and thrombocytopenia was reported in 8 of these; in one case, platelet levels were normal. It is recognised that although thrombosis in a setting of classical HIT does not have to result in thrombocytopenia (a decrease in platelet levels >50% from baseline is also considered suggestive of HIT, which could thus occur also with platelet levels within the normal range), the case with normal platelet levels has not been considered further.

For the 8 cases with concomitant thrombosis and thrombocytopenia, 7 cases were females and 1 was male. Age distribution was 18-59 years. Cerebral vein and sinus thrombosis (CVST) were reported in 7 cases. Arterial femoral thrombosis in addition to deep vein thrombosis was reported in one case. Concomitant thrombosis in addition to CVST was reported in 3 cases, including portal vein thrombosis + pulmonary embolism, splanchnic vein thrombosis and deep vein thrombosis. Concomitant bleeding was reported in 6 cases.

Platelet counts ranged from 10,000/cmm to 120,000/cmm (normal range 150,000-400,000/cmm). Elevated D-dimer values were reported in several cases, which is expected in patients with acute thrombosis, however, notably high levels were reported in some cases. In three of the cases, disseminated intravascular coagulation (DIC) was reported or is considered likely based on provided lab values (primarily a combination of thrombocytopenia, increased D-dimer, decreased fibrinogen, prolonged aPTT and/or prolonged prothrombin time).

There was no reported significant medical history in 6 of the cases with concomitant thrombosis and thrombocytopenia. One case had a history of depression (treated with fluoxetine); one reported multiple co-morbidities (including coronary artery disease / hypertension / asthma / COPD / bipolar / depression / hypothyroidism). One female patient was taking oral contraceptives.

For the case in the clinical trial, female aged between 18-28, the finding of negative anti-PF 4 antibodies at baseline that were positive on day 29 are of high interest. The comment that the patient received heparin which complicates interpretation of anti-PF4 antibody results is not considered to explain this finding; based on the clinical scenario, the patient presented with thrombocytopenia before heparin was initiated, and the platelet count improved despite heparin treatment. Therefore, in light of recent findings with anti-PF 4 antibodies having been detected and found pathogenic in patients with thrombosis and thrombocytopenia following vaccination with another adenoviral vector COVID-19 vaccine, the development of such antibodies, in addition to the overall clinical and laboratory picture, is considered to strongly strengthen an association with the vaccine.

Positive antibodies to platelet factor 4 was found in five additional cases. There is no case report in which anti-PF4 antibodies were analysed and not found positive. In a minority of the cases, a detailed

work-up has been provided, excluding potential factors of interest including no antiphospholipid antibodies; normal ADAMTS13; no JAK2 gene mutation; normal levels of homocysteine, Factor VIII, antithrombin, protein C, protein S; no Factor V Leiden R506Q mutation or prothrombin gene mutation. SARS-CoV2 was tested in 3 of the cases, all of which were negative.

Deterioration during heparin treatment was reported for one case; in two cases with concomitant thrombosis and thrombocytopenia, platelet count was reported to have started increasing during treatment with heparin. For the case with deterioration during heparin treatment, the patient was diagnosed with disseminated intravascular coagulation (DIC) and anti-PF4/heparin antibodies by latex-enhanced immunoassay was negative; results of a PF4/polyanion ELISA were strongly positive.

It is currently unknown whether treatment with heparin could be used or should be avoided in patients with thrombotic thrombocytopenia following COVID-19 vaccination. One argument against use of heparin is the clinical similarity to HIT (heparin induced thrombocytopenia), in which heparin is part of the antigen complex against which the anti-PF4/heparin-antibodies can bind, and thus, in HIT, heparin treatment must be stopped. However, for patients with thrombotic thrombocytopenia following vaccination, it has been found that the anti-PF4-antibodies are not similar to the ones in HIT; rather, they are directed towards PF4 only.

For one of the post-marketing cases with multiple thromboses including CVST and thrombocytopenia, progressive thromboses were noted during heparin treatment. However, it cannot be concluded whether this was due to heparin or despite heparin. This patient was diagnosed with DIC, which is well-known to be difficult to treat regardless of underlying disease or coagulation disorder, and anti-PF4/heparin antibodies by latex-enhanced immunoassay was negative in that case. There are two other cases (one post-marketing case and one clinical study case) in which platelet numbers started to increase during treatment with heparin.

In HIT, effective anticoagulation could be difficult in cases with severe thrombocytopenia and/or bleeding. The labelled anticoagulant therapies for HIT (such as argatroban, danaparoid) are not available in many hospitals and warrant certain considerations for correct use. Treatment with other agents is therefore sometimes used, e.g. fondaparinux and bivalirudin, however, such treatment is strictly considered off-label for HIT. Oral anticoagulation in a patient with thrombocytopenia is not straightforward; vitamin K antagonists are not recommended in HIT or similar clinical entities due to the initial decrease in protein C associated with these agents, which could aggravate thromboses initially. The DOACs could be an alternative but would likely not be considered in an unstable patient or a patient with severe thrombocytopenia at high risk of bleeding.

For patients with thrombosis without thrombocytopenia after vaccination, there would be no or very low suspicion of the specific syndrome of thrombotic thrombocytopenia (again, in HIT, one diagnostic criteria is a 50% platelet count decrease from baseline thus potentially allowing for values within the normal range – whether this could be the case for thrombotic thrombocytopenia associated with vaccination is unknown). The majority of patients with thromboses after vaccination will not have concomitant thrombocytopenia. Any message to avoid heparin could potentially cause a delay in effective anticoagulation also in these patients.

In patients with concomitant thrombosis and bleeding in whom anticoagulation is considered warranted, an ideal anticoagulant agent should be readily available, familiar to use, and have a rapid onset, short half-life and an effective antidote. To date, the only agents in many situations that fulfil these criteria reasonably well are heparins. The knowledge about thrombotic thrombocytopenia after vaccination against COVID-19 is growing rapidly and treatment guidelines/advice are frequently updated. Based on the currently available data, it cannot be concluded neither how these patients

should be optimally managed nor whether heparin is safe and effective or not. Therefore, the Rapporteur proposes not to specifically give advice to avoid heparin in patients with thrombotic thrombocytopenia neither in the product information nor in the DHPC. However, it should be clearly stated that specialist advice (such as haematologists or coagulation expertise) should be consulted in the diagnosis and treatment of suspected thrombotic thrombocytopenia after vaccination. This is also considered to be the most long-lasting wording.

In addition, for patients with thrombosis without thrombocytopenia after vaccination, there would be no or very low suspicion of the specific syndrome of thrombotic thrombocytopenia (again, in HIT, one diagnostic criteria is a 50% platelet count decrease from baseline thus potentially allowing for values within the normal range – whether this could be the case for thrombotic thrombocytopenia associated with vaccination is unknown). The majority of patients with thromboses after vaccination will not have concomitant thrombocytopenia. Any message to avoid heparin could potentially cause a delay in effective anticoagulation also in these patients.

In conclusion, there are currently 8 reported cases in EV and VAERS, all originating from the US, with concomitant thromboembolism (primarily CVST) and thrombocytopenia. The majority (7 out of 8 cases) are females, with age range 18-59 years. There are no findings with regards to previous disease or concomitant treatment that are suggestive of any common risk factors for developing the combination of thrombosis and thrombocytopenia; the majority had no medical history and no medication. Work-up includes anti-PF4 antibodies in 6 cases, all of which were found positive/strongly positive. It is currently unclear if platelet activation testing has been performed; however, a strongly positive ELISA result is considered highly suggestive of anti-PF4-antibodies being a causative factor. Extensive work-up was provided in only a minority of the cases, however, no findings suggestive of an alternative cause were found in any of these. For the clinical trial case with a male patient aged between 18-28 with CVST, thrombocytopenia and cerebral haemorrhage, it is noted that he did not have any anti-PF4-antibodies prior to vaccination but developed these in conjunction with symptoms of thrombosis and thrombocytopenia; this is considered to strongly support an association with the vaccine.

3.1.3. EVDAS Search Summary

SMQ Embolic and Thrombotic events SMQ (DLP: 14/04/2021)

- Search at the level of SMQ Haemorrhages in EVDAS (DLP 14/04/2021) retrieved 33 cases in association with Covid-19 Janssen vaccine.
- Of the 33 cases, the following events were reported:
 - Myocardial Infarction (n=5);
 - Cerebrovascular accident (n=6);
 - Deep vein thrombosis (DVT) + pulmonary embolism (PE) (n=1);
 - PE (n=1);
 - DVT (n=1);
 - Hemiplegia (n=1);
 - Coronary artery stent insertion (n=1);
 - Hemiparesis (n=2);

- Blindness transient (n=1);
 - Thrombosis (n=1);
 - Peripheral embolism (n=1);
 - Myocardial infarction & thrombosis (n=1);
 - Renal infarct (n=1);
 - Capillary leak syndrome, DIC, distributive shock, renal disorder (n=1);
 - Retinal vein thrombosis (n=1);
 - DVT, PE, Renal haemorrhage (n=1);
 - Superior sagittal sinus thrombosis, cerebral haemorrhage, thrombocytopenia (n=1)
 - Cerebral venous sinus thrombosis, cerebral haematoma, headache (n=1);
 - Cerebral venous thrombosis, cerebral haemorrhage, cerebral haemorrhage, thrombocytopenia (n=1);
 - CVST, DIC, hepatic vein thrombosis, splenic vein thrombosis, haemorrhagic stroke, visceral venous thrombosis (n=1);
 - CVST, PE, portal vein thrombosis, thrombocytopenia (n=1);
 - Transverse sinus thrombosis, cerebral haemorrhage, thrombocytopenia (n=1);
 - DVT, peripheral artery occlusion, peripheral artery thrombosis, thrombocytopenia (n=1)
- One potential duplicate identified.
 - Of the 33 cases, 6 were fatal.
 - Seven cases of interest were identified from EVDAS including:
 - Superior sagittal sinus thrombosis, cerebral haemorrhage, thrombocytopenia (n=1)
 - Cerebral venous sinus thrombosis (CVST), cerebral haematoma(n=1);
 - CVST, cerebral haemorrhage, thrombocytopenia (n=1);
 - CVST, Disseminated Intravascular coagulation, hepatic vein thrombosis, splenic vein thrombosis, haemorrhagic stroke, visceral venous thrombosis (n=1);
 - CVST, Pulmonary embolism (PE), portal vein thrombosis, thrombocytopenia (n=1);
 - Transverse sinus thrombosis, cerebral haemorrhage, thrombocytopenia (n=1);
 - Deep vein thrombosis, peripheral artery occlusion, peripheral artery thrombosis, thrombocytopenia (n=1)
 - An additional index case of sagittal vein thrombosis, right lower extremity (RLE) DVT& thrombocytopenia was received from FDA.
 - Gender: Male (n=1), Female (n=7).
 - Fatal: fatal (n=1), non-fatal (n=7)

- One clinical trial case, 7 post-marketing reports. All originate from the US.
- Median Time to onset (TTO) of first symptoms: 8 days;
- Median Time to onset (TTO) of first thromboembolic (TE) event: 14 days;
- Anti-PF4 antibodies:
 - Of note, information regarding positive anti-PF4 antibodies is available in the ICSRs submitted for 3 cases.
 - No information specified for the remaining four cases submitted to EVDAS.
 - Diagnostic data received on the 19th of April which revealed that anti-PF4 antibodies were detected in an additional three cases.
- An overview of the cases is presented in table 1A below.

Table 1A shows a summary over cases in EudraVigilance (updated based on additional diagnostic data received on the 19th April)

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8*
Age	18-28	52-62	31-41	38-48	41-51	19-29	18-28	21-31
Gender	F	F	F	F	F	F	M	F
Country	US	US	US	US	US	US	US	US
Source	Physician, consumer, pharmacist	Consumer	Consumer	Consumer, other HCP	Physician, consumer, other HCP	Consumer, physician	Physician, consumer	HCP (NOS)
Fatal	No	No	No	Yes	No	No	No	No
Co-morbidities	None		Amoxicillin allergy	Depression	Unremarkable	Not reported	None	None
Concomitant medication	None	Multiple	Not reported	Fluoxetine	Not reported	None	Ibuprofen (400mg as required) for 9 days (initiated 9 days post-vaccination), Naproxen 1000mg	COC
Risk factors	No apparent risk factors	COPD, Coronary artery disease, Hypertension	No apparent risk factors	No apparent risk factors	Obesity (BMI: 39.68)	Over-weight (BMI: NOS)	Significant stenosis in right sigmoid	No apparent risk factors
TTO 1st symptoms (days)	16	11	9	7	11	7	0	6
First symptoms	Headaches, vomiting, mental status changes	Bruising, left leg swelling	Headache, aphasia	Headache	Malaise, abdominal pain	Headache	Fatigue, nausea, headache (moderate), myalgia, fever (38.2)	“Viral syndrome”: fever, rigors, muscle pain, shortness of breath (SOB)
TTO 1st TE event (days)	16	11	16	12	14	14	18	11
TE event	Sagittal sinus thrombosis	Deep vein thrombosis, Peripheral artery thrombosis	Cerebral venous sinus thrombosis (CVST)	CVST	Disseminated intravascular coagulation, CVST, hepatic vein	PE, portal vein thrombosis, CVST	Transverse sinus thrombosis	Sagittal vein thrombosis, Right lower extremity (RLE) DVT

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8*
					thrombosis, splenic vein thrombosis, visceral venous thrombosis			
Haemorrhage	Cerebral haemorrhage	Gross haematuria	Intraparenchymal haemorrhage, cerebral haematoma	Intracerebral haemorrhage, intracerebral haematoma	Haemorrhagic stroke		Cerebral haemorrhage (right temporo-occipital haematoma)	Peri-orbital haemorrhage
Thrombocytopenia (Platelet count)	Yes (18,000)	Yes (N/S)	Yes (69,000)	Yes (12,000)	Yes (13,000)	Yes (127,000)	Yes (64,000)	Yes (10,000)
Anti-PF4 antibodies	Positive (2.7)	N/S	Positive (1.2)	N/S	Strongly positive (ELISA)	Positive (3.0)	Negative (0.246) prior to vaccination, Positive (2.137) 31 days post vaccination	Positive (1.2)
D-dimer	Elevated (NOS)	N/S	N/S	N/S	Elevated (117,512ng/ml)	N/S	N/S	N/S
Fibrinogen	Low (NOS)	N/S	N/S	N/S	Low (89mg/dL)	N/S	154mg/dL (18 days post vaccination)	N/S
ADAMTS13	N/S	N/S	N/S	N/S	72%	N/S	TTP/ADAMTS13 gene mutation negative	
Peripheral blood smear	N/S	N/S	N/S	N/S	Occasional schistocytes	N/S	Neutrophilic leucocytosis, no blasts	No clumping, no schistocytes
SARS-COV2 infection	Negative (test NOS)		Negative (test NOS)	Negative (test NOS)	Negative PCR	Negative (test NOS)	3 negative PCR tests	Negative (test NOS)
Treatment	"British guidelines" -platelet transfusion, thrombectomy,	Bilateral thrombectomy, bilateral common iliac	N/S	N/S	Intravenous (IV) Immunoglobulin (1g/kg 2 times per day)	IV Immunoglobulin	Thrombectomy, Angioplasty on stenosed sinus, 2 nd thrombectomy,	N/S

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8*
	Anti-epileptics	stent placement.						
Anticoagulant	Anticoagulant (NOS)	N/S	Heparin	N/S	Heparin which was switched to argatroban after anti-PF4 antibodies detected	Heparin (stopped after anti-PF4 antibodies detected), Discharged on oral anticoagulants (NOS)	ASA, Heparin (LMWH)+ tissue plasminogen activator (tPA)+heparin drips, apixiban	N/S
Outcome at time of report	Recovered from thrombocytopenia, outcome of sagittal sinus thrombosis and cerebral haemorrhage unknown	Not recovered	Unknown	Death	Critically ill	Hospitalisation for 1-1.5 weeks. Discharged home.	Recovered (back to work & doing very well five months post vaccination).	Not recovered

. Not identified in EVDAS (DLP: 14/04/2021)

SMQ Haemorrhages (DLP: 14/04/2021)

- Search at the level of SMQ Haemorrhages in EVDAS (DLP 14/04/2021) retrieved 13 cases in association with Covid-19 Janssen vaccine.
- Of these, 8 were previously identified via a search at the level of SMQ Embolic and thrombotic events SMQ (i.e. co-reported with events of thrombosis).
- The remaining 5 cases concerned consumer reports which reported:
 - Uterine haemorrhage (n=1)
 - Hematemesis (n=1)
 - Contusion (n=1)
 - Epistaxis (n=1)
 - Henoch Schoenlein Purpura (n=1)
- Of the 5 cases, 4 were subject to limited information which precluded causality assessment and one was confounded by medical history.

HLT Thrombocytopenia (DLP: 14/04/2021)

- Search at the level of HLT Haemorrhages in EVDAS (DLP 14/04/2021) retrieved 5 cases in association with Covid-19 Janssen vaccine.
- All 5 were previously identified via a search at the level of SMQ Embolic and thrombotic events SMQ (i.e. co-reported with events of thrombosis).

SMQ Haematopoietic cytopenias (DLP: 14/04/2021)

- Search at the level of SMQ Haematopoietic cytopenias in EVDAS (DLP 14/04/2021) retrieved 8 cases in association with Covid-19 Janssen vaccine.
- Of these, 5 were previously identified via a search at the level of SMQ Embolic and thrombotic events SMQ (i.e. co-reported with events of thrombosis).
- The remaining 3 cases were concern consumer reports and include events of:
 - Platelet count decreased;
 - White blood cell count decreased;
 - Lymphocyte count decreased &granulocyte count increased
- Of the three reports one was subject to limited information and two were confounded+ subject to limited information.

3.1.3.1. Opinions of EMA neurology and haematology experts

Opinion of neurology expert (EMA)

Case reference	Expert opinion
Case 1	<p>Cerebral venous sinus thrombosis + Lobar haemorrhage + thrombocytopenia (18000) in a female aged between 18-28 non-smoker healthy person. It is remarkable that no oral contraceptives and no personal/familial history of clotting. The information on oral contraception/smoking status is relevant as they can both increase (synergic) risk for thrombosis.</p> <p>From the narrative, it looks like the course was unusually acute (headache + mental status changes on the same day after 16 days of vaccination). The diagnosis of CVST and L-H is done at the same time. In fact, the vomiting + mental status changes + seizures are probably due to L-H. Either the headache due to CVST was not there or it was not reported. It may be also the case that the thrombocytopenia was</p>

Case reference	Expert opinion
	<p>developed fast leading to the spontaneous L-H that dominated the clinical course.</p> <p>Outcome unknown but it can be understood that she was transferred while intubated-> Likely not recovered.</p>
Case 2	<p>Cerebral venous sinus thrombosis + Portal thrombosis + Pulmonary embolism + thrombocytopenia (120000) in a female aged between 19-29 healthy person. It is said overweight, but I assume not due to central obesity. Again, No oral contraceptives.</p> <p>From the narrative, this follows the more typical sub-acute course +7D of vaccine with a new and severe headache not responding to analgesics followed after some days by other symptoms in this case abdominal pain (no further CNS symptoms in this case). The subacute course should serve as an opportunity -> new headache in a person who has not regular headache + no improvement with analgesia is suspicious.</p> <p>Antibodies to platelet factor 4 (she was treated with heparin). Platelet count was reported to have <u>started</u> increasing <u>prior</u> to IVIG administration.</p> <p>Outcome recovering and she was released home.</p>
Case 4	<p>Cerebral venous sinus thrombosis + Hemispheric haemorrhage + thrombocytopenia (levels NA) in female aged between 38-48 with depression. Unknow status about prior pregnancies and personal/familial history of clotting. Prior treatments: Fluoxetine.</p> <p>The diagnosis encompasses two CNS findings: Hemispheric haemorrhage + Cerebral venous sinus thrombosis diagnosed at the same time (+11D) by neuroimaging following the cortical CNS symptoms.</p> <p>However, from the narrative, the most likely scenario is (1) Subacute course of the Cerebral venous sinus thrombosis-> Headache + 7D. It is unknown whether she sought for attention. Severity of headache is unknown // response to analgesia unknown as well. (2) Hemispheric haemorrhage -> worsening headache (due to mass effect= new bleeding) + hemiparesis. Of note main arteries were not primarily affected. No malformations. No aneurysms. Thrombocytopenia (unknown value) seems to be the plausible cause of a spontaneous haemorrhage</p> <p>Outcome: death</p>
Case 5	<p>Cerebral venous sinus thrombosis + thrombocytopenia (125000) in a female aged between 21-31 apparently healthy person.</p> <p>Subacute course (+6D) of a diffuse syndrome (Viral syndrome) followed by a headache (pain behind the eyes). No focal CNS signs. Petechiae.</p> <p>Outcome: not recovered.</p>
Case 6	<p>Cerebral venous sinus thrombosis + Hemispheric haemorrhage + in a female aged between 31-41 apparently healthy person. No concomitant medication. Level of platelets unknown.</p> <p>From the narrative, this follows the more typical sub-acute course +7D of vaccine with a new headache only followed later by a CNS focal sign (aphasia) after another week (+14-16years).</p>

Case reference	Expert opinion
	<p>Treated with heparin.</p> <p>Again, the diagnosis of Hemispheric haemorrhage + Cerebral venous sinus thrombosis was likely done at the same time but the narrative suggests a pattern similar to another case. Cerebral venous sinus thrombosis (headache only) + Hemispheric haemorrhage (aphasia)</p> <p>Outcome unknown.</p>
New case lit publication.	<p>Cerebral venous sinus thrombosis + Hemispheric haemorrhage + Splanchnic/hepatic/splenic thrombosis + thrombocytopenia (13000) + DIC in a female aged between 41-51 apparently healthy person.</p> <p>Narrative +11 D abdominal pain + thrombocytopenia + schistocytes. After the abdominal pain, the patient presented new onset of headache (CVST). She was treated with heparin and developed a Hemispheric haemorrhage</p> <p>Treated with IgIV. -> Platelet level increased.</p> <p>Outcome remarkable ill</p>

Opinion of haematology expert in EMA

Case Reference	Expert opinion
Case 1:	A male aged between 18-28 without significant prior medical history. Received vaccine and had inflammatory syndrome the same day (fever, myalgia, fatigue, nausea, headache) that improved within 3 days (except headache). 9 days after vaccination he had a similar inflammatory syndrome (plus abdominal pain, sore throat, chills and rhinorrhoea) and the pt took ibuprofen. Repeated COVID tests were negative. Symptoms improved except headache. 18 days after vaccination the patient had seizures. CT scans confirmed cerebral haemorrhage + CVST (2 days later). He also had moderate thrombocytopenia (65). CVST + cerebral bleeding + thrombocytopenia suggests aHIT-like syndrome
Case 2:	A female aged between 52-62 with multiple co-morbidities, 11 days after the vaccination the patient had bruising and leg oedema, with a diagnose of severe thrombocytopenia (15) and extensive DVT → IVC filter placed. The next day the patient developed arterial thrombosis as well (superficial femoral and iliac arteries) requiring thrombectomy + stent. The thrombotic events are not unusual in themselves (i.e. frequent locations), but the coexistence of venous + arterial thrombosis + thrombocytopenia is unusual and consistent with aHIT-like syndrome
Case 3:	A female aged between 38-48 with prior medical history including depression. 1 wk after vaccination developed headache and hemiparesis. CT revealed severe cerebral haemorrhage + CVST, leading to brain herniation and death. Thrombocytopenia is also mentioned (severity unknown). The coexistence of CVST + bleeding + thrombocytopenia is unusual and consistent with aHIT-like syndrome.
Case 4:	A female aged between 18-28,, with no prior medical history. 2 wks after vaccination she developed headache, vomiting and altered mental status. CT revealed CVST + intracranial bleeding + severe thrombocytopenia (18). The pt eventually developed seizures → (sedated), requiring anticoagulants, platelet transfusions and thrombectomy. The case is consistent with aHIT-like syndrome
Case 5:	A female aged between 19-29, with no prior medical history (overweight but healthy). 1 wk after vaccination she developed headache, and 2 wks

Case Reference	Expert opinion
	after vaccination abdominal pain was added. Imaging tests revealed CVST + portal vein thrombosis + PE + mild thrombocytopenia (120). PF4 Abs+ → heparin stopped and IVIg initiated + oral anticoagulants. Platelets improved upon heparin discontinuation (+ IVIg). The case is consistent with aHIT-like syndrome
Case 6:	A female aged between 31-41, with no prior medical history. 9 days after vaccination she developed headache followed by aphasia → intracranial bleeding + CVST. Platelets not mentioned. It could be aHIT, but platelets unknown.
Case 7:	A female aged between 41-51, with no prior medical history. 11 days after vaccination she presented with abdominal pain. Blood tests revealed severe thrombocytopenia (13) but also signs of DIC (schistocytes, low fibrinogen, prolonged aPTT, increased DD). Imaging studies revealed SVT. Headache also appeared → CVST also diagnosed. Heparin did not seem to improve matters and PF4 Abs were positive (ELISA) → heparin stopped and IVIg + argatroban initiated → improvement in platelet count. This is a very severe case of aHIT-like syndrome, including SVT + CVST + DIC.
Case 8:	A female aged between 21-31 with no prior medical history. 1 day after vaccination she developed severe inflammatory syndrome (fever, rigors, myalgia). 11 days after vaccination she noted bruising, leg swelling and syncope → CVST + DVT + thrombocytopenia (severity unknown. This is suggestive of aHIT-like syndrome.

PRAC Rapporteur comment:

Based on the EVDAS search, seven cases of interest from the SMQ Embolic and thrombotic events were found; these are included in section 3.1.2 and further discussed there. It is assumed that the other reports (26/33) that were not deemed of interest did not include any embolic and thrombotic events with concomitant thrombocytopenia. Notably, not only unusual locations of thrombi are of interest for this signal but any thrombosis in any location in which thrombocytopenia is reported should be included among cases of interest.

For the SMQs Haemorrhages and Haematopoietic cytopenias and the HLT Thrombocytopenia, no new cases were identified in which there was sufficient information to suspect a relation to the Covid-19 Janssen vaccine (excluding cases with confounding).

The opinions of the EMA neurology and haematology experts are fully concurred; however, the Rapporteur proposes to avoid the terminology a-HIT-like for the further review since both the knowledge and the terminology of the combination of thrombosis and thrombocytopenia following COVID-19 vaccination are rapidly evolving. The course in one of the cases of very acute onset of illness with severe thrombocytopenia concomitant with CVST and intracerebral bleeding is found worrisome; for the other reports, a more sub-acute course is noted which could enable medical attention and treatment in time to avoid further deterioration. Outcome is unknown or not yet recovering in the majority of cases, with only two cases reported to be recovering so far.

3.1.4. PRAC Rapporteur discussion updated

At the approval of the CMA for Covid-19 Vaccine Janssen on 11 March 2021, "Venous thromboembolism" was included as important potential risk in the RMP, due to a numerical imbalance of venous thromboembolism observed in the main clinical study, VAC31518COV3001.

On 12 March 2021, a signal procedure regarding thrombotic and embolic events was started for another adenovirus vector Covid-19 vaccine, which recently has been finalised⁵. During that assessment, very rare cases showing a combination of thrombosis and thrombocytopenia, and in some cases accompanied by bleeding, have gained particular attention.

For the Covid-19 Vaccine Janssen, a signal procedure was started at the PRAC meeting held on 6-9 April 2021, due to at that time in total four cases with such unusual clinical characteristics of thrombosis in combination with thrombocytopenia, occurring after vaccination with this vaccine.

On 15 April 2021, the MAH responded to questions, and the PRAC rapporteur also received further information from the EMA regarding data in EudraVigilance. The latter was updated on 17 April 2021.

The PRAC Rapporteur assessment to be sent to the PRAC on 19 April 2021, is the first step in the further evaluation of this signal. As agreed with the EMA on 15 April 2021, the aim of this first step is to review of cases of unusual thrombosis in combination with thrombocytopenia, and taking experience gained from a recently finalised signal evaluation⁶, and based on that, evaluate the need for updates of the product information, as well as the need for additional risk minimisation measures. For the AR to be sent out on 19 April, 17 April 2021 is the cut-off for new data.

A more in-depth evaluation of any mechanistic aspects, as well as of the pharmacovigilance plan, and thereby the responses to Q7, will be undertaken in the second step of the assessment of the MAH responses. In addition, review of laboratory results from clinical studies and post-marketing on conditions not predominantly related to the combination of thrombosis and thrombocytopenia will be assessed in more depth in the second step as well.

Post marketing exposure

Regarding cumulative (US) post-marketing exposure, the MAH refers to the Center of Disease Control (CDC), which reports a total of 7,688,499 doses of the COVID-19 vaccine Janssen being used as of 15 April 2021.

As of 12 April 2021 (of a total of 6,453,740 doses), it is estimated, that approximately 66.5% of recipients of the Janssen COVID-19 vaccine were in the 18 to 59 -year age group and approximately 33.5% of recipients were in the ≥60-year age group. However, this estimation appears based on use of all vaccines, and is therefore uncertain.

The MAH has also specified the approximate number of individuals being within the 21-day post vaccination period as of 13 April; namely 2,489,153 individuals. Although not entirely clear what is meant, review of the cumulative presentation above, this exact number of subjects appear to have been more than three weeks ago, and thus possibly having past the main risk window for this unusual clinical event.

By end of March 2021, the clinical study exposure is estimated to about 286 000 subjects with the Covid-19 Vaccine Janssen, and more than 200 000 individuals with the Ad26 platform. In the evaluation supporting the CMA on 11 March 2021, approximately 27,200 vaccinated subjects had been assessed in clinical studies for death and SAEs⁷. Since the additional clinical study data referred to by the MAH have not been assessed by EMA, the safety data base within the CMA is most relevant one.

⁵ https://www.ema.europa.eu/en/documents/prac-recommendation/signal-assessment-report-embolic-thrombotic-events-smq-covid-19-vaccine-chadox1-s-recombinant_en.pdf

⁶ https://www.ema.europa.eu/en/documents/prac-recommendation/signal-assessment-report-embolic-thrombotic-events-smq-covid-19-vaccine-chadox1-s-recombinant_en.pdf

⁷ EPAR for [COVID-19 Vaccine Janssen, INN-Ad26.COV2-S, recombinant \(europa.eu\)](https://www.ema.europa.eu/en/medicines/human/EPAR/covid-19-vaccine-janssen/covid-19-vaccine-janssen.htm)

Laboratory evaluations

Questions (Q2, Q3, parts of Q4) were raised regarding laboratory results from clinical studies and from post-marketing data, regarding e.g. thrombocytopenia. Further data presentation is asked for to allow final assessment of whether thrombocytopenia without thrombosis or bleeding, may be caused by the Covid-19 vaccine Janssen. Also, further laboratory data are warranted for cases with thromboembolic events in the clinical studies, to allow for a more precise assessment of frequency of thrombotic thrombocytopenia.

Thrombosis

Cumulative reviews have also been presented with respect to thrombosis solely, from clinical studies as well as from post marketing experience. These show a numerical imbalance in the clinical trials with regards to overall thromboembolic events (35 individuals who received the vaccine, 27 placebo, 20 still blinded). In the phase 3b study in South Africa, five serious cases have been reported with thromboembolic events. There are currently 27 post-marketing case reports of thromboembolism; 22 of these occurred within 28 days following vaccination. Laboratory data to conclude on any concomitant thrombocytopenia are however missing in the majority of cases. There are 7 cases of cerebral vein and sinus thrombosis (CVST); six of these with concomitant thrombocytopenia (see below) and one in whom platelet counts are not reported.

Thrombosis with thrombocytopenia

Regarding cases with thrombotic/ thromboembolic events and low platelets, there is a total of eight well described cases and one potential study case. There is one very well described case from study 3001, one additional potential case in study 3001 (see assessment of Q2) as well as 7 additional post marketing cases. Seven of these had CVST; one had concomitant arterial thrombosis and DVT and one had DVT. Three of the cases with CVST had additional thromboses including splanchnic vein thromboses, pulmonary embolism and DVT. One case was fatal. Age ranges from 18-63 years (excluding the potential clinical study case for whom very little information is given, age ranges from 18-59 years). Seven of the 8 well described cases are female (all post-marketing). Outcome is unknown or not yet recovering in the majority of cases, with only two cases reported to be recovering so far.

It is unclear if treatment with heparin could be used in cases with thrombotic thrombocytopenia following COVID-19 vaccination. The antibodies that are considered to be involved in this syndrome (anti-PF4) are different from those in HIT (heparin-induced thrombocytopenia). Currently, it is not considered sufficiently justified that heparin must be avoided (see Rapporteur's comment in section 3.1.2 for a more detailed discussion).

O/E analyses

The O/E analysis submitted by the MAH is based on very limited data since CVST in combination with thrombocytopenia is an extremely rare medical condition, and reported cases so far are few. Also, some incorrect data are identified among the few cases included. Nevertheless, despite the use of some incorrect data, the provided O/E analysis shows a clear signal of increased risk for CVST with thrombocytopenia in female subjects aged <64 years compared to what can be expected in this population.

Causality discussion

Across the non-clinical studies with Ad26.COVID.S and other Ad26-based vaccines there were no observations indicating an adverse vaccine-related effect on thrombosis and/or thrombocytopenia. The

study findings were generally limited to mild and transient effects expected from a local and general inflammatory reaction subsequent to vaccination. Given the very low incidence of the thromboembolic events or coagulopathies associated with Ad26.COVS.S, likely of multifactorial aetiology, it is not unexpected that no signals are observed in healthy animals.

Taken together, the non-clinical data with Ad26.COVS.S and other Ad26-based vaccines provide no further understanding on potential causal relationship between vaccination with Covid-19 vaccine Janssen and the events of thrombosis and thrombocytopenia.

The MAH concludes that the number of thrombotic events with thrombocytopenia are low and there is insufficient data to conclude a definitive causal association with the Ad26.COVS.S vaccine. This is not supported. The PRAC Rapporteur considers that a causal association is sufficiently supported based on the following:

- The observed cases with CVST and concomitant thrombocytopenia represent clinical entities that are extremely rare in an overall population. Although CVST is well-known to occur predominantly in younger females, often related to hormonal factors such as pregnancy, puerperium or oestrogen-containing medications, concomitant thrombocytopenia is not part of any usual clinical picture for CVST.
- The findings of positive anti-PF4-antibodies in several cases, in one case with documented non-existing anti-PF4-antibodies before vaccination, suggest that the clinical picture is likely due to these antibodies. A similarity with HIT (heparin-induced thrombocytopenia) is evident based on the clinical picture; however, there is no known exposure to heparin before the events of thrombosis and thrombocytopenia in any of the reported cases, and in one case, a screening test for anti-PF4/heparin antibodies by latex-enhanced immunoassay was negative whereas results of a PF4/polyanion ELISA were strongly positive.
- In several cases, there was no apparent risk factor for CVST or other thrombosis or for thrombocytopenia. For a picture of thrombotic thrombocytopenia with positive anti-PF4-antibodies, this is similar to "spontaneous HIT" which is characterized by a similar clinical and laboratory picture in patients without exposure to heparin; however, some trigger is warranted in such cases (such as surgery, infectious disease etc). The only common trigger in these cases is the vaccination with the Ad26.COVS.S vaccine.
- The timing of events is congruent for all of the cases, with symptoms of thrombosis and/or thrombocytopenia occurring within three weeks from the vaccination. This is also in line with what is known for HIT type II and spontaneous HIT as well as for the thrombotic thrombocytopenia related to another adenoviral vector COVID-19 vaccine.
- Extensive work-up excluding other potential causes of thrombosis and/or thrombocytopenia has been provided for two of the cases. This includes antiphospholipid antibodies, homocysteine, Factor VIII, antithrombin, protein C, protein S, Factor V Leiden, prothrombin gene mutation, hepatitis/HIV, ADAMTS 13, PNH and JAK2. The only abnormality that could explain the clinical picture in these cases was positive anti-PF4-antibodies.

Furthermore, it remains unknown how many cases with thrombosis and concomitant thrombocytopenia that occurred in the clinical trials with the Ad26.COVS.S vaccine. An imbalance was noted with regards to venous thromboembolism in the initial assessment of these studies, with more cases in the vaccine vs the placebo group. However, platelet levels have not been provided for more than very few of these

cases. In addition, the post-marketing exposure to COVID-19 vaccine Janssen has increased rapidly within recent weeks and thus, the numbers at risk for having developed these symptoms does not correspond to actual doses given.

Based on the above, the PRAC Rapporteur considers that 'thrombotic thrombocytopenia' should be included in the product information section 4.4 and 4.8.

Regulatory action

The MAH concludes that there is insufficient evidence to conclude on a causal relationship with the vaccine, but strongly supports making vaccinees aware of the signs and symptoms of this very rare event, as well as recommendations to health care professionals to ensure the early and correct diagnosis and treatment of the patients and reporting of the events. Based on that they propose updates of section 4.4 of the SmPC, and of section 2 of the PL. This is supported, although the proposed wording needs revision. It is currently unknown if heparin could be used in patients with thrombotic thrombocytopenia following COVID-19 vaccination; however, the recommendation to consult expertise for diagnosing and treatment decisions in patients with thrombotic thrombocytopenia is strongly supported.

As outlined above, following evaluation of the currently available data, the PRAC rapporteur is of the opinion that there is sufficient evidence to, with a reasonable possibility, conclude *thrombosis in combination with thrombocytopenia* being a very rare adverse drug reaction of the Covid-19 vaccine Janssen. Therefore, update of section 4.8 of the SmPC is also warranted.

Regarding additional risk minimisation measures, a DHPC is warranted to inform health care professionals. Draft proposal is attached.

Evaluation of the RMP, including the pharmacovigilance plan, will be undertaken in the next step of this signal procedure.

For an oral explanation at the PRAC; the MAH is asked to address the proposed updates of the product information, the proposed DHPC, based on the available data.

Furthermore, there are a number of issues that need to be further clarified by the MAH, as outlined in the RSI below.

3.1.5. Rapporteur's proposed recommendation

The PRAC rapporteur recommends updates of section 4.4 and 4.8 of the SmPC, and of section 2 and 4 of the Package leaflets. Furthermore, a DHPC is proposed (see Annex).

The following wording is proposed, based on the MAH's proposal.

Section 4.4

Thrombocytopenia and coagulation disorders

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

venous thrombosis at unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis concomitant with thrombocytopenia. Fatal outcome has been reported. These cases occurred within the first three weeks following vaccination, and mostly in women under 60 years of age.

Healthcare professionals should be alert to the signs and symptoms of thromboembolism and/or thrombocytopenia. Those vaccinated should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg swelling, or 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.

Since management may be different than usual medical practice for thromboembolic events if patients present with concomitant thrombocytopenia, healthcare professionals should consult applicable guidance and/or consult specialists (e.g., haematologists, specialists in coagulation) to diagnose and treat this condition.

Risk of bleeding with intramuscular administration

Section 4.8

In the Table

SOC: Vascular disorders: Thrombosis in combination with thrombocytopenia*

* *Severe and very rare cases of thrombosis in combination with thrombocytopenia have been reported post-marketing. These included venous thrombosis such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis (see section 4.4).

Frequency: Very rare

Package leaflet

Section 2

[...]

As with any vaccine, vaccination with COVID-19 Vaccine Janssen may not fully protect all those who receive it. It is not known how long you will be protected.

Blood disorders

A combination of blood clots and low levels of 'platelets' (cells that help blood to clot) in the blood has been observed very rarely following vaccination with COVID-19 Vaccine Janssen. This includes severe cases with blood clots and, in unusual locations, such as the brain and liver, in some cases in combination with bleeding. These cases occurred within the first three weeks following vaccination and occurred mostly in women below 60 years of age. Fatal outcome has been reported.

Seek immediate medical attention, if you experience severe or persistent headaches or blurred vision, unexplained skin bruising beyond the site of vaccination which appear a few days after vaccination, develop shortness of breath, chest pain, leg pain or swelling, or persistent abdominal pain. Inform your health care provider that you have recently received COVID-19 Vaccine Janssen.

Section 4

Very Rare (may affect up to 1 in 10,000 people) - blood clots often in unusual locations (e.g. brain, liver) in combination with low level of blood platelets

3.1.6. Issues for an oral explanation at the PRAC

Please address the following points, based on relevant data:

- Proposed updates of the product information
- Proposal to send out a DHPC
- Explain why some of the requested information has not been submitted as asked for, and comment on if / how this will be improved in the future.

3.1.7. Request for supplementary information

3.1.7.1. Immediate RSI (to be submitted by 19 April 2021, at 20:00)

- Based on Response Table 6, there appears to be one additional clinical study case (study 3001) with concomitant thrombosis and thrombocytopenia. Full details on this case including a complete CIOMS report should be provided, along with a discussion on why this case was not included in the presentation of clinical study cases of concomitant thrombosis and thrombocytopenia.

3.1.7.2. Subsequent RSI

- For a case in study 3001, it should be clarified when the tests for PF4 antibodies actually were performed, as well as reported to the investigator, and when the sponsor/MAH became aware of these results.
- Questions (Q2, Q3, parts of Q4) were raised regarding laboratory results from clinical studies and from post-marketing data, regarding e.g. thrombocytopenia. Further data presentation is asked for to allow final assessment of whether thrombocytopenia without thrombosis or bleeding, may be caused by the Covid-19 vaccine Janssen.

In that presentation, the cases of 'haematopoietic cytopenias' in the clinical trials should be further detailed specifically addressing whether any of these are attributable to thrombocytopenia.

- Laboratory data, primarily CBC/platelet counts remain missing for the majority of cases with thromboembolism in both the clinical trials as well as post-marketing. Additional information on CBC/platelet levels are expected to be presented for these cases, including all cases with thromboembolic events regardless of location and severity.
- For COVID3012 SISONKE, an open label single arm Phase 3b study in South Africa, there were five cases of thromboembolism that occurred between less than 24 hours and 23 days after vaccination. Normal platelet counts have been provided for only one of these; for one case, pulmonary embolism was diagnosed post mortem and is thus not expected to provide further laboratory testing. For the remaining three cases, platelet levels are expected to be submitted.

- In the Responses Table 5, there were 13 subjects with 'AEs of interest' of venous or arterial thrombosis in the clinical studies. There appears to be an additional 19 or 22 cases (different numbers appear in the Responses) with events of thromboembolism in the clinical studies. The MAH should summarise the main reasons for not including the additional cases among AEs of interest. Notably, laboratory data (primarily CBC/platelet counts) are expected for all cases.
- For the O/E analysis, it is noted that the the 18-28 male from the phase III study that was reported with CVST and thrombocytopenia has not been included, in addition, the 52-62 year-old female subject included in this analysis had thrombosis located in the legs but not CVST. Revised, and updated analyses, with the most current amount of data are requested.
- It is not clear which cut-off date that was used for post-marketing data in the O/E analysis, which should be provided. Furthermore, the MAH should provide the time frame that was used to calculate the expected rate of these rare events of CVST in combination with thrombocytopenia.
- One case of capillary leak syndrome was reported among cases described for this signal. This condition should be followed up in monthly safety summary reports.

3.1.8. Comments from other PRAC members and MAH

Updated information on the cases with CVST and concomitant thrombocytopenia has been provided after the circulation of the preliminary AR; these data have been incorporated into sections 3.1.2, 3.1.3 and 3.1.4 (highlighted).

Member state 1 comments

We generally endorse the assessment report and the proposed recommendation.

However,

1) considering sparse data, the statement "These cases occurred [...] mostly in women under 60 years of age" (used throughout in PI and DHPC) does not allow for defining age-based risk groups and may be omitted

2) the TTO's stated in 2.1 "Time to onset included 11 days (n=2) and 19 days (n=1)", seems at odds with the case narratives presented (Case 1: 7 days?, Case 2: 11 days, Case 3: CNS symptoms from day 11).

PRAC Rapporteur Comment

We agree that the data are sparse, however, the clear trend of cases reported being mostly women under 60 years of age is considered of high relevance for prescribers (this wording is also proposed in order to avoid different wordings as compared to another covid-19 adenoviral vector vaccine).

For section 2.1, this was part of the signal validation with limited information at hand. Notably, the first three cases in the table 1A in section 3.1.3 that shows a summary over cases in Eudra Vigilance are not the same cases as those that were available at the signal validation stage (the three validation cases are Cases no 2, 5 and 7 in the EudraVigilance table).

Member state 2 comments

We overall support the PRAC Rapp's assessment however we propose some changes in the proposed wording in the Section 4.4. of the SmPC: We propose not to include the recommendation on the treatment of combination of thrombosis and thrombocytopaenia as specific treatment for this condition is not known at this time. Additionally, the term „venous“should be deleted from the first sentence as arterial thrombosis is also stated as one example of unusual type of thrombosis. The last sentence in the proposed wording was probably copied by mistake.

Section 4.4

Thrombocytopenia and coagulation disorders

A combination of venous thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with COVID-19 Vaccine Janssen. This includes venous thrombosis at unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis concomitant with thrombocytopenia. Fatal outcome has been reported. These cases occurred within the first three weeks following vaccination, and mostly in women under 60 years of age.

Healthcare professionals should be alert to the signs and symptoms of thromboembolism and/or thrombocytopenia. Those vaccinated should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg swelling, or 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.

~~Since management may be different than usual medical practice for thromboembolic events if patients present with concomitant thrombocytopenia, healthcare professionals should consult applicable guidance and/or consult specialists (e.g., haematologists, specialists in coagulation) to diagnose and treat this condition.~~

PRAC Rapporteur Comment

We fully agree to delete the word 'venous' from the first sentence in the SmPC section 4.4.

For the proposed recommendation on management, we consider that it is of high relevance to inform prescribers that these cases will likely warrant special considerations and early involvement with specialists. Some amendments are however proposed, see also comment from BE and updated proposal for section 4.4 below (AR section 3.4).

The last sentence has been added as a new subheading, for clarity in relation to the current text in section 4.4.

Member state 3 comments

Overall, **member state 3** agrees with the high-quality assessment report and conclusions, also considering the short time frame and some issues in data presentation.

Member state 3 fully agrees that available data are sufficient to support a plausible causal association and the inclusion of thrombosis in combination with thrombocytopenia in section 4.8 of the SmPC.

Member state 3 has some additional comments on proposed update of the product information (**in bold**):

SmPC

Section 4.4

Thrombocytopenia and coagulation disorders

A combination of venous thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with COVID-19 Vaccine Janssen. This includes **severe cases of venous thrombosis at unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis concomitant with thrombocytopenia. Fatal outcome has been reported. These cases occurred within the first three weeks following vaccination, and mostly in women under 60 years of age.**

Healthcare professionals should be alert to the signs and symptoms of thromboembolism and/or thrombocytopenia. Those vaccinated should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg swelling, or 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.

~~Since management may be different than usual medical practice for thromboembolic events if patients present with concomitant thrombocytopenia.~~ **Thrombosis in combination with thrombocytopenia requires specialised clinical management.** Healthcare professionals should consult applicable guidance and/or consult specialists (e.g., haematologists, specialists in coagulation) to diagnose and treat this condition.

Section 4.8

In the Table

SOC: Vascular disorders: Thrombosis in combination with thrombocytopenia*

* *Severe and very rare cases of thrombosis in combination with thrombocytopenia have been reported post-marketing. These included venous thrombosis such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis (see section 4.4).

Frequency: Very rare

Package leaflet

Section 2

[...]

As with any vaccine, vaccination with COVID-19 Vaccine Janssen may not fully protect all those who receive it. It is not known how long you will be protected.

Blood disorders

A combination of blood clots and low levels of 'platelets' (cells that help blood to clot) in the blood has been observed very rarely following vaccination with COVID-19 Vaccine Janssen. This includes severe cases with blood clots and, in unusual locations, such as the brain **and** liver, **bowel and spleen**, (as reported in case 5) in some cases in combination with bleeding. These cases occurred within the first three weeks following vaccination and occurred mostly in women below 60 years of age. Fatal outcome has been reported.

Seek immediate medical attention, if you experience severe or persistent headaches or blurred vision, unexplained skin bruising beyond the site of vaccination which appear a few days after vaccination, develop shortness of breath, chest pain, leg pain or swelling, or persistent abdominal pain. Inform your health care provider that you have recently received COVID-19 Vaccine Janssen.

Section 4

Very Rare (may affect up to 1 in 10,000 people) - blood clots often in unusual locations (e.g. brain, liver, **bowel, spleen**) (as reported in case 5) in combination with low level of blood platelets

PRAC Rapporteur Comment

The proposed amendments are supported and have been included in the updated proposal for the product information, see below (AR section 3.4)

Member state 5 Comments

Member state 5 supports the PRAC RAPP recommendations and considers that a plausible causal association is sufficiently supported based on the data provided. Therefore, updates of section 4.4 and 4.8 of the SmPC, section 2 and 4 of the Package leaflet is appropriate.

PRAC Rapporteur Comment

Noted

Member state 6 comments

- We endorse PRAC Rapporteur's Signal AR, however, have one additional remark. We consider that a stratified analysis by gender of the populations exposed would be helpful for further interpretation of the data. A request for such analysis by gender could be added to the 2nd RSI.

- Comments on the proposed draft DHPC were attached.

- We have no additional comments on the communication plan.

PRAC Rapporteur Comment

The suggestion to ask for a stratified analysis by gender of the populations exposed is endorsed; the RSI has been updated accordingly.

Some comments on the DHPC are endorsed, but details to be further discussed.

Member state 7 comments

In general, we agree with the case descriptions and agree that a causal association is sufficiently supported by the data submitted.

The request for supplemental information is supported.

We agree with the proposed wording in SmPC and PIL, being in line with that previously included for the AstraZeneca vaccine, in particular the wording in SmPC 4.4.

In SmPC 4.4 the following sentence is added: *Risk of bleeding with intramuscular administration*. We suggest adding the common phrase used for other vaccines for im 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.

We propose the current potential risk of Venous thromboembolism to be upgraded to identified risk in the RMP.

We have no objections to the proposed DHPC and the proposed communication plan.

PRAC Rapporteur Comment

For the intramuscular administration, what is new is the subheading "Risk of bleeding with intramuscular administration". Other than that, the text proposed is already included in section 4.4.

For the RMP, this will be further assessed within the next round of this procedure.

Member state 8 comments

Overall, we agree with the assessment report and recommendation provided by the rapporteur. Please, find attached **Member state 8** comments to the DHPC.

PRAC Rapporteur Comment

Noted; for the DHPC, see separate document.

Member state 9 comments

Overall, **Member state 9** endorses the PRAC Rapporteur's assessment report and conclusion.

Moreover, we strongly support that further details are needed on cases of 'haematopoietic cytopenias' from the clinical trials, since it is considered relevant to investigate the risk of thrombocytopenia, also in light of the imbalance observed for adenovirus platform ["Platelet count decrease was observed following 70 out of 4,105 Ad26 doses (1.7%) and 7 out of 719 placebo doses (1.0%)"].

Conclusions on this issue might be reflected in the product information, as appropriate.

Some comments to the proposed DHPC have been also formulated (see attachment).

PRAC Rapporteur Comment

Noted; for the DHPC, see separate document.

3.1.9. Response from MAH (submitted 19 April 2021)

MAH response

Reference is made to the PAM-SDA procedure related to the signal of Embolic and Thrombotic events (SMQ) for COVID-19 Vaccine (Ad26.COVID-S [recombinant]) - COVID-19 Vaccine Janssen (EPITT ref. No.

19689). Further to the PRAC AR, proposed PRAC EUIPI and DHCP letter received today 19th April 2021, I am hereby providing you the below documentation:

- MAH's proposed DHCP letter in Track changes
- MAH proposed EUIPI, clean and Track changes version
- CIOMS report for one Subject

The response to question below will be submitted shortly, today:

"Based on Response Table 6, there appears to be one additional clinical study case (study 3001) with concomitant thrombosis and thrombocytopenia. Full details on this case including a complete CIOMS report should be provided, along with a discussion on why this case was not included in the presentation of clinical study cases of concomitant thrombosis and thrombocytopenia".

As requested, the response to the additional questions listed in the PRAC AR will be submitted by April 23rd, 2021.

Revised wording for PI

The MAH has accepted the wording for section 4.4 as outlined in the PRAC Rapp's AR of 19 April, but has also proposed additional wording (see below). For section 4.8, the wording proposed by the PRAC rapporteur has been agreed, without revision.

Section 4.4

A combination of venous thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely (with an approximate incidence of 1-2 cases per 1 million vaccinations after the first 7.9 million vaccinations) following vaccination with COVID-19 Vaccine Janssen. This includes venous thrombosis at unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis as well as arterial thrombosis, concomitant with thrombocytopenia. Fatal outcome has been reported. These cases occurred within the first three weeks following vaccination, and mostly in women under 60 years of age.

Healthcare professionals should be alert to the signs and symptoms of thromboembolism and/or thrombocytopenia. Those vaccinated should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg swelling, or 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.

Since management may be different than usual medical practice for thromboembolic events if patients present with concomitant thrombocytopenia, healthcare professionals should consult applicable guidance and/or consult specialists (e.g., haematologists, specialists in coagulation) to diagnose and treat this condition.

MAH comment: The Company proposes to include the frequency rate to clarify the very rarely statement, as this could be interpreted as 1 in 10,000, which would be an over estimate; namely by adding (with an approximate incidence of 1-2 cases per 1 million vaccinations after the first 7.9 million vaccinations).

PRAC rapporteur comment: The MAH has accepted the proposed wording for section 4.4, as outlined in the AR of 19 April 21. In addition, they proposed to add an approximate incidence (with an approximate incidence of 1-2 cases per 1 million vaccinations after the first 7.9 million vaccinations).

This is not agreed. The proposed incidence is very uncertain and is likely an underestimation; see also PRAC Rapp's comments to Q8 above.

The PRAC Rapp's proposal of 19 April for section 4.8, and the PIL, both section 2 and 4 is agreed by the MAH.

Furthermore, the same wording as in 4.4 regarding awareness, signs and symptoms is added to a section on 'The following information is intended for healthcare professionals only:', which is endorsed. It should reflect the finally agreed wording, accordingly.

DHPC

PRAC rapporteur comment: For the DHPC, the MAH proposes to add the frequency as proposed for the SmPC, which is not agreed. Some other smaller comments have also been proposed. These will be considered together with other comments received from MSs

3.1.10. Updated rapporteur's proposed recommendation

The following wording is proposed, based on the MAH's proposal and comments from MSs.

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 COVID-19 Vaccine Janssen. This includes severe cases of venous thrombosis at unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis concomitant with thrombocytopenia. Fatal outcome has been reported. These cases occurred within the first three weeks following vaccination, and mostly in women under 60 years of age.

Healthcare professionals should be alert to the signs and symptoms of thromboembolism and/or thrombocytopenia. Those vaccinated should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg swelling, or 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.

Thrombosis in combination with thrombocytopenia requires specialised clinical management. Healthcare professionals should consult applicable guidance and/or consult specialists (e.g., haematologists, specialists in coagulation) to diagnose and treat this condition.

Risk of bleeding with intramuscular administration

Section 4.8

In the Table

SOC: Vascular disorders: Thrombosis in combination with thrombocytopenia*

* *Severe and very rare cases of thrombosis in combination with thrombocytopenia have been reported post-marketing. These included venous thrombosis such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis (see section 4.4).

Frequency: Very rare

Package leaflet

Section 2

[...]

As with any vaccine, vaccination with COVID-19 Vaccine Janssen may not fully protect all those who receive it. It is not known how long you will be protected.

Blood disorders

A combination of blood clots and low levels of 'platelets' (cells that help blood to clot) in the blood has been observed very rarely following vaccination with COVID-19 Vaccine Janssen. This includes severe cases with blood clots, including in unusual locations such as the brain, liver, bowel and spleen, in some cases in combination with bleeding. These cases occurred within the first three weeks following vaccination and occurred mostly in women below 60 years of age. Fatal outcome has been reported.

Seek immediate medical attention if you experience severe or persistent headaches or blurred vision, unexplained skin bruising beyond the site of vaccination which appear a few days after vaccination, develop shortness of breath, chest pain, leg swelling, or persistent abdominal pain. Inform your health care provider that you have recently received COVID-19 Vaccine Janssen.

Section 4

Very Rare (may affect up to 1 in 10,000 people) - blood clots often in unusual locations (e.g. brain, liver, bowel, spleen) in combination with low level of blood platelets

Section 6

The following information is intended for healthcare professionals only:

[...]

- 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, or 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. Thrombosis in combination with thrombocytopenia requires specialised clinical management. Healthcare professionals should consult applicable guidance and/or consult specialists (e.g., haematologists, specialists in coagulation) to diagnose and treat this condition.

3.1.10.1. Subsequent RSI

- For a case in study 3001, it should be clarified when the tests for PF4 antibodies actually were performed, as well as reported to the investigator, and when the sponsor/MAH became aware of these results.
- Questions (Q2, Q3, parts of Q4) were raised regarding laboratory results from clinical studies and from post-marketing data, regarding e.g. thrombocytopenia. Further data presentation is asked for to allow final assessment of whether thrombocytopenia without thrombosis or bleeding, may be caused by the Covid-19 vaccine Janssen.

In that presentation, the cases of 'haematopoietic cytopenias' in the clinical trials should be further detailed specifically addressing whether any of these are attributable to thrombocytopenia.

- Laboratory data, primarily CBC/platelet counts remain missing for the majority of cases with thromboembolism in both the clinical trials as well as post-marketing. Additional information on CBC/platelet levels are expected to be presented for these cases, including all cases with thromboembolic events regardless of location and severity.
- For COVID3012 SISONKE, an open label single arm Phase 3b study in South Africa, there were five cases of thromboembolism that occurred between less than 24 hours and 23 days after vaccination. Normal platelet counts have been provided for only one of these; for one case, pulmonary embolism was diagnosed post mortem and is thus not expected to provide further laboratory testing. For the remaining three cases, platelet levels are expected to be submitted.
- In the Responses Table 5, there were 13 subjects with 'AEs of interest' of venous or arterial thrombosis in the clinical studies. There appears to be an additional 19 or 22 cases (different numbers appear in the Responses) with events of thromboembolism in the clinical studies. The MAH should summarise the main reasons for not including the additional cases among AEs of interest. Notably, laboratory data (primarily CBC/platelet counts) are expected for all cases.
- For the O/E analysis, it is noted that the 18-28 old male from the phase III study that was reported with CVST and thrombocytopenia has not been included, in addition, the 52-62 year-old female subject included in this analysis had thrombosis located in the legs but not CVST. Revised, and updated analyses, with the most current amount of data are requested.
- It is not clear which cut-off date that was used for post-marketing data in the O/E analysis, which should be provided. Furthermore, the MAH should provide the time frame that was used to calculate the expected rate of these rare events of CVST in combination with thrombocytopenia.
- A stratified analysis by gender of the populations exposed should be provided.
- One case of capillary leak syndrome was reported among cases described for this signal. This condition should be followed up in monthly safety summary reports.
- For the case with concomitant DVT and low platelet counts in a male study subject aged between 56-66 in study 3001, this case should be discussed in more detail, including a discussion on the laboratory findings at admission that indicate coagulopathy. In light of recent findings, a discussion on whether this could be a case of thrombotic thrombocytopenia related to the Covid-19 Vaccine Janssen should be provided. Any previous CBC/platelet counts in the medical history of this case should be provided.

3.1.11. Adopted PRAC recommendation

The PRAC has reviewed the available evidence on the occurrence of thromboembolic events following the administration of COVID-19 Vaccine Janssen, including data ascertained from spontaneous case reports identified in EudraVigilance, clinical trials and additional data from the MAH. The evaluation of the data revealed eight reports of interest, which included severe cases of venous thrombosis at unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis concomitant with thrombocytopenia. Fatal outcome has been reported. These cases occurred within the first three weeks following vaccination, and mostly in women under 60 years of age.

PRAC is of the view that there is sufficient evidence to conclude, with a reasonable possibility, that *thrombosis in combination with thrombocytopenia* can be considered as a very rare adverse drug reaction of the Covid-19 Vaccine Janssen.

Regarding additional risk minimisation measures, a DHPC is warranted to inform health care professionals.

The PRAC recommends that the MAH for Covid-19 Vaccine Janssen (Janssen-Cilag International NV) should submit a variation to amend the product information as described below (new text underlined/text to be removed with strikethrough):

Summary of Product Characteristics (SmPC)

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 COVID-19 Vaccine Janssen. This includes severe cases of venous thrombosis at unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis concomitant with thrombocytopenia. Fatal outcome has been reported. These cases occurred within the first three weeks following vaccination, and mostly in women under 60 years of age.

Healthcare professionals should be alert to the signs and symptoms of thromboembolism and/or thrombocytopenia. Those vaccinated should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg swelling, or 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.

Thrombosis in combination with thrombocytopenia requires specialised clinical management. Healthcare professionals should consult applicable guidance and/or consult specialists (e.g., haematologists, specialists in coagulation) to diagnose and treat this condition.

Risk of bleeding with intramuscular administration

Section 4.8

In the Table

SOC: Vascular disorders: Thrombosis in combination with thrombocytopenia*

* *Severe and very rare cases of thrombosis in combination with thrombocytopenia have been reported post-marketing. These included venous thrombosis such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis (see section 4.4).

Frequency: Very rare

Package leaflet

Section 2

[...]

As with any vaccine, vaccination with COVID-19 Vaccine Janssen may not fully protect all those who receive it. It is not known how long you will be protected.

Blood disorders

A combination of blood clots and low levels of 'platelets' (cells that help blood to clot) in the blood has been observed very rarely following vaccination with COVID-19 Vaccine Janssen. This includes severe cases with blood clots, including in unusual locations such as the brain, liver, bowel and spleen, in some cases in combination with bleeding. These cases occurred within the first three weeks following vaccination and occurred mostly in women below 60 years of age. Fatal outcome has been reported.

Seek immediate medical attention if you experience severe or persistent headaches or blurred vision, unexplained skin bruising beyond the site of vaccination which appear a few days after vaccination, develop shortness of breath, chest pain, leg swelling, or persistent abdominal pain. Inform your health care provider that you have recently received COVID-19 Vaccine Janssen.

Section 4

Very Rare (may affect up to 1 in 10,000 people) - blood clots often in unusual locations (e.g. brain, liver, bowel, spleen) in combination with low level of blood platelets

Section 6

The following information is intended for healthcare professionals only:

[...]

- 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, or 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. Thrombosis in combination with thrombocytopenia requires specialised clinical management. Healthcare professionals should consult applicable guidance and/or consult specialists (e.g., haematologists, specialists in coagulation) to diagnose and treat this condition.

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

The MAH for COVID-19 Vaccine Janssen (Janssen-Cilag International NV) is also requested to submit responses to the following list of questions:

1. For a case in study 3001, it should be clarified when the tests for PF4 antibodies actually were performed, as well as reported to the investigator, and when the sponsor/MAH became aware of these results.
2. Questions (Q2, Q3, parts of Q4) were raised regarding laboratory results from clinical studies and from post-marketing data, regarding e.g. thrombocytopenia. Further data presentation is asked for to allow final assessment of whether thrombocytopenia without thrombosis or bleeding, may be caused by the Covid-19 vaccine Janssen.
3. In that presentation, the cases of 'haematopoietic cytopenias' in the clinical trials should be further detailed specifically addressing whether any of these are attributable to thrombocytopenia.
4. Laboratory data, primarily CBC/platelet counts remain missing for the majority of cases with thromboembolism in both the clinical trials as well as post-marketing. Additional information on CBC/platelet levels are expected to be presented for these cases, including all cases with thromboembolic events regardless of location and severity.
5. For COVID3012 SISONKE, an open label single arm Phase 3b study in South Africa, there were five cases of thromboembolism that occurred between less than 24 hours and 23 days after vaccination. Normal platelet counts have been provided for only one of these; for one case, pulmonary embolism was diagnosed postmortem and is thus not expected to provide further laboratory testing. For the remaining three cases, platelet levels are expected to be submitted.
6. In the Responses Table 5, there were 13 subjects with 'AEs of interest' of venous or arterial thrombosis in the clinical studies. There appears to be an additional 19 or 22 cases (different numbers appear in the Responses) with events of thromboembolism in the clinical studies. The MAH should summarise the main reasons for not including the additional cases among AEs of interest. Notably, laboratory data (primarily CBC/platelet counts) are expected for all cases.
7. For the O/E analysis, it is noted that the 18-28-year-old male from the phase III study that was reported with CVST and thrombocytopenia has not been included, in addition, the 52-62 year-old female subject included in this analysis had thrombosis located in the legs but not CVST. Revised, and updated analyses, with the most current amount of data are requested.
8. It is not clear which cut-off date that was used for post-marketing data in the O/E analysis, which should be provided. Furthermore, the MAH should provide the time frame that was used to calculate the expected rate of these rare events of CVST in combination with thrombocytopenia.
9. A stratified analysis by gender of the populations exposed should be provided.
10. One case of capillary leak syndrome was reported among cases described for this signal. This condition should be followed up in monthly safety summary reports.
11. For the case with concomitant DVT and low platelet counts in a male study subject aged between 56-66 in study 3001, this case should be discussed in more detail, including a discussion on the laboratory findings at admission that indicate coagulopathy. In light of recent findings, a discussion on whether this could be a case of thrombotic thrombocytopenia related to the Covid-19 Vaccine Janssen should be provided. Any previous CBC/platelet counts in the medical history of this case should be provided.
12. The MAH should discuss whether there is a need to further revise the product information, to advice against use of the Covid-19 vaccine Janssen, in a subject who has developed thrombosis

in combination with thrombocytopenia, including after vaccination with any Covid-19 vaccine. Revision of sections 4.3 and / or 4.4 should be addressed.

Post opinion note: During the Oral explanation provided by Janssen Cilag International N.V. to PRAC on the 20th of April, further clarification was provided on a number of issues raised within the assessment report. Tests for anti-PF4 antibodies were performed on frozen samples in April 2021 and were thus not available at the time of events in 2020 or before this signal procedure was initiated. Table 6 (i.e. Lab results for subjects in COV1001, COV1002, COV2001 and COV3001 for subjects with vein and arterial thrombotic events) lists all data available to the MAH at the time of submission. Janssen Cilag International N.V. provided reassurance that they have implemented a number of measures to ensure follow-up of all relevant cases ascertained from post-marketing sources and clinical trials. The PRAC noted the clarifications provided by the MAH during the oral explanation.

3.2. Assessment of second set of additional data

3.2.1. MAH response as of 22nd April 2021

An Erratum to the Responses submitted on 16th April 2021 was provided; these do not affect the overall conclusions in the previous round. Errata pertaining to specific questions is discussed in relation to the questions addressed below.

3.2.1.1. QUESTION 1

Despite requests in Q4 of all information on all available data, as well as case narratives for important cases in the clinical studies, certain important information seems to be missing. Several questions are raised in the RSI and should be submitted for review.

MAH RESPONSE

The MAH acknowledges the concern of the PRAC and is committed to providing the requested information to the extent possible. The MAH continues to monitor for thrombotic events with and without thrombocytopenia and is working with experts and health authorities to understand these events, including evaluating potential risk factors and biological mechanisms for causality.

Additional actions are being taken to enhance follow-up on cases in a study setting as well as post marketing cases and to retrieve the requested information as outlined below.

Cases in a study setting

Study sites have been contacted and requested to provide additional laboratory values such as platelet counts. Currently, sites are returning additional supportive documents, including medical records. Additional information received to date is included in this response document (see the response to QUESTION 3). In addition, field monitors have been asked to follow-up where responses are pending.

For cases reported as non-serious unsolicited adverse events (AEs), in line with the study protocol, narratives were not routinely required throughout the clinical study. Therefore, information needs to be collected retrospectively from source documents at the study site, where available.

Study COV3012 (Sisonke) is a collaborative study conducted in South Africa for which Janssen is not the Sponsor. The MAH therefore does not hold the clinical database. There are pharmacovigilance provisions for the exchange of serious adverse events (SAEs) included in the collaboration agreement. Similar to other SAEs, the MAH routinely follows up with the principal investigator of the study with

requests for additional or missing information. The principal investigator is expediting efforts to contact the vaccination centers to retrieve laboratory results for cases of interest that have been reported. The MAH will update the case reports received as additional data are obtained and submit these to EudraVigilance in an expedited manner.

Post marketing cases

The MAH may not have been aware of all cases not directly reported to the MAH or might not have been able to collect follow-up information regarding the case details. The MAH is making every effort to obtain the cases reported to the Vaccine Adverse Event Reporting System (VAERS) through the provisions under the Freedom of Information Act. The MAH follows up on all SAEs (including events of thrombosis, thrombocytopenia and haemorrhage) with 2 phone call attempts to the reporter/healthcare provider and 2 parallel attempts via email or postal mail. A standard vaccine AE follow-up questionnaire is sent either to the reporter or healthcare provider. As part of the enhanced investigation of thrombosis cases, a process is in place to identify these cases early in the case processing workflow, and a company safety physician follows up with the reporter, by phone when available and/or email or with the treating physician if the initial contact is with a consumer. An accelerated case processing and submission process, prior to regulatory clock requirements, is in place for these cases of thrombosis.

PRAC Rapporteur assessment comment

The MAH discussion is noted. Regarding quality of submissions, the MAH has in the most recent response clarified various mistakes including significant formatting errors, which had been included in the previous response. This has clarified certain issues. Regarding missing information for cases in clinical studies as well as from other sources, given the severity of events, additional actions to enhance follow-up on potential cases are of utmost importance. Overall, the MAH has ensured undertaking such efforts. New important data is expected to be provided to the regulatory authorities as soon as possible. Further information on e.g. case reports are expected in upcoming Monthly safety summary reports (MSSRs).

3.2.1.2. QUESTION 2

For a case in study 3001, it should be clarified when the tests for PF4 antibodies actually were performed, as well as reported to the investigator, and when the sponsor/MAH became aware of these results.

MAH RESPONSE

For a case transverse sinus venous thrombosis and cerebral haemorrhage after Ad26.COV2.S vaccination) the MAH received the SAE report. In March 2021, the putative mechanism of vaccine-induced thrombosis with thrombocytopenia in association with anti-PF4 antibodies was first reported in scientific literature (Greinacher 2021, Pai 2021). On 1 April 2021, the MAH requested tests for anti-PF4 antibodies. These tests were performed on frozen samples previously collected for immunogenicity and other assessments as specified in the COV3001 protocol. The MAH received the results of the test on 12 April 2021 and the investigator was informed of these results.

PRAC Rapporteur assessment comment

The MAH has clarified that the tests for anti-PF4 antibodies were performed on frozen samples in April 2021 and were thus not available at the time of events in 2020 or before this signal procedure was initiated.

3.2.1.3. QUESTION 3

Questions (Q2, Q3, parts of Q4) were raised regarding laboratory results from clinical studies and from post-marketing data, regarding e.g. thrombocytopenia. Further data presentation is asked for to allow final assessment of whether thrombocytopenia without thrombosis or bleeding, may be caused by the Covid-19 vaccine Janssen.

MAH RESPONSE

The MAH is making every effort to obtain additional data, including laboratory data, for cases of thrombosis, thrombocytopenia, and haemorrhage to complement the information provided in the responses to Question 2, Question 3, and Question 4 submitted on 16 April 2021. See the response to Question 1. for the actions taken by the MAH to collect the requested information.

Any new clinical laboratory results that the MAH was able to receive from the clinical study sites up to 20 April 2021 is described below. In addition, cumulative data searches for spontaneously reported cases in the Global Medical Safety (GMS) safety database were performed up to 20 April 2021 as described below. Note that cases may be included in the output of more than one of the performed SMQ searches.

Question 2: Laboratory values for cases with venous or arterial thrombosis reported for the COVID-19 vaccine Janssen in clinical trials

COVID-19 vaccine studies:

"Table 6" that was provided in answer to Question 2, has been updated with additional laboratory data received and is provided as Table 1 in this document.

In addition, SAEs (CIOMS forms) were manually reviewed for reported laboratory information related to **thrombosis**, and the information retrieved from this new search is provided in Table 2 of this document.

Question 3: Laboratory values for cases of haemorrhagic (i.e., bleeding) events reported for the COVID-19 vaccine Janssen in clinical trials

There are no additional laboratory data presently available from the clinical studies regarding cases of haemorrhagic events. As described in answer to Question 1, this information needs to be collected retrospectively from source documents at the study site, where available, and queries are ongoing.

Question 4: Laboratory values for cases of (a) thrombosis, (b) thrombosis (any) and concomitant thrombocytopenia/low platelet count and (c) thrombocytopenia/low platelet count regardless of symptoms.

COVID-19 vaccine studies:

As stated in the response to Question 1, the MAH has reached out to the investigators of the study to expedite efforts to contact the study centers to retrieve laboratory results for the reported cases of interest.

Newly available laboratory information on thrombosis cases from clinical studies is provided in table 1 and table 2 new information on thrombocytopenia cases are provided in table 4.

Please note that the data received from the sites may still not be fully complete in some instances the units or ranges are missing. Hence, it is at present not always possible to conclude on whether a reported result is normal or abnormal. As this is an ongoing process the MAH provides here the status up to 21 April 2021.

Of importance, some events of thrombocytopenia that were experienced by clinical study participants were not reported as an 'AE' in the clinical database. The investigators have been contacted so that these events are encoded into the clinical trial database. In future searches, these cases will be retrieved. The following events are therefore not included in the table output presented in answer to Question 4. The cases of thrombosis and concomitant thrombocytopenia are described in the result section of this response to QUESTION 3.

Spontaneous reports:

Additionally, a cumulative data search was performed for spontaneously reported cases in the GMS Safety Database through 20 April 2021. See below for more (new) information on the data retrieved. The cumulative data search was performed for events using the following search criteria:

- a. SMQ: Embolic and thrombotic events

In total, 80 cases were retrieved that met the search criteria. Of these 80 cases, 34 had results of investigations including imaging studies and laboratory tests from blood samples provided. SMQ: Embolic and thrombotic events SMQ AND (SMQ: Haematopoietic thrombocytopenia OR HLT of Thrombocytopenias)

In total, 9 cases were retrieved that met the search criteria. A table is provided in **Error! Reference source not found.**

- b. SMQ: Haematopoietic thrombocytopenia OR HLT of Thrombocytopenias

In total, 11 cases were retrieved that met the search criteria. All 11 cases had laboratory values provided.

Results:

Additional information was received from the COVID-19 clinical studies, identifying 2 additional cases of thrombosis and concomitant thrombocytopenia. A narrative for these new cases is provided below. In total, including the two previously reported cases, a total of 4 cases are identified:

- A Subject from study COV3001 (study pause case); reported at the time of the cMAA with further updates provided thereafter. A Subject from study COV3001 (deep vein thrombosis [DVT]); information was provided in the response submitted to PRAC on 19 April 2021. Refer to the response to QUESTION 12 and the most recent CIOMS report in Attachment 2 for additional information.
- A Subject from Study COV3001 (venous embolism, COVID positive case) (questionable; confounded)

A 66-76-year-old obese male participant (BMI 32.7) with hypertension experienced COVID-19 22 days after receiving Ad26.COVS. He was hospitalized for grade 2 COVID-19, acute kidney injury, venous embolism and grade 1 hypoxemia 13 days later (35 days after the blinded vaccination). The subject did not have any symptoms of COVID-19. COVID test was positive. Doppler scan confirmed DVT in distal left popliteal vein. He had platelet count of $142 \times 10^3/\text{mm}^3$, D-Dimer 47546 (normal range [NR]: <229) and creatinine of 3.22 and was treated with heparin. The following day, a

ventilation/perfusion (V/Q) scan showed multiple wedge-shaped segmental and subsegmental filling defects in both lungs that was consistent with acute pulmonary embolism (PE). In the same study, scattered ground glass and consolidative opacities in both lungs were seen that was consistent with multifocal pneumonia. Treatment included: glucose (D5W) and heparin. The subject remained on room air. Two days after admission, the subject was discharged on anticoagulation in stable condition with creatinine 2.46, platelets $137 \times 10^3/\text{mm}^3$ ($150-400 \times 10^3/\text{mm}^3$), D-Dimer 14,664 and was to follow-up with a primary care physician. Treatment medications included: apixaban and glucose (D5W). At the time of this report, the events, venous embolism was resolving. Considering risk factors of obesity and hypertension in this subject, a lack of pharmacological plausibility for the study vaccine to cause COVID-19 infection and acute kidney injury, as well as high risk of venous embolism in COVID-19 patients, all the reported events are considered inconsistent with the causal association to immunization, per the World Health Organization (WHO) causality classification for AEs following immunization. Company causality is considered not related to the study vaccine.

- A subject from blinded study COV3009 (Stroke;)

A 50-60-year-old male participant was hospitalized for grade 3 right sided hemiparesis secondary to cerebrovascular accident (CVA), 35 days after blinded COVID 19 Vaccine. Ad26.COVID.S/placebo was administered intramuscularly for prevention of symptomatic SAR-CoV-2 virus infection. The participant had a history of high blood pressure and diabetes mellitus type 2. No concomitant medications were reported. Thirty-five days after vaccine administration, participant experienced right sided hemiparesis secondary to CVA and was hospitalized on the same day. Signs and symptoms included right sided facial weakness, slurred speech, weakness of his right arm and leg, difficulty walking, and ataxia. On an unspecified date the participant had reported platelet count (NR: not provided) 119 (units not provided), Mean platelet volume (NR: not provided) 9.4 (units not provided). Ten days later he was discharged to an acute rehabilitation facility where he remained for 19 days. His second dose of vaccine was scheduled 70 days after the first dose. Based on the participant's history of high blood pressure and diabetes mellitus, which are known risk factors for CVA, the event is considered inconsistent with the causal association to immunization, per the WHO causality classification for AEs following immunization. Company causality is considered not related to blinded study vaccine.

There have been new cases received via spontaneous sources since the previous submission dated 16 April 2021. Of the 80 cumulative cases retrieved for Question 4a Embolic and thrombotic events SMQ, 53 have been received since the data cut off for the previous submission. Potential explanations for the influx of spontaneous cases include the fact that Janssen has begun to receive data via VAERS downloads and that additional cases and new information on existing cases were received from VAERS through the Freedom of Information Act process. Furthermore, stimulated reporting secondary to the increased awareness on these events in the news, literature publications and social media and increased use of the Janssen COVID-19 vaccine in the US could be considered contributing factors.

Table 1: Updated Table 6 of the Responses Submitted 16 April 2021: Laboratory Results for Participants in Clinical Studies COV1001, COV1002, COV2001, COV3001 for Participants With Venous and Arterial Thrombotic Events – Cut-off 20 April 2021

Study ID Subject ID Treatment	Age Sex Race	Reported Term	AE Star t Date End Date	Onset Durati on	SAE Outcome Severity Grade	Relationsh ip to Vaccine	Date of Positive PCR Test / Concomitant Thrombocto penia/Low Platelets	Additional Information ^a
COV1001 Dose 1 Ad26.COV2.S 1x10¹¹ vp, Dose 2 Placebo	65-75 M WHIT E	DEEP VEIN THROMBOSIS		52 175	N NOT RECOVERED/ NOT RESOLVED Grade 1	NOT RELATED	No positive PCR No	No laboratory results available for the AE. The following results are available for pre and post vaccination timepoints (Please note that subject received placebo on day 57) PT=10.9, aPTT=28, PLT=207 PT=11, aPTT=26, PLT=219 PT=10.9, aPTT=28, PLT=182 PT=13.1, aPTT=33, PLT=199 PT=13, aPTT=33, PLT=207
COV1002 BLIND	58-68 M ASIAN	CEREBRA L THROMBO SIS		161 8	Y RECOVERED /RESOLVED Grade 4	NOT RELATED	No positive PCR No	Day 1 Platelets=26.5 10 ¹⁰ /L Day 15 Platelets=24.3 10 ¹⁰ /L Day 57 Platelets=23.5 10 ¹⁰ /L Day 71 Platelets=24.0 10 ¹⁰ /L
COV3001 Ad26.COV2.S 5x10¹⁰ vp	18-28 M WHIT E	TRANSVE RSE SINUS VENOUS THROMBO SIS		21 4	Y RECOVERED /RESOLVED Grade 4	NOT RELATED	No positive PCR Yes	Platelets= 64 (L) (normal range 140-400) Platelets= 123 (following transfusion) Platelets= 334 Add SPF4 data aPTT 24.8, 30.3 sec, 57.0 seconds at 01:09 hours, 118.8 seconds at 08:42 hours, 136.9 seconds at 17:36 hours; Antiphospholipid AB 1.66, 34.6 sec, 57.3 sec, Lupus Anticoagulant not detected, Negative; Antithrombin III 97%; Blood Fibrinogen 154 mg/dL, 154, 274 mg/dL; INR 1.1, 1.29, 1.46; Platelet count 204 10 ³ /uL, 60 10e3/ul at 01:13 hours, 113 10e3/ul at 17:55 hours, 64, 123, 334 10e3/mcl (after discharge); PTT 11.2 sec, 15.7 sec, 17.7. Work up revealed sigmoid sinus stenosis, transverse sinus thrombosis and secondary hemorrhage. Hematology and infectious disease work up were performed; results showed non-conclusive abnormalities. Anti-PF4 antibodies were negative 0.246 (Day 1) and positive 2.137 (Day 29) and 1.451 (Day 71). On Day 155: Lyme disease test: high IgM (interpreted as negative), Lupus anticoagulant: normal, N-ELISA: negative. Please refer also to the CIOMS form in Error! Reference source not found.
COV3001 Ad26.COV2.S 5x10¹⁰ vp	35-45 M MULT IPLE	DEEP VEIN THROMBO SIS		19 123	N NOT RECOVERED /NOT RESOLVED Grade 2	NOT RELATED	/ Not known	The participant underwent echo color doppler of lower limb veins on , which showed a small thrombus adhered to the right common femoral vein and acute thrombosis of the left gastrocnemius veins. At present time, data on laboratory values are not available and the MAH is not able to confirm whether data will become available.

Study ID Subject ID Treatment	Age Sex Race	Reported Term	AE Start Date End Date	Onset Duration	SAE Outcome Severity Grade	Relationship to Vaccine	Date of Positive PCR Test / Concomitant Thrombocyto penia/Low Platelets	Additional Information ^a
COV3001 Placebo	50-60 M WHIT E	DEEP VEIN THROMBOSIS IN LOWER LEFT LEG		3 141	N NOT RECOVERED /NOT RESOLVED Grade 2	NOT RELATED	No positive PCR/ Not known	The participant had previous history of DVT. Most recently with the present DVT, participant was seen, no laboratory assessments were done before starting on blood thinner apixaban, which participant remains on.
COV3001 Placebo	33-43 M WHIT E	RIGHT LEG DEEP VEIN THROMBOSIS		89 53	Y RECOVERING/RESOLVING Grade 3	NOT RELATED	/ No	Platelets = 257 (normal range 140-420); PT normal; INR=1.12; PT normal; INR=1; aPTT 31.4 (H) (normal range 22.4-29.3); Platelets =251 (normal range 140-420); D-dimer 5.55 (H) (normal range 0-0.5 mg/L);
COV3001 Placebo	18-28 F MULTIPLE	CEREBRAL VENOUS SINUS THROMBOSIS		65 56	Y RECOVERED /RESOLVED Grade 2	NOT RELATED	No positive PCR/ No	Platelets = 289 (normal range 140-440); Normal fibrinogen, thromboplastin time, PT, INR, Lupus anticoagulant negative
COV3001 Placebo	35-45 F ASIAN	HEMORRHOIDAL THROMBOSIS		24 14	N RECOVERED /RESOLVED Grade 2	NOT RELATED	No positive PCR/ Not known	No additional information currently available.
COV3001 Ad26.COV2.S 5x10 ¹⁰ vp	56-66 M WHIT E	VENOUS THROMBOSIS IN THE LEFT LOWER LIMB AFTER TRAUMA		23 1	N RECOVERED /RESOLVED Grade 2	NOT RELATED	No positive PCR/ Not known	No additional information currently available.
COV3001 Ad26.COV2.S 5x10 ¹⁰ vp	39-49 M WHIT E	DEEP VEIN THROMBOSIS OF IN THE LEFT CALF		98 31	N NOT RECOVERED /NOT RESOLVED Grade 2	NOT RELATED	No positive PCR/ No	Platelets =209 (normal range 150-400); 07 Mar 2021: Platelets = 215; 08 Apr 2021: D-dimer <0.17 (normal range<0.59 mg/L FEU)
COV3001 Ad26.COV2.S 5x10 ¹⁰ vp	44-54 M WHIT E	DEEP VEIN THROMBOSIS IN RIGHT LEG		108 19	Y NOT RECOVERED /NOT RESOLVED Grade 3	NOT RELATED	No positive PCR/ No	Platelets 203 (normal range 150-450); 200; 205; 211; 202; D-dimer 1.74 (H) (normal<0.5mg/L); Lupus anticoagulant present on dilute RVVT screen;
COV3001 Ad26.COV2.S 5x10 ¹⁰ vp	56-66 M WHIT E	DEEP VEIN THROMBOSIS		22 5	Y RECOVERED /RESOLVED Grade 4	NOT RELATED	No positive PCR/ No	(admission date, as per the medical records); Platelets 141 (L) (normal range not known); PT 24.6 (H); INR 2.1 (H) A low platelet count was reported according to the analyzing laboratory reference ranges, however the treating physician considered this result unremarkable, as per the medical records. Platelet count of 141 is considered normal, according to the FDA Guidance document "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (September 2007) used in this clinical study protocol. No AE of thrombocytopenia was reported by the study investigator.

Study ID Subject ID Treatment	Age Sex Race	Reported Term	AE Start Date End Date	Onset Duration	SAE Outcome Severity Grade	Relationship to Vaccine	Date of Positive PCR Test / Concomitant Thrombocyto penia/Low Platelets	Additional Information ^a
COV3001 Ad26.COVS.2.S 5x10 ¹⁰ vp	58-68 M WHIT E	LEFT EYE VENOUS THROMBO SIS		50 64	Y RECOVERIN G/RESOLVIN G Grade 3	RELATED	No positive PCR/ No	Platelets = 190.000/mm ³ other laboratory data included: erythrocyte sedimentation rate 3 mm/h, immunoglobulin G negative, immunoglobulin M negative, Lupus anticoagulant conclusion tests were not compatible with the presence of lupus inhibitor, protein C 126 %, protein S 121 %, and thromboplastin 28.2 (normal ranges and units not provided).
COV3001 Ad26.COVS.2.S 5x10 ¹⁰ vp	53-63 M WHIT E	DEEP VEIN THROMBO SIS		76 1	N RECOVERIN G/RESOLVIN G Grade 2	NOT RELATED	No positive PCR/ No	Doppler echo: left DVT. Enoxaparin (Lovenox) initiated. Platelet count 241, INR 1.02, PTT 28.
COV3001 Ad26.COVS.2.S 5x10 ¹⁰ vp	45-55 M WHIT E	DEEP VEIN THROMBO SIS		27 93	N RECOVERIN G/RESOLVIN G Grade 2	RELATED	No positive PCR/ No	Platelets = 216.000/mm ³
COV3001 Placebo	37-47 M BLAC K OR AFRIC AN AMER ICAN	DEEP VEIN THROMBO SIS		6 110	Y RECOVERIN G/RESOLVIN G Grade 4	RELATED	No positive PCR/ No	Platelets = 266
COV3001 Ad26.COVS.2.S 5x10 ¹⁰ vp	83-93 M WHIT E	DEEP VEIN THROMBO SIS IN HEMORAL VEIN		13 18	N RECOVERIN G/RESOLVIN G Grade 2	NOT RELATED	No positive PCR/ No	PT/INR = normal = 11.3 sec/1.1 ; APTT = normal = 23 sec ; Normal CBC = normal platelets = 204 x10 ³ /uL (normal range 140-400), the WBC was elevated to 11.59 x10 ³ /uL, with slight increase in IMMATURE GRANULOCYTES ABSOLUTE = 0.07 x10 ³ /uL and MONOCYTE ABSOLUTE COUNT = 1.24 x10 ³ /uL, and with low Mean Cell Hemoglobin Concentration 31.3 g/dL; CMP = all normal; Lactic acid = 0.8 mmol/L; D-Dimer and fibrinogen were not evaluated; Follow-up CBC CBC is unremarkable, normal Platelets = 197 x10 ³ /uL
COV3001 Ad26.COVS.2.S 5x10 ¹⁰ vp	53-63 F WHIT E	DEEP VEIN THROMBO SIS		54 59	N RECOVERIN G/RESOLVIN G Grade 1	NOT RELATED	No positive PCR/ No	The patient was on Lovenox SC + Pneumoboots for DVT prophylaxis while being hospitalized , and Lovenox SC only after being transferred to rehabilitation facility. Lovenox was administered at rehabilitation facility. DVT was suspected and confirmed with ultrasound. The PT/INR since her admission to hospital: 13.8/1.1; 12.0/0.9; 12.8/1.0; 12.7/1.0; The platelet count since her admission to hospital: 266 ~ 374; The platelet counts since her admission to rehabilitation facility:

Study ID Subject ID Treatment	Age Sex Race	Reported Term	AE Start Date End Date	Onset Duration	SAE Outcome Severity Grade	Relationship to Vaccine	Date of Positive PCR Test / Concomitant Thrombocyto penia/Low Platelets	Additional Information ^a
								: 269; 326; 408; 364; 410; 443 (H); 400; 288; 346; 339; 241; 276; 289; 317; Other laboratory parameters such as aPTT, D-dimer and fibrinogen were not done.
COV3001 Ad26.COV2.S 5x10¹⁰ vp	57-67 M MULTIPLE	ACUTE DEEP VEIN THROMBOSIS OF THE RIGHT LOWER LIMB		98 4	N NOT RECOVERED /NOT RESOLVED Grade 3	NOT RELATED	No positive PCR/ No	Platelet count : 254,000 cells/ul Platelet count ; 300,000 cells/ ul, D-Dimer 5,285 mcg / ml (normal <0.5), PT 12.6 sec, PTT 32.1 sec and INR 1.1. Platelet count: 305,000 cells/ul
COV3001 Ad26.COV2.S 5x10¹⁰ vp	30-40 M WHITE	DVT		40 2	Y RECOVERED /RESOLVED Grade 3	NOT RELATED	No positive PCR/ No	Platelets: 241; Prothrombin time: 13.6; INR: 1.0; aPTT: 28.7; Fibrinogen and d-dimer were not collected;
COV3009 BLIND	54-64 M WHITE	THROMBOSIS OF THE ARTERIO FEMORALIS SUPERFICIALIS		52 3	Y RECOVERED /RESOLVED Grade 3	NOT RELATED	No positive PCR/ Not known	No local laboratory results for platelets and coagulation parameters were obtained; last PCR result was negative.
COV3009 BLIND	31-41 F WHITE	DEEP VEIN THROMBOSIS		68 10	N RECOVERING /RESOLVING Grade 2	NOT RELATED	No positive PCR/ No	COVID-19 PCR negative; platelets – normal and D-Dimer was 925.
COV3009 BLIND	46-56 M WHITE	DEEP VEIN THROMBOSIS		74 8	N RECOVERING /RESOLVING Grade 2	NOT RELATED	No positive PCR/ Not known	Since the subject only went to the ER and the event was a non-serious AE, the investigator had initially not requested medical records and did not have the local laboratory results for platelets and coagulation parameters (PT/PTT, bleeding time etc).
COV3009 Blind	65-75 F WHITE	Embolic and thrombotic events Nervous system disorders Cerebrovascular accident THROMBOSIS - VASCULAR CVA RIGHT		35 22	Y NOT RECOVERED /NOT RESOLVED Grade 4	NOT RELATED	No positive PCR/ Not known	No local laboratory results for the platelets and coagulation parameters were obtained; no local PCR test taken
COV3009 Blind	46-56 F	Embolic and thrombotic events		18 32	N	NOT RELATED	2021-02-2020/ Not known	Platelets were 203x10e3/ml (normal 150-370), D-dimer 350 ng/ml (normal 0-500); PT 10.6 sec; INR 1.0;

Study ID Subject ID Treatment	Age Sex Race	Reported Term	AE Start Date End Date	Onset Duration	SAE Outcome Severity Grade	Relationship to Vaccine	Date of Positive PCR Test / Concomitant Thrombocyto penia/Low Platelets	Additional Information ^a
	WHIT E	Respiratory, thoracic and mediastinal disorders Pulmonary embolism SUSPICION OF PULMONA RY THROMBO EMBOLIS M			RECOVERIN G/RESOLVIN G Grade 2			Fibrinogen 660 mg/dl (normal 150 – 450); antibiotic was initiated with cephalexin. Participant had local positive result for COVID-19. positive to antigens and data entered in EDC positive local PCR on COVID-19 day 3-5.
COV3009 Blind	78-88 M WHIT E	Embolic and thrombotic events Respiratory, thoracic and mediastinal disorders Pulmonary embolism PULMONA RY EMBOLIS M		34 30	Y RECOVERIN G/RESOLVIN G Grade 4	NOT RELATED	/ Not known	No additional information currently available.
COV3009 Blind	72-82 M WHIT E	Embolic and thrombotic events Respiratory, thoracic and mediastinal disorders Pulmonary embolism PULMONA RY EMBOLIS M		37 6	Y RECOVERED /RESOLVED Grade 4	NOT RELATED	No positive PCR/ Not known	No additional information currently available.

a Additional Information (throughout the table, platelet counts are reported in thousands per microliter [equivalent to $\times 10^9/L$], and PT and aPTT are reported in seconds, unless stated otherwise)

Table 2: Laboratory Results from CIOMS forms from Clinical Studies – Related to Thrombosis

Study ID Actual Vaccination Group Subject ID	Age Sex Race	Reported Term	Serious AE	Onset of AE	Start Date End Date Duration	Laboratories	COVID Testing
VAC31518COV3001 Ad26.COV2.S 5x10 ¹⁰ vp	65-75 M	EMBOLISM VENOUS	Y	36	78	doppler scan confirmed deep vein thrombosis in distal left popliteal vein. Laboratory data (NR/ units not provided) included: Alanine aminotransferase was 17, Alkaline phosphatase was 58, Aspartate aminotransferase was 27, Platelet 142 k/cmm (150-400) at 10am 135 k/cmm (150-400) at 10:46pm 120 k/cmm (150-400) at 3am 137 k/cmm (150-400) at 3 am D-Dimer checked during the admission: D-Dimer 47,546 (<229); D-Dimer 30,822; D-Dimer 14,664 , Serum creatinine was 3.22, and White blood cell count was 14.5, hemoglobin 18.9 and hematocrit 59.1. a ventilation/perfusion (V/Q) scan showed multiple wedge-shaped segmental and subsegmental filling defects in both lungs that was consistent with acute pulmonary emboli. The V/Q scan demonstrated bilateral pulmonary emboli. In the same study, scattered ground glass and consolidative opacities in both lungs were seen that was consistent with multifocal pneumonia revealed BUN (NR: not provided) 21 (units not provided), Serum creatinine (NR: not provided) 1.75 (units not provided), Sodium (NR: not provided) 141 (units not provided), Potassium (NR: not provided) 3.9 (units not provided), Chloride (NR: not provided) 100 (units not provided), Carbon dioxide (NR: not provided) 27 (units not provided), Aspartate aminotransferase (NR: not provided) 22 (units not provided), alanine aminotransferase (NR: not provided) 25 (units not provided) and Alkaline phosphatase (NR: not provided) 79 (units not provided).	Positive
VAC31518COV3009 BLIND	49-59 M	STROKE	Y	36	59	Laboratory tests included Prothrombin time (NR: not provided) 13.4 (unit not provided), Partial thromboplastin time (NR: not provided) 26.6 (unit not provided), International normalized ratio (NR: not provided) 1.14 (unit not provided), Fecal occult blood: negative, COVID-19 virus test: negative, Blood pressure 154/92, White blood cell count (NR: not provided) 7.5 (unit not provided), Red blood cell count (NR: not provided) 5.52 (unit not provided), Hemoglobin (NR: not provided) 16.6 (unit not provided), Hematocrit (NR: not provided) 49.8 (units not provided), Mean cell volume (NR: not provided) 90.2 (unit not provided), Mean cell hemoglobin (NR: not provided) 30.1 (units not provided), Mean cell	Negative

Study ID Actual Vaccination Group Subject ID	Age Sex Race	Reported Term	Serious AE	Onset of AE	Start Date End Date Duration	Laboratories	COVID Testing
						hemoglobin concentration (NR: not provided) 33.4 (units not provided), Red cell distribution width (NR: not provided) 13.8 (units not provided), Platelet count: 119 (normal range 150-450) 10 ³ /uL Mean platelet volume (NR: not provided) 9.4 (units not provided), Glucose (NR: not provided) 205 (units not provided), Heart rate (NR: not provided) 136 (units not provided), Potassium (NR: not provided) 3.2 (units not provided), Glucose (NR; not provided) 187 (unit not provided), Prothrombin time (NR: not provided) 13.9 (units not provided), International normalized ratio (NR: not provided) 1.2 (units not provided), Activated partial thromboplastin time (NR: not provided) 26.9 (units not provided).	
VAC31518COV3001 Ad26.COV2.S 5x10¹⁰ vp	69-79 F	STROKE	Y	71	44	and a CT brain done confirmed a sub-acute, non-hemorrhagic infarct of the left MCA branch territory. Other blood results were within normal ranges. WBC 7.32, HB 12.2, platelets 284 (units for the tests were not provided) and unspecified test reported as other was negative. ECG was normal upon admission and showed sinus rhythm.	Not reported
VAC31518COV3009 BLIND	60-70 M	ISCHEMIC (WAKE-UP) STROKE	Y	32	6	CT scan of brain did not show bleeding. Carotid angiography (NR: not provided) some minor calcifications on the left carotid interna, no significant stenosis and ECG (NR: not provided) normal sinus rhythm. Laboratory data included: EEG normal. Laboratory data included: Transesophageal echocardiogram (NR: not provided) non dilated normotrophic left ventricle. Laboratory data included: Carotid artery ultrasound (NR: not provided) no DVT visible, and MRI brain (NR: not provided) recent ischemic event lenticuloatrial left. Laboratory data (dates unspecified) included: APTT (NR: 28.9 - 38.1) 34.2 sec, Activated partial thromboplastin time abnormal (NR: 2 - 3) 1.02, Body mass index (NR: not provided) 27.5 kg/m ² , C-reactive protein (NR: not provided) <1.0 mg/dL, Cholesterol (NR: 15 - 30) 21.8 %, Cholesterol (NR: 32 - 72) 43 mg/dL, Cholesterol (NR: not provided) 155 mg/dL, 126 mg/dL, 129 mg/dL, 198 mg/dL, Creatinine (NR: 0.72 - 1.17) 1.07 mg/dL, Ejection fraction (NR: not provided) 66 %, Fibrinogen (NR: 200 - 400) 320 mg/dL, GFR (NR: not provided) 71.3 mL/min, Glucose (NR: 82 - 115) 107 mg/dL, Chloride 108mmol/l (NR: 98-107), Hematocrit (NR: 39.9 - 51) 47.6 %, Hemoglobin (NR: 13.5 - 17) 15.9 g/dL, INR (NR: 0.9 - 1.1) 0.95, MCH (NR: 27.7 - 32.8) 34.0 pg/[cells], MCHC (NR: not provided) 33.4 g/dL, MCV (NR: 83.9 - 98) 101.7 fL, Mean platelet volume (NR: 9.3 - 12.7) 10.4 fL,	Negative

Study ID Actual Vaccination Group Subject ID	Age Sex Race	Reported Term	Serious AE	Onset of AE	Start Date End Date Duration	Laboratories	COVID Testing
						Platelet count (NR: 143 - 32) 222 10*3/mL, Potassium (NR: 3.6 - 4.8) 4.2 mmol/L, Prothrombin time (NR: 70 - 120) 106 %, Red blood cell count abnormal (NR: 4.36 - 5.78) 4.68 10*6/uL, Red cell distribution width (NR: 11.5 - 13.9) 12.8 %, Sodium (NR: 136 - 145) 142 mmol/L, Triglycerides (NR: 57 - 267) 147 mg/dL, Urea (NR: 13 - 43) 23 mg/dL, White blood cells (NR: 4.30 - 9.64) 8.14 10*3/mL, <1.0 10*3/mL, and (NR: 98 - 107) 108 mmol/L, normoblast (captured as investigation) <1.0/100	
VAC31518COV3009 BLIND	57-67 F	HOSPITALIZATION FOR MYOCARDIAL INFARCTION WITHOUT ELEVATED ST	Y	49	5	On, electrocardiogram results: 1. Heart disease of presumed ischemic origin, with slightly decreased left ventricular systolic function, left ventricular ejection fraction 40%. 2. Type I diastolic dysfunction. 3. No shunts observed. 4. Study performed in sinus rhythm. 14 Mar 2021 troponin level elevated at 209.6. Laboratory data included (NR: not provided): APTT 33.2 Control 30 sec, BUN 13.5, Basophils 1.25, Blood glucose Basal 100.3, Chloride 936, Creatinine 0.75, Eosinophils 1.57, Hematocrit 43.1, Hemoglobin 14.4, INR 1.04, Lymphocytes 21.2, Monocytes 6.80, Neutrophils 62.9, Platelet count 216,000, Potassium 4.33, Sodium 131, Thrombin time 13.5 sec control 13 sec and White blood cell count 10.2.	Not reported

PRAC Rapporteur assessment comment

In the MAH response, updated data concerning case reports with thrombosis, thrombocytopenia and thrombosis in combination with thrombocytopenia have been provided.

In total, from the COVID-19 clinical studies, 4 cases of thrombosis and concomitant thrombocytopenia are identified. The first case was assessed within the signal validation (18-28-year-old male with CVST and thrombocytopenia who developed anti-PF4-antibodies after vaccination). The second case pertains to a 56-66-year-old male with DVT and thrombocytopenia; further discussed in Q12 below. Two additional cases were provided with this response; one in a 65-75-year-old male, confounded by concomitant COVID-19 infection, who was hospitalized with acute kidney injury, DVT + pulmonary embolism 35 days after vaccination; platelet count was $142 \times 10^3/\text{mm}^3$. Given the concomitant covid-19 infection, any relation to the vaccination is unclear; this case will not be further discussed here. The second additional case concerns a 50-60-year-old male with previous hypertension and type 2 DM who suffered a cerebrovascular accident 35 days after study vaccination (assignment still blinded) in study 3009. Platelet levels were 119. Despite a history of hypertension and diabetes type 2, which are well known risk factors for CVA, the platelet findings are conspicuous and without any clear explanation. No further work-up has been provided. Based on the current knowledge, this case could potentially be related to the vaccination, however, since treatment is still blinded, no conclusion can be made. For the updated table on laboratory results for participants in covid-19 clinical studies reporting thrombotic

events, there are additional thrombotic events occurring within 3 weeks from vaccination (excluding placebo cases and cases reporting e.g. trauma or concomitant COVID-19 infection): 36-46 male with DVT 19 days after vaccination (lab data incl platelets unknown); 83-93 with DVT 13 days after vaccination (platelets, PT/INR, APTT all normal).

From the spontaneous reports on embolic/thrombotic events and thrombocytopenia, 9 cases were found. One case concerns concomitant CVST and thrombocytopenia in a 32-42 female; however, this case is confounded by concomitant COVID-19 infection. Six of the cases were assessed previously (included in the EudraVigilance reports above). Two additional cases were found: one case of pulmonary embolism (saddle pulmonary embolism) and platelet count of 120 in a 51-61 male with history of hypertension, and one case of fatal pulmonary embolism and thrombocytopenia (platelet count not reported) in a 53-63 male with a past history of malignant neoplasm. No time to onset has been provided for any of these cases. These cases were also found in the EudraVigilance search and are further discussed in section 3.5.2 below.

There were 80 cumulative case reports of embolic and thrombotic events, however, for the majority of cases, lab results are not included and/or time to onset is not known; the majority of case reports were recently received. There are some additional cases of interest, such as one male patient (age unknown with a history of DVT (heterozygote for FV Leiden), with concomitant DVT/pulmonary embolism and renal haemorrhage with platelet count at 191 (renal haemorrhage is not frequently seen in DVT/PE); one case of mesenteric artery thrombosis (unknown age and sex) 6 days after vaccination with concomitant diagnosis of disseminated intravascular coagulation and one case of thrombosis not further specified in a 48-58 female occurring 15 days after vaccination with no information on platelet levels but with an INR of 1.2 potentially suggesting coagulopathy. There are additional thromboses occurring within three weeks from vaccination, however information is insufficient to assess these cases further. There were two cases of CVST with normal platelet counts, one in a 35-45 female 6 days after vaccination with platelet count 270, HIT-antibodies (ELISA) negative, anti-PF4 not provided. The second case of CVST occurred in a 31-41 female with TTO of 19 days that despite normal platelet counts had a positive HIT-antibody test (exact type of test not specified); anti-PF4-antibodies are pending. As previously discussed, in heparin-induced thrombocytopenia, a decrease in platelet levels >50% from baseline is also considered suggestive of HIT, which could thus occur also with platelet levels within the normal range. It could be possible that a similar clinical picture might occur also in thrombosis with thrombocytopenia after vaccination with COVID-19 Vaccine Janssen, however, it has not been confirmed whether the anti-PF4-antibodies in the reported case could be considered pathogenic or not (presence of antibodies needs to be separated from antibodies that can activate platelets). It appears also that this patient was treated with heparin before HIT-antibodies were detected.

For spontaneous case reports of thrombocytopenia, 11 cases were found, 9 of which had concomitant thrombosis (same cases as those discussed above). One case report concerned a 65-75 year old female with COPD who had a non-serious event of low platelet counts (138) 5 days after vaccination with no further information, and one case report concerned a female of unknown age with concomitant autoimmune disorder not further specified, who had low platelet counts (not further specified), TTO unknown.

In conclusion, in the clinical COVID-19 studies, one clear case of a 18-28 -year-old male with CVST and thrombocytopenia was reported. One case of DVT and thrombocytopenia in a 63-year-old male is considered potentially related to the vaccination. One case of CVA and thrombocytopenia in a 56-66 50-60-old male is unclear since treatment assignment has not been unblinded, and one case of DVT in a 35-45-year-old male does not have any laboratory values reported. From post-marketing case

reports, additional cases of concomitant thrombosis and thrombocytopenia have been found but lack of information precludes any firm conclusion on most of these cases. Additional post-marketing case reports of interest from EudraVigilance are discussed in section 3.6.2 below. There are no additional case reports on thrombocytopenia without thrombosis that warrant further action at present.

Currently, the COVID-19 Vaccine Janssen RMP includes 'thromboembolism' as an important potential risk. This should be maintained. The PRAC Rapporteur also proposes that 'Thrombosis in combination with thrombocytopenia' should be included as an important identified risk (similar to Vaxzevria), see section 3.6.4/5.

3.2.1.4. QUESTION 4

In that presentation, the cases of 'hematopoietic cytopenias' in the clinical trials should be further detailed specifically addressing whether any of these are attributable to thrombocytopenia.

MAH RESPONSE

In answer to Question 4 of the responses submitted to PRAC on 16 April 2021, the MAH presented Table 12, in the context of the search that was performed on the clinical studies, to retrieve cases of thrombocytopenia/low platelet count regardless of symptoms.

Table 12 had a formatting error, as it contained the summary of all 'haematopoietic cytopenias' in the study as well as the individual cases by preferred term. The MAH apologizes for this formatting error and corrected the table. Apart from the events listed in the corrected Table 3. below, there are no additional cases.

Table 3: Corrected Table 12 (Response 16 April 2021)- COVID-19 Vaccine Janssen Clinical Studies: Cases of Thrombocytopenia/Low Platelet Count Regardless of Symptoms									
SMQ term / Preferred term	Study	N	Ad26 5e10	N	Ad26 1e11	N	Placebo	N	Blinded
Thrombocytopenia									
Immune thrombocytopenia	3001	21895	0			21888	1 (<0.1%)		
Thrombocytopenia^	1001	323	0	319	1 (0.3%)	163	0	271	1 (0.4%)
Hematopoietic cytopenia									
Anemia	3001	21895	7 (<0.1%)			21888	4 (<0.1%)		
	3009							225 58	3 (<0.1%)
Blood disorder	3009							225 58	1 (<0.1%)
Hematopoietic cytopenia	1001	323	0	319	3 (0.9%)	163	0	271	2 (0.7%)
	3001	21895	9 (<0.1%)	-	-	21888	4 (<0.1%)	-	-
	3009	-	-	-	-	-	-	225 58	4 (<0.1%)
Hemoglobin decreased	1001	323	0	319	1 (0.3%)	163	0	271	1 (0.4%)
Leukopenia	1001	323	0	319	1 (0.3%)	163	0	271	0
	3001	21895	1 (<0.1%)			21888	0		
Neutropenia	1001	323	0	319	1 (0.3%)	163	0	271	0
Neutrophil count decreased	1001	323	0	319	1 (0.3%)	163	0	271	0
Thrombocytopenia^	1001	323	0	319	1 (0.3%)	163	0	271	1 (0.4%)
White blood cell count decreased	3001	21895	1 (<0.1%)			21888	0		

Table 12 corrected April 21, 2021

From this table, the laboratory values of thrombocytopenia cases are provided in Table 4.

Of importance, some events of thrombocytopenia that were experienced by clinical study participants were not reported as an 'AE' in the clinical database. Moving forward the MAH will ensure these cases are captured from clinical studies. In future searches, these cases will be retrieved through implementation of specific follow-up on cases that meet case definition of thrombocytopenia and the use of specific forms to document each event. For each case specific laboratory work up will be requested (e.g., platelet, SP4). The following events are therefore not included in the table output presented above. A short narrative on the new cases are provided in the results section of the response to QUESTION 3:

- A Subject from study COV3001 (study pause case)
- A Subject from study COV3001 (DVT;
- A Subject from Study COV3001 (venous embolism, COVID positive case;) (questionable; confounded)

A Subject from blinded study COV3009 (Stroke;)

Table 4: Laboratory Values of Thrombocytopenia Cases Listed in Table 3					
Study ID Subject ID Treatment	Age Sex Race	Preferred Term	Serious AE	Day of AE Onset	Laboratory information
VAC31518COV1001 Ad26.COV2.S 1x10 ¹¹ vp, (2 doses)	69-79 M WHITE	Thrombocytopenia	N	91	PLT baseline: 181 PLT Day 8: 197 PLT D57 (pre vaccination: 98 aggregation of PLT in this sample). AE reported, grade 3 PLT Day 64: 166 (range 150-450)
VAC31518COV1001 Ad26.COV2.S 5x10 ¹⁰ vp	18-28 M WHITE	Thrombocytopenia	N	8	PLT baseline: 136 PLT Day 8: 105 , repeat 1 weak later PLT 162 PLT D57 : not collected PLT Day 64: not collected (range 150-450)
VAC31518COV3001 Placebo	18-28 F BLACK OR AFRICAN AMERICAN	Immune thrombocytopenia	Y	77	BLOOD TESTS DONE (RESULTS OBTAINED) SHOWED PLATELET COUNT 6L X 10(9)L (REF RANGE 186 - 454). HB AND WHITE CELL COUNT NORMAL. LFT NORMAL. CREATININE NORMAL. REFERRED TO EDENDALE HOSPITAL INTERNAL MEDICINE DEPARTMENT ON 04 FEB 2021 FOR ADMISSION, FURTHER INVESTIGATION AND TREATMENT. The result PLATELET COUNT 6L X 10(9)L is being queried

PRAC Rapporteur assessment comment

The MAH has clarified that there were no additional cases of haematopoietic cytopenias; this was a formatting error in the previously submitted response. There were two subjects who received the Ad26.COV2.S in whom 'thrombocytopenia' was reported as an AE, one with apparently aggregation of platelets in the blood sample at day 57 and thus not actually thrombocytopenia, and one in a 18-28 - year-old male with low platelets at baseline (136) that decreased to 105 at day 8 ; one week later platelets were 162. Given the pre-existing low platelet values at baseline, this case is not considered to clearly support a relationship between vaccination and thrombocytopenia.

There was one additional case of thrombocytopenia in the placebo group (18-25 25-year-old female reporting ITP 77 days after placebo). From table 3 above, there appears to be one additional case of thrombocytopenia in whom treatment remains blinded, no further details available.

Based on the presented data, it is not considered justified to include 'thrombocytopenia' without thrombosis as an adverse reaction to COVID-19 Vaccine Janssen. However, based on the platform data as discussed in the previous round, with a clear imbalance of low platelet counts in vaccinees as compared to placebo, the PRAC Rapporteur suggests that 'thrombocytopenia' should be included in the list of safety concerns as an important potential risk. It should as feasible therefore be actively followed up on ongoing PhV studies. The RMP should be updated accordingly, see section 3.6.4/5.

3.2.1.5. QUESTION 5

Laboratory data, primarily CBC/platelet counts remain missing for the majority of cases with thromboembolism in both the clinical trials as well as post-marketing. Additional

information on CBC/platelet levels are expected to be presented for these cases, including all cases with thromboembolic events regardless of location and severity.

MAH RESPONSE

Table 6 of the response to the Question 2, received from PRAC on 9 April 2021, provided the data available up to 15 April 2021. The MAH acknowledges the table was incomplete and is putting in every effort to obtain laboratory data for the cases with thromboembolism reported in clinical studies and post marketing.

As outlined in the response to **Error! Reference source not found.**, the MAH is following up on cases received and will submit all available information.

Please refer to the response to the QUESTION 3 for new information that the MAH was able to obtain from the clinical studies and from the post marketing events, since the previous submission.

PRAC Rapporteur assessment comment

The available data was presented in the response to Q3; see assessment of this question above.

3.2.1.6. QUESTION 6

For COVID3012 SISONKE, an open label single arm Phase 3b study in South Africa, there were five cases of thromboembolism that occurred between less than 24 hours and 23 days after vaccination. Normal platelet counts have been provided for only one of these; for one case, pulmonary embolism was diagnosed postmortem and is thus not expected to provide further laboratory testing. For the remaining three cases, platelet levels are expected to be submitted.

MAH RESPONSE

As stated in the response to Question 1 the MAH has reached out to the principal investigator of the study to expedite efforts to contact the study centers to retrieve laboratory results for the reported cases of interest. By the cut-off date of 20 April 2021, no additional platelet counts were available for any of these cases. The MAH will provide any additional information received on these cases.

PRAC Rapporteur assessment comment

No additional laboratory data was retrieved for the thromboembolic cases in study 3012. Any updates on these cases should be provided in upcoming MSSRs.

3.2.1.7. QUESTION 7

In the Responses Table 5, there were 13 subjects with 'AEs of interest' of venous or arterial thrombosis in the clinical studies. There appears to be an additional 19 or 22 cases (different numbers appear in the Responses) with events of thromboembolism in the clinical studies. The MAH should summarize the main reasons for not including the additional cases among AEs of interest. Notably, laboratory data (primarily CBC/platelet counts) are expected for all cases.

MAH RESPONSE

In answer to Question 2 of the responses submitted to PRAC on 16 April 2021, Table 4 included all AEs that were retrieved from the COVID Vaccine Janssen clinical study databases using the SMQ search term "Embolitic and thrombotic events" (all cases).

From the cases included in Table 4, the MAH made a manual selection of events which the MAH believed would be of interest to the PRAC. These "13 selected AEs of interest" were presented in Table 5. This manual selection was made because the focus of the initial discussions was mainly on certain types of venous events and it was believed that inclusion of Table 5 would facilitate the work of the PRAC reviewers.

In retrospect, the MAH acknowledges that this Table 5 could lead to confusion as to the total number of cases provided and, hence, the MAH would like to point out to the reviewer that for each study (COV1001, COV1002, COV2001, COV3001, COV3009) the number of participants included in Table 4 with an AE of Interest by System Organ Class and Preferred Term are presented in the Subject Listings within the Appendices of the responses submitted on 16 April 2021.

Please note that Table 6 in the response document submitted on 16 April 2021 listed all available laboratory data for the cases in Table 4 of that response document (as of data lock point 15 April 2021). Many of these cases were reported as unsolicited (non-serious) AEs; for these cases, very limited additional information was available at the time because it had to be retrieved manually from source documents at the site (see response to QUESTION 1). In answer to QUESTION 3 of the present document, the Table 6 from the responses submitted 16 April 2021 has been updated with the laboratory data that has become available (Table 1).

PRAC Rapporteur assessment comment

The MAH has clarified the selection of potential cases of interest. The assessor agrees that a selection could be helpful, however, given that this signal warrants consideration on all potential cases, a broad assessment is warranted. Data on all cases has been presented in the new Table 1, assessed in Q3.

3.2.1.8. QUESTION 8

For the O/E analysis, it is noted that the 18-28-year-old male from the phase III study that was reported with CVST and thrombocytopenia has not been included, in addition, the 52-62-year-old female subject included in this analysis had thrombosis located in the legs but not CVST. Revised, and updated analyses, with the most current amount of data are requested.

MAH RESPONSE

Revised and updated analyses including all cases of cerebral venous sinus thrombosis (CVST) with/without thrombocytopenia in the company safety database at the cut-off date of 19 April 2021 are provided in Table 5. To Table 7. The time-at-risk window used for the analysis is 28 days and the assumed reporting percentage 100%. Exposure data, as well as the age group percentages and the gender percentages used for the analysis are per the CDC COVID data tracker website (CDC 2021).

Please note that the two new cases of thrombosis and concomitant thrombocytopenia specified in the response QUESTION 3, are not included in the analysis because the first case is confounded by COVID-19 infection and the second case is still blinded and could, therefore, have received either COVID -19 Vaccine Janssen or placebo.

Table 5: CVST (10 Females; 1 Male)

AGE GROUP	SEX	Observed	Exposure (100,000 PY)	Incidence Rate (/100,000 PY)	LB Incidence Rate	UB Incidence Rate	Expected	LB Expected	UB Expected	Obs/Exp	LB Obs/Exp	UB Obs/Exp
ALL	ALL	11	3.6333	1.16	0.13	19.87	4.21	0.5	72.2	2.6	0.2	23.8
18-34	FEMALE	3	0.4179	1.87	0.24	14.24	0.78	0.1	6.0	3.8	0.5	29.4
35-54	FEMALE	7	0.6779	1.60	0.15	17.17	1.08	0.1	11.6	6.5	0.6	69.7
55-64	FEMALE	0	0.4666	0.99	0.04	27.07	0.46	0.02	12.6	0.0	0.0	0.0

Table 6: CVST With Thrombocytopenia (6 Females. 1 Male)

AGE GROUP	SEX	Observed	Exposure (100,000 PY)	Incidence Rate (/100,000 PY)	LB Incidence Rate	UB Incidence Rate	Expected	LB Expected	UB Expected	Obs/Exp	LB Obs/Exp	UB Obs/Exp
ALL	ALL	7	3.6333	0.17	0.03	2.04	0.62	0.10	7.4	11.3	0.9	67.1
18-34	FEMALE	3	0.4179	0.18	0.05	0.69	0.07	0.02	0.3	40.6	10.4	158.3
35-54	FEMALE	3	0.6779	0.07	0.01	0.47	0.05	0.01	0.3	59.4	9.5	371.8
55-64	FEMALE	0	0.4666	0.15	0.00	10.03	0.07	0.00	4.7	0.0	0.0	0.0

Table 7: CVST Without Thrombocytopenia (2 Females)

AGE GROUP	SEX	Observed	Exposure (100,000 PY)	Incidence Rate (/100,000 PY)	LB Incidence Rate	UB Incidence Rate	Expected	LB Expected	UB Expected	Obs/Exp	LB Obs/Exp	UB Obs/Exp
ALL	ALL	2	3.6333	1.03	0.10	19.57	3.75	0.35	71.1	0.5	0.0	5.7
18-34	FEMALE	0	0.4179	1.68	0.19	14.90	0.70	0.08	6.2	0.0	0.0	0.0
35-54	FEMALE	2	0.6779	1.52	0.13	18.35	1.03	0.09	12.4	1.9	0.2	23.4
55-64	FEMALE	0	0.4666	0.93	0.05	17.74	0.43	0.02	8.3	0.0	0.0	0.0

PRAC Rapporteur assessment comment

The MAH has submitted revised O/E analyses as requested. The picture of an increased incidence of CVST, as well as CVST + thrombocytopenia in women below 55 years of age who have been vaccinated compared to the expected incidences remains.

QUESTION 9

It is not clear which cut-off date that was used for post-marketing data in the O/E analysis, which should be provided. Furthermore, the MAH should provide the time frame that was used to calculate the expected rate of these rare events of CVST in combination with thrombocytopenia.

MAH RESPONSE

The cut-off date for the analysis included in the responses submitted on 16 April 2021 was 12 April 2021. Refer to the response to QUESTION 8 for the updated O/E analysis with a cut-off date of 19 April 2021. The time-at-risk window used for the analyses is 28 days.

PRAC Rapporteur assessment comment

Response noted.

3.2.1.9. QUESTION 10

A stratified analysis by gender of the populations exposed should be provided.

MAH RESPONSE

Of the total population in the US who received under the EUA at least one dose of any COVID-19 vaccine on 7 April 2021, 54.3% were female and 45.7% were male (CDC, 2021).

The total doses of the COVID-19 Vaccine Janssen (as of mid-day 7 April 2021) by age is provided in Table 8.

Table 8: Total Doses Administered, Janssen COVID-19 Vaccine (as of Mid-day April 7) – Source: Direct CDC Communication

AGE	Female	Male	Unknown	Total	PERCENT
0-4 Years	68	78	1	147	0.0%
5-17 Years	2,075	1,960	45	4,080	0.1%
18-29 Years	237,830	227,115	6,709	471,654	11.3%
30-39 Years	272,644	279,028	8,543	560,215	13.4%
40-49 Years	339,370	319,233	10,009	668,612	16.0%
50-64 Years	783,648	754,828	19,795	1,558,271	37.2%
65-74 Years	320,649	293,329	4,767	618,745	14.8%
75-84 Years	137,899	101,381	1,650	240,930	5.8%
85+ Years	39,113	20,688	446	60,247	1.4%
INVALID Age	225	263	35	523	0.0%
Total	2,133,521	1,997,903	52,000	4,183,424	100.0%

PRAC Rapporteur assessment comment

The MAH has provided the requested data. As of mid-day 7 April 2021, 4,183,424 doses of the COVID-19 Vaccine Janssen had been administered (source: direct CDC communication). Of these vaccinees, 54.3% were female and 45.7% were male. Divided by age groups, 40.8% were <50 years of age, 37.2% were administered to 50-64 -year-old vaccinees and 22% were >=65 years old. Thus, the distribution of vaccinees appears to not fully explain the young female predominance of cases of thrombosis in combination with thrombocytopenia.

3.2.1.10. QUESTION 11

One case of capillary leak syndrome was reported among cases described for this signal. This condition should be followed up in monthly safety summary reports.

MAH RESPONSE:

The MAH agrees to monitor cases of capillary leak syndrome in the monthly safety summary reports.

PRAC Rapporteur assessment comment

Noted.

3.2.1.11. QUESTION 12

For the case with concomitant DVT and low platelet counts in a 56-66-year-old male study subject in 3001, this case should be discussed in more detail, including a discussion on the laboratory findings at admission that indicate coagulopathy. In light of recent findings, a discussion on whether this could be a case of thrombotic thrombocytopenia related to the Covid-19 Vaccine Janssen should be provided. Any previous CBC/platelet counts in the medical history of this case should be provided.

MAH RESPONSE

All available information on a case was discussed in the response to the immediate request for supplementary information submitted to PRAC on 19 April 2021. . Based on the underlying genetic condition and cessation from the blood thinners which provide plausible explanation the deep vein thrombosis, the event is assessed to have an inconsistent causal association to immunization, per the WHO causality classification for AE following immunization. Therefore, the company causality is considered not related to the study vaccine.

PRAC Rapporteur assessment comment

Based on the CIOMS report, this subject had symptoms of DVT 13 days after vaccination and presented at hospital two days later. Lower extremity doppler showed left acute occlusive DVT visualized in the proximal femoral, mid femoral, distal, popliteal and peroneal veins and posterior tibial veins. Platelet count at admission was 141; INR was 2.1.

It is agreed that this subject had strong risk factors for venous thrombosis, however, the coagulation laboratory parameters are deemed conspicuous, and the timing of events is consistent with other reports of thrombosis and thrombocytopenia. The MAH was asked to discuss this case in light of the recent findings of cases with thrombocytopenia and thrombosis following vaccination. No such discussion has been provided. No laboratory data that could indicate whether the low platelet count was new, or pre-existing have been provided.

In conclusion, this case is considered possibly related to the COVID-19 Vaccine Janssen.

3.2.1.12. QUESTION 13

The MAH should discuss whether there is a need to further revise the product information, to advice against use of the Covid-19 vaccine Janssen, in a subject who has developed thrombosis in combination with thrombocytopenia, including after vaccination with any Covid-19 vaccine. Revision of sections 4.3 and / or 4.4 should be addressed.

MAH RESPONSE

The MAH acknowledges that this is an important question. At present, Janssen is not in a position to make a recommendation regarding the use of COVID-19 Vaccine Janssen in subjects who had previously developed thrombosis with thrombocytopenia, including after vaccination with any Covid-19

vaccine. COVID-19 Vaccine Janssen is a single dose regimen. No safety data are currently available for mixed vaccination schedules including other COVID-19 vaccines. Thrombosis in combination with thrombocytopenia is very rare. An update of the product information in either the Contraindications (section 4.3) or Warnings and Precautions (section 4.4) is not proposed at this time as it may prevent individuals with any previous thrombotic events without thrombocytopenia or where platelets are not available, from receiving the vaccine. The Applicant will continue to monitor and gather additional information and expert insights before making a recommendation.

PRAC Rapporteur assessment comment

There are currently no clear findings that suggest that individuals with a history of thrombosis or thrombocytopenia are more at risk of developing the serious events of concomitant thrombosis and thrombocytopenia as compared to those without any history of thrombosis or thrombocytopenia. Therefore, the PRAC Rapporteur agrees that no update of the product information is currently warranted to warn against use in such individuals. Notably, this could potentially lead to false reassurance, and also unjustified exclusion of individuals with a history of thrombosis or thrombocytopenia from receiving the vaccine.

COVID-19 Vaccine Janssen is not approved for mixing with other covid-19 vaccines; therefore, no contraindication in individuals with a history of thrombosis and thrombocytopenia following a different vaccine is warranted.

For individuals with a history of concomitant thrombosis and thrombocytopenia, including individuals with a history of HIT (heparin-induced thrombocytopenia), there could be a theoretical concern that these individuals could be more prone to react with anti-PF4-antibodies; however, this has not been justified in any of the case reports. HIT antibodies are usually short-lived once heparin is discontinued. Individuals with a history of HIT have all been exposed to heparin for some reason in the past, e.g. due to a previous thromboembolic event. Such a medical history could potentially correlate with an increased risk of complications of covid-19 disease, given that covid-19 infection is associated with a substantially increased risk of thrombosis. Therefore, any warning or recommendation not to use COVID-19 Vaccine Janssen in patients with previous HIT should be robustly justified; a theoretical concern is not considered sufficient at this time point.

However, an additional warning (section 4.4) regarding particular attention and need for active further investigation of signs of thrombosis in case a person is diagnosed with thrombocytopenia relatively recently after vaccination should be added. The reason is partly a late breaking case report for Vaxzevria, where a person came into primary care with headache and was found to have thrombocytopenia, but who was not further investigated, and sent home instead. The following day, she developed a very serious condition of thrombosis and thrombocytopenia, and shortly thereafter died. Although thrombocytopenia is not a labelled adverse event for COVID-19 Vaccine Janssen, as it is for Vaxzevria, a similar clinical scenario is not considered unlikely since thrombocytopenia could potentially be present early in a thrombotic thrombocytopenia scenario. In addition, there is one fatal case among the EudraVigilance-reported cases (see section 3.6.2 below) in which thrombosis appears not to have been sufficiently investigated early after onset of symptoms in a patient with fatal outcome. For proposed wording in section 4.4, see section 3.6.5 below.

3.2.1.13. QUESTION 7 (MAH response 15th April)

The MAH is asked to discuss how, beyond the already agreed studies in the PhV plan, the important potential risk venous thromboembolism, including the potential occurrence of the

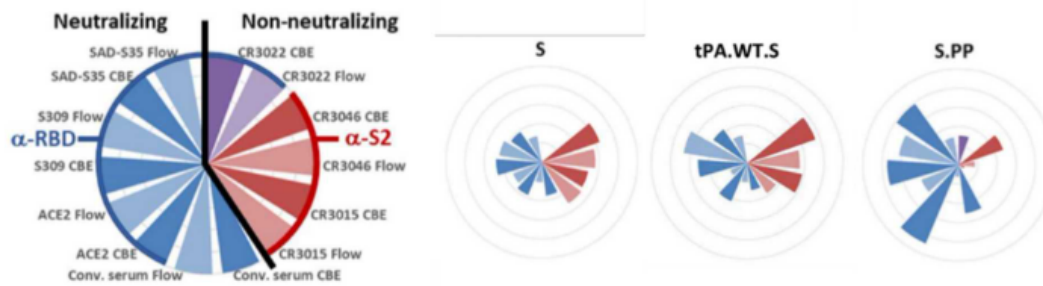
combination of thrombosis and thrombocytopenia can be further studied. Ways of gaining further mechanistic data, both non-clinical and clinical, regarding potential interactions of the Covid-19 vaccine Janssen and the coagulation system should specifically be addressed; and the following commented:

MAH RESPONSE

Study the in-vitro expression of the spike protein of the Janssen Covid-19 vaccine, and the relative proportions of the spike protein expressed in the pre-fusion and post-fusion state after administration of the vaccine.

The MAH has studied the in vitro expression of the stabilized SARS-CoV-2 spike protein compared to expression of the wild type spike protein. We have shown that stabilization of S results in differential binding of neutralizing and non-neutralizing monoclonal antibodies, reduced cell-cell fusion activity and avoids shedding of the S1 portion of the spike protein (Bos et al., 2020). Moreover, the stabilization of the S immunogen results in improved immunogenicity and efficacy in animal models compared to use of a wild type S based immunogen (Bos et al., 2020; Mercado et al., 2020). The Janssen COVID-19 vaccine contains a gene encoding a stabilized version of the SARS-CoV-2 spike protein. The transgene in Ad26.COVS has a wild type signal peptide and codes for the spike protein stabilized in its prefusion conformation by knocking out the furin cleavage site between the S1/S2 domains of the protein and by changing two additional amino acids (positions 986 and 987) to proline to arrest the possible hinging of the loop at the top of the S2 domain between the refolding region or heptad repeat 1 and the central or base helix (Palessen et al., 2017; Wrapp et al., 2020; Bos et al., 2020). Compared to a closely related Bat virus, the SARS-CoV-2 Spike protein has a cleavage site that is cleaved by a furin-like protease at the S1/S2 junction. Furin cleavage facilitates the binding of a higher proportion of the S protein to the human ACE2 receptor (Wrobel et al., 2020) and is important for infectivity of the virus. Furin cleavage is stabilizing the Spike and is an early step in the refolding of the protein from the metastable prefusion conformation to the more stable post fusion conformation. In Figure 2 differential antibody binding to wt spike and stabilized spike proteins is shown. From this analysis it can be concluded that with the stabilized spike antigen in Ad26.COVS the highest ratio of neutralizing to non-neutralizing antibody binding was observed indicating a native prefusion conformation.

Figure 2: Radar plots showing luminescence intensities measured with cell-based ELISA (CBE) and median fluorescence intensity (MFI) measured with flow cytometry (“Flow”).

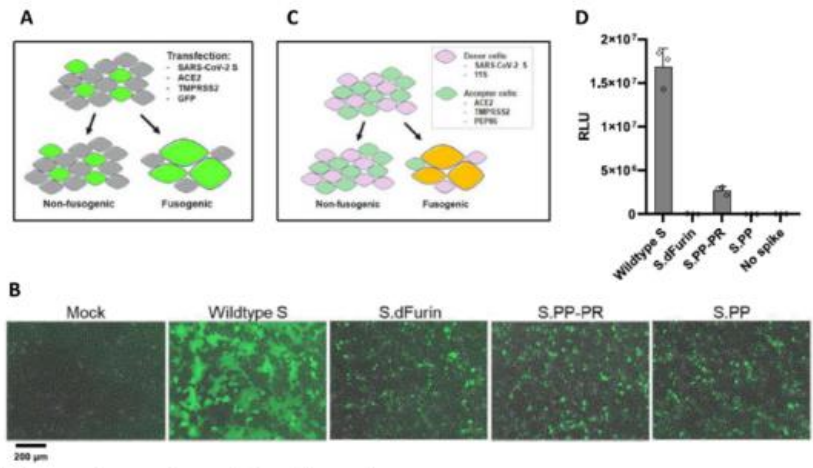


Radar plots showing luminescence intensities measured with cell-based ELISA (CBE) and median fluorescence intensity (MFI) measured with flow cytometry (“Flow”). For CBE, cells were transfected with DNA constructs, whereas for flow cytometry cells were transduced with Ad26 vectors. Luminescence and MFI were calculated as an average of a duplicate and the MFI were normalized (by multiplying with a factor 342) to have the highest intensity the same as the highest CBE luminescence intensity. The outer ring of the circles represents a value of 10,000,000. Conv. serum stands for convalescent serum. Left panel shows the different antibodies or binding molecules that have been tested and three different constructs are shown: **S** = wild type spike, **tPA.WT.S** = the spike design similar as in ChAdOx1.nCOV19, **S.PP** = spike insert as in Ad26.COVS. Neutralizing RBD antibodies can only bind to spike in the prefusion conformation. Antibodies CR3046 and CR3015 bind S2 only in the postfusion conformation.

Figure modified from Bos et al., 2020.

A consequence of the cleavage of S into the S1 head domain and the S2 fusion domain is shedding of the S1 head, which is induced by ACE2 binding, and concomitant refolding of the S2 fusion domain. In absence of the furin cleavage site mutation and the double proline substitution the protein is less likely maintained in its prefusion conformation and more likely to suffer from S1 shedding. Knocking out the furin cleavage site and adding two prolines in the S2 domain completely abolishes cell-cell fusion activity while a wild type spike protein is still fusion active (Figure 3). Stabilization of the SARS-CoV-2 spike insert sequence also prevents shedding of S1 in contrast when expressing a wild type spike insert sequence where significant S1 shedding is observed in vitro (Figure 4).

Figure 3: Effect of stabilizing mutations on fusogenicity of S protein.



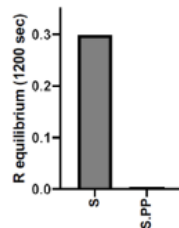
Figure

Effect of stabilizing mutations on fusogenicity of S protein.

- S protein fusogenicity as measured in a cell-cell fusion assay in HEK293 cells by co-transfection of plasmids encoding S protein, ACE2, TMPRSS2, and GFP.
- Overlay of GFP and brightfield channels 24 h after transfection, as in the setup of a. The different S protein constructs are indicated; mock is an untransfected monolayer. The scale bar is indicating 200 μm.
- Quantitative cell-cell fusion assay setup.
- Luciferase signal shown as relative light units (RLU) measured at 4 h post mixing of donor and acceptor cells, as in the setup of c. The error bars represent one s.d. From (b) it is clear that expression of the wild type spike results in substantial cell-cell fusion as can be seen by the green staining whereas expression of modified forms of the spike protein (S.PP is the insert in Ad26.COVS) have no or very minimal fusion activity.

Figure modified from Bos et al., 2020.

Figure 4: Shedding of SARS-CoV-2 S1.



Shedding of SARS-CoV-2 S1. Biolayer interferometry to determine the binding of ACE2 to Expi293F cell culture supernatants expressing S (wild type spike) and S.PP (stabilized spike) three days after transfection (Bos et al., 2020). *Free S1 is detected in transfection supernatants by binding to ACE2 in the case of expression of the wild type spike protein and not when stabilized spike was expressed.*

In conclusion, the Janssen Ad26.COVS vaccine expresses a prefusion stabilized S protein which in vitro displays differential binding to prefusion (neutralizing) and postfusion specific antibodies (non-neutralizing) compared to the wild type S protein. In addition, stabilization of SARS-CoV-2 S in the prefusion conformation abolished cell-cell fusion activity and shedding of S1 whereas expression of wild type S can result in cell-cell fusion and shedding of the S1 portion of the spike protein. Shedding of S1 is indicative of a conformational change from prefusion to a post fusion state.

PRAC Rapporteur assessment comment

Following in vitro expression of the Ad26.COVS vector in MRC-5 cells, the stabilized S protein displays a differential binding to prefusion (neutralizing) and postfusion specific antibodies (non-neutralizing) compared to the wild type S protein, indicating that the majority of the spike protein is expressed in the prefusion conformation. Further, the consequence of the stabilized S protein on fusogenicity was examined in cell-cell fusion assays indicating that the stabilized S protein in the prefusion conformation abolished cell-cell fusion activity. Moreover, no shedding of free S1 was observed in vitro, further indicating that the stabilized S protein is in a prefusion state.

Study the interaction of the Janssen Covid-19 vaccine with blood components such as thrombocytes, erythrocytes, leucocytes etc., as well as coagulation factors, natural IgM antibodies; both in the presence and absence of pre-existing immunity to recombinant, replication-incompetent adenovirus type 26 (Ad26) vector.

The MAH is investigating whether suitable and valuable in vitro models are available to study interactions between human blood components and the COVID-19 vaccine Janssen. In addition, the MAH is proactively reaching out to academic investigators/experts in the field to identify any relevant in vitro models that may help us to study the above-mentioned interactions and any downstream effects.

PRAC Rapporteur assessment comment

No interaction studies of the JanssenCovid-19 vaccine with blood components have been provided. The MAH is exploring whether suitable and valuable in vitro models are available and are planning to collaborate with experts in the field. Timelines are further discussed under 3.5.6.

Discuss how additional non-clinical as well as human studies can provide further data regarding potential effects of the i) Ad26 vector; ii) the spike protein on the coagulation system, including potential triggers of platelet activation and subsequent thrombotic effects. This should include addressing whether the Ad26 vector may activate platelets via interaction with the cell adhesion molecule CAR (i.e. coxsackie and adenovirus receptors) or affect the structure of PF4.

The baseline rate of cerebral venous sinus thrombosis (CVST) in the most recent 2020 and analysis of insurance claims in the United States was estimated to be approximately 1.49 CVST per 100,000 patient years which is equivalent 1.231 CVST/million patient months. If we assume that most CVST occurs within 1 month after immunization and with over 5 million doses distributed globally by 9 April 2021 approximately 5 cases of CVST would have been expected to be seen based on baseline incidence and 6 have been seen in the context of 6.8 million doses of COVID-19 vaccine Janssen administered in the US. The incidence is therefore extremely low making studies on vaccine induced predisposing factors quite difficult in the clinic other than measuring coagulation and other parameters that may have occurred in those cases that do occur and for which samples are run by the treating physicians or can be obtained. We have had one case in over 39,000 participants who have received active vaccine in clinical trials. This participant had low platelets, elevated cytokines, borderline coagulation disorders and PF4 antibodies. Prospectively newly vaccinated individuals can have platelet counts, coagulation studies, anti- PF4 antibodies and cytokine studies at baseline and at 14 or 28 days performed to estimate the incidence of such events following vaccination. The extremely low incidence of CVST and other outcomes may make the effort to measure these precursors post vaccination difficult to interpret but it will be worth getting some idea of incidence after immunization compared to matched control population for some of these parameters. It will also be important to determine in the rare cases of CVST that do occur following vaccination if there were predisposing factors such as narrowing of the transverse venous sinus in the cases where this occurs. This may allow us to determine if vaccine induced inflammation and subsequent hyper-coagulability is the cause of CVST or merely a trigger for an event that would occur naturally outside the context of vaccination. This should be investigated because the overall incidence of CVST following vaccination appears similar to what would be predicted in a non-vaccinated population and the cases that have been seen thus far all seem to be with low platelets suggesting inflammation following vaccination may be a triggering rather than a causal event.

As outlined in the next section of the question, the MAH will proactively collect clinical and laboratory data from cases that are reported into the clinical trials. MAH will be working closely with experts to assess the data, including evaluation of possible mechanisms on platelet activation and subsequent thrombotic events in both the vaccinated and unvaccinated population. The MAH will keep the authorities informed on the outcome of these evaluations and will seek regulatory advice on possible investigative clinical/non-clinical study proposals.

Human adenovirus type 26 is classified as species D, the largest among all human species. Although a few specific types within human adenovirus species D are associated with epidemic keratoconjunctivitis (EKC) (Ad D8, 37, 53, 54, 56 and 64), the majority of the species D adenoviruses including human adenovirus 26 do not cause clinically significant infections (Ismail 2018). More specific, there is currently no disease known to be associated with human adenovirus 26. The tropism of adenoviruses differs substantially between species and is determined by the interaction of the main adenoviral capsid proteins, fiber, hexon and penton base with host factors. Specifically, the fiber protein is important for vector tropism. The distal knob domain of the fiber protein can establish an initial binding to a host cell surface molecule followed by an interaction between a tri-peptide Arg-Gly-Asp (RGD) motif on the viral penton base and cellular αv integrins to facilitate clathrin-dependent endocytosis. Other entry mechanisms like micropinocytosis have been described for some adenovirus types. Both the adenovirus fiber and the flexible penton RGD loop exhibit considerable sequence heterogeneity between viral species (for example, Ad26 and ChAdOx1 share only 38.8% amino acid sequence homology in the fiber protein). In vitro studies have shown that Ad26 can use CD46, CAR, sialic acid and $\alpha v\beta 3$ integrin as a receptor for infecting cells (Abbink 2007; Li 2012; Baker 2019; Nestic 2018). Although some publications suggested a role for CD46 as a receptor for infecting cells (Abbink 2007; Li 2012), Baker and co-workers performed in-depth in silico and in vitro experiments and were unable to provide evidence of interaction between Ad26 fiber-knob and CD46 (Baker 2019). These experiments did show a low affinity interaction with CAR (Baker 2019) and aligns with earlier publications that showed some binding to CAR protein, but not to CAR+ cells (Roelvink 1998). Additional in vitro experiments also observed no transduction of CAR+ cells (Abbink 2007; Nestic 2019), or only with a high dose of $10E4$ VP/cell (Chen 2010). Sialic acid was previously described to interact with other adenoviruses and in vitro transduction by Ad26 was also shown to be significantly reduced following neuraminidase treatment. In addition, a high-resolution crystal structure showed Ad26 fiber-knob in complex with sialic acid demonstrating sialic acid as cell entry receptor for Ad26 (Baker 2019). Another receptor that Ad26 uses for infecting epithelial cells is $\alpha v\beta 3$ integrin. This was shown by in vitro transduction and internalization experiments with several cell lines by downregulating αv integrin and using $\alpha v(\beta 3)$ integrin positive and negative cell lines (Nestic 2018). Collectively, these data show that (human) adenoviruses can use a variety of host cell receptors and that different adenovirus types may use different host cell receptors and consequently display different biological characteristics.

For on-going clinical studies, should cases of thrombocytopenia and/or thrombosis occur, a thorough laboratory testing should be performed including, but not limited to: complete blood count incl platelets, haemolysis parameters, D-dimer, fibrinogen, PTT, PT/INR, antiphospholipid antibodies and anti-PF4 antibodies.

In view of the evolving situation, the MAH has decided to pause further vaccinations with the COVID-19 vaccine in its clinical trials. The Investigator Brochure will be updated with the recent safety information, as well as the informed consent forms. The MAH is implementing processes for evaluating thromboembolic events in clinical trials. This will involve:

- Categorization of thrombotic and bleeding events associated with low platelets for immediate reporting to the MAH.

- Current laboratory assessments include Lupus anticoagulans, Anti-β2 glycoprotein. Anti-cardiolipin, and D-dimers as well as prothrombin time and activated partial thromboplastin time. A standardized workup of laboratory assessments will be proposed to identify potential cases of thrombocytopenia and/or thrombosis based on input from external experts and haematologists.
- Provide guidance to investigators on diagnosis and treatment of thrombosis cases, including guidance for combined thrombosis/thrombocytopenia

PRAC Rapporteur assessment comment

From a non-clinical perspective, no discussion has been provided on how additional studies can provide further data regarding potential effects of the i) Ad26 vector; ii) the spike protein on the coagulation system, including potential triggers of platelet activation and subsequent thrombotic effects. The MAH plans to collaborate with experts and will seek regulatory advice on possible investigative non-clinical study proposals. Gaining further clinical data from the rare cases of thrombosis in combination with thrombocytopenia is endorsed prior to design of meaningful hypothesis-driven *in vitro* or *in vivo* non-clinical studies.

A discussion on the putative cell surface receptors for AD26 viral cell entry, based on literature, has been provided. *In vitro* experiments have shown that Ad26 can use CAR (coxsackievirus B and adenovirus receptor), CD46 (membrane cofactor protein or cluster of differentiation 46), sialic acid and αvβ3 integrin as cell surface receptors for infecting target cells. The main receptor of human adenovirus type 26 seems not fully established, but current knowledge appears to identify sialic acid-bearing glycans as a primary entry receptor and that this interaction can form a productive infection. These cell surface receptors are all reported to be expressed on human platelets (Gupalo 2011; Seya 1988; Baker 2019; Kasirer-Friede 2007).

While putative cell surface receptors of Ad26 are discussed, whether Ad26 and cell surface interaction may activate platelets has not been touched upon. In the literature, it is reported that adenoviral vectors of serotype 5 can activate platelets and cause a transient thrombocytopenia following intravenous administration in monkeys (Wolins 2002), rabbits (Cichon 1999), and mice (Varnavski 2005; Othman 2009). In mice, it has been described that after intravenous administration, Ad5 rapidly binds to circulating platelets, which causes their activation/aggregation and subsequent entrapment in liver sinusoids whereafter virus-platelet aggregates are taken up by Kupffer cells and degraded (Stone 2007).

Finally, no discussion addressing whether the AD26 vector may affect the structure of PF4 has been provided.

In order to further establish the mechanism for this adverse event, the most critical information is a thorough collection of clinical and laboratory data from the affected individuals, including all relevant previous clinical experience. It can be assumed that so far unidentified risk factors are needed for developing this rare condition. A genome analysis of the affected individuals for the potential identification of genetic associations would be highly informative and should be performed if feasible. Based on the collected knowledge, testable hypotheses for the mechanism of the condition should be set up and further mechanistic studies aiming at testing these hypotheses should be designed. A time plan for the mechanistic studies should be provided.

Time lines are discussed in 3.5.6.

3.2.2. Updated review of EudraVigilance data with case reports of interest

A search in EudraVigilance at the level of SMQ Embolic and thrombotic events SMQ (DLP 24th April) retrieved 123 unique cases. Of these, 33 were presented within a prior analysis (i.e. DLP 14th April). The remaining 90 cases originated from the US (n=87), France (n=1), Vietnam (n=1) and Puerto Rico (n=1). The case from originated from a phase III clinical trial (i.e. COV3009: to evaluate the efficacy, safety, reactogenicity & immunogenicity of 2 doses of Ad26.COV.2) and concerned an event of pulmonary embolism (PE) in a 58-68-year-old male patient (TTO:9 days after the second dose). Platelet count at the time of the event was 185,000/mm³.

Of the 90 cases, 33 (37%) occurred in male patients, 50 (56%) in female patients and gender was not specified in the remaining seven. Sixteen cases (18%) concerned fatal events. Age was specified as ≤50 years in 27 cases (32%), ≥50 years in 34 cases (38%) and not specified in the remaining 27 cases (30%).

Twelve cases reported thrombocytopenia (or related preferred terms) in combination with thrombosis. This included one case in a 21-31-year-old female patient from the, which was provided within a prior analysis (DLP: 14th April 2021) (i.e. VAERs case report received). This case will not be provided again. The CIOMS for an additional four cases concerning events of thrombosis which were co-reported with thrombocytopenia were received via direct correspondence from Janssen-Cilag International N.V. Therefore, a total of 15 cases were identified which co-reported events of thrombosis with thrombocytopenia.

Of these 15 additional cases, events were preceded by Covid-19 infection in one fatal case concerning a 32-42-year old female patient. Of the remaining 14 cases, two met the Level 4 interim Brighton collaboration case definition (i.e. reported as TTS but insufficient evidence to meet any level of the case definition) One case, concerned a 53-63 -year-old male patient with a medical history of alcoholic cirrhosis of the liver (potential risk factor for thrombocytopenia) and hypertension. Concomitant medication included ciprofloxacin, famotidine, furosemide, lactulose, nadolol, rifaximin and senna. He developed profound thrombocytopenia (i.e. platelet count of 7) within 13 days of vaccination. While it is specified that the patient developed disseminated intravascular coagulation, no additional information was provided regarding the event. The patient was transfused with platelets which did not resolve the thrombocytopenia. Following consultation with haematology, IV methylprednisolone was initiated, and the platelet count rose to 41. Outcome at the time of the report was unknown. Another case concerns a consumer report regarding a 52-62-year old female patient from the, which is subject to limited information. She developed peripheral swelling within one week following vaccination. At an unspecified date she developed thrombosis (NOS) (i.e. "blood clots all over her body") and platelet count was specified as 7. The narrative specifies that the patient received "3 doses of platelets". Outcome at the time of the report was unknown. A third case reported thrombocytopenia, but a specific platelet count was not provided. The patient's previous medical history included cancer and current medical history included general physical health deterioration.

The remaining 11 cases met the Brighton collaboration interim case definition for TTS (i.e. Levels 1-3). Of the 11 cases, three occurred in males and 8 in females. Outcome was specified as fatal in one case and brain death occurred in a second. Median age was 40.5 years (range: 34-58). Median TTO of first thromboembolic event was 11 days (range: 7-15 days). Median TTO of first symptom was 7 days (range: 1-15). An overview of the cases is presented within table 3-1.

Table 1: Overview of cases of TTS identified since previous EVDAS analysis which met the Brighton Collaboration interim case definition (Levels 1-3)

Age (yrs)	Gender	Co-morbidities	First symptoms (TTO, days)	Event (TTO, days)	Diagnostics	Risk factors for thrombosis	Platelet count	Additional diagnostic data	Treatment	Anti-coagulant	Outcome
51-61	M	Hypertension	Cold symptoms (1 day)	Pulmonary embolism (PE), thrombosis (leg) (11days)	CT, Ultrasound	Obesity (BMI:32.4)	120k	N/S	N/A	Apixiban	Not reported
29-39	F	No apparent co-morbidities	Severe headache (3days)	Cerebral venous sinus thrombosis (CVST) (15 days)	MRI Venography	No apparent risk factors	64k	INR:1.2, Pro-thrombin time: 15.4	N/S	Anti-coagulant (NOS)	Not recovered
31-41	F	Morbid obesity	Abdominal pain (7 days)	Disseminated intravascular coagulation (DIC), mesenteric artery thrombosis (7days)	CT scan	Obesity	20k	Fibrin D dimer:10.1, Fibrinogen: 127.	Platelet transfusion, laparoscopy with resection of small bowel, TPN and IV antibiotics.	N/S	At time of report event of DIC & small bowel necrosis were recovering. Outcome of other events were unknown
N/S	M	Inner ear disorder (NOS)	Dizziness, nausea, diplopia (15 days)	Cerebrovascular accident (15 days)	MRI Imaging scan	N/S	90k	N/S	N/S	N/S	Discharged home at time of the report
38-48	F	N/S	Dizziness, headache, vomiting (7days)	CVST (TTO: N/S)	N/A	No apparent risk factors	47k	N/S	N/S	N/S	Fatal
36-46	F	Obesity	Dizziness, headache, mild shortness of breath.	Cerebral venous thrombosis (CVT), PE, CVA.	N/A	Obesity	17k	Anti-PF4 antibodies positive (2.5 or 2.7)	Treated with IVIG (platelet count increased after 5 days to 137).	N/S	Discharged after 4 days.
42-52	M	Diabetes	Seizure (11 days)	DIC (11 days)	CT scan of the head	Diabetes	10	Blood fibrinogen decreased: 107, Fibrin D-Dimer	Platelet transfusion	N/S	Not recovered.

Age (yrs)	Gender	Co-morbidities	First symptoms (TTO, days)	Event (TTO, days)	Diagnostics	Risk factors for thrombosis	Platelet count	Additional diagnostic data	Treatment	Anti-coagulant	Outcome
28-38	F	Codeine allergy, migraine, depression, chronic thrombocytopenia	Severe frontal ocular headache, nausea, vomiting, photophobia (N/S)	CVST (i.e. Dural venous sinus thrombosis) (7 days)	CT scan	No apparent risk factors	10	increased: 37 N/S	N/S	N/S	Brain death
44-54	F	No apparent co-morbidities	Periorbital right headaches (7 days)	CVST (Superior sagittal sinus thrombosis) (11 days)	CT scan, CT venogram	No apparent risk factors	78k	Elevated D-dimer (> 4mcg/ml)	IVIG, Nicardipine	Argatroban	Not recovered
27-37	F	No apparent co-morbidities	Headache, blurred vision, neck stiffness, nausea with 1 episode of vomiting	CVST, Jugular vein thrombosis (12 days)	MRI, MRI venography	Four months post-partum	126k	N/S	N/S	N/S	Unknown
30-40	F	N/S	Severe headache (3 days)	CVST, Jugular vein thrombosis, DVT (10 days)		No apparent risk factors	90k, 122k, 143k.	SARS-CoV2 test negative	N/S	Argatroban	Not reported

*CIOMS received via direct correspondence from Janssen-Cilag International NV

Additional cases of interest which did not co-report thrombocytopenia

An additional two cases concerning events of CVST which did not report thrombocytopenia were also identified.

One case concerns a 35-45-year old female patient from the who experienced headache, right internal jugular vein thrombosis, right transverse sinus and right sigmoid sinus thrombosis. The report notes that the patient had no predisposing conditions and was not taking COC. No concomitant medications were reported. Her only apparent symptom at the time of the event was headache. Platelet count was specified as very normal (i.e. "in the 270s"). Test for PF4 was specified as negative. CT venogram and MR venogram showed right jugular vein thrombosis and right transverse and sigmoid sinus thrombosis. Treatment included apixaban 10mg twice daily. At the time of the report, the events were specified as recovering.

The other case concerns a 31-41-year-old female patient who experienced a dural venous sinus thrombosis (CVST) and cerebral haemorrhage 19 days after vaccine. Concomitant medications included spironolactone for acne breakouts due to polycystic ovarian syndrome (PCOS). The initial symptom was a severe headache located in the right posterior head. The next day a CT scan showed a cerebral haemorrhage, confirmed on repeat CT, and she was admitted to intensive care unit. A magnetic resonance angiography (MRA) showed a dural venous sinus thrombosis. The next day, 23 days after vaccination, heparin was started, and she was noted to be heparin resistant. A heparin antibody test was found to be positive 9 days later and the heparin was stopped, replaced by an unspecified anticoagulant. The transaminases were mildly elevated during hospitalization. The platelet counts were normal at 235, 3 days after admission and 177 on the day of discharge, 34 days after vaccination. The D-dimer was 0.49 on the day of discharge. The subject is recovering with headaches that are 2 out of 10. In this case the platelet counts were within normal range and the positive heparin antibody is confounded by the use of heparin. PCOS is known to increase the risk for thrombosis.

Further information has been provided concerning both cases within the expert neurologist review:

Table 3-2. Review by expert neurologist

Case reference	Expert opinion
Case 1	<p>Cerebral sinus vein thrombosis + stroke + pulmonary embolism + thrombopenia (17.000) in a 36-46 years old obese female not taking any concomitant medications (no taking oral contraception) without personal history of immune-mediated conditions.</p> <p>-2D headache + respiratory difficulties +1D diagnosed with CSVT + stroke + PE + thrombopenia (17.000) + APF-4 Treated with IVIG-> CSVT recovered, platelet back to 137.000. Likely a good recovery.</p> <p>As described, the clinical course and the findings are very unusual: (1) sentinel symptoms (headache for CSVT and respiratory difficulties for PE) started before vaccination; (2) a diagnosis of stroke is mentioned but no focal symptoms are reported; (3) a complete resolution of the CSVT in the CT within 4 days as described ("a repeat scan within 4 days did not showed a thrombosis") is an odd finding.</p> <p>A post-vaccination thrombo-haemorrhagic complication is the most likely explanation, but a complete assessment of this case would need further information and clarification for the above-mentioned odd findings.</p>
Case 2	<p>Cerebral sinus vein thrombosis + cerebral haemorrhage + thrombopenia (10.000) in a 28-38 years old female with depression, migraines, codeine allergy and chronic thrombocytopenia. Chronic medications: aripiprazole, bupropion hydrochloride, fluoxetine, risperidone, butalbital/caffeine/paracetamol, propranolol hydrochloride and topiramate.</p> <ul style="list-style-type: none"> +0-7D severe frontal headache-> CT normal. Thrombopenia 114.000 within a range expected as per her background. +0-7D headache reported to be more severe and different to her typical migraines. Discharged with analgesia. No new CT +7D more severe headache followed in 30 minutes by abrupt loss of level of consciousness = intraparenchymal + SAH + herniation. In the neuroimaging, findings compatible with dural venous sinus thrombosis. Platelets levels "10" 10.000? <p>Outcome death A post-vaccination thrombo-haemorrhagic complication is the most likely explanation. Chronic thrombopenia may have had a deleterious role.</p> <p>Overall, headaches that are described as different by people suffering from migraine should be carefully assessed with imaging!</p>

Case reference	Expert opinion
Case 3	<p>Cerebral sinus vein thrombosis + cerebral lobar haemorrhage + thrombopenia (78.000) in a 45-55-year-old healthy female not taking any medications</p> <p>+7D headache (alleviated with ibuprofen) +11 D Focal symptoms (aphasia + hemiparesis) [lobar haemorrhage]</p> <p>Outcome not recovery A post-vaccination thrombo-haemorrhagic complication is the most likely explanation.</p>
Case 4	<p>Cerebral venous and sinus thrombosis + Deep venous thrombosis + thrombopenia (90.000-143.000) in a 30-40-year-old healthy female, not taking any medications</p> <p>+3-10D Severe headache. +10D headache + left foot paresis not confirmed in a neuro-exam. CT (IV) normal</p> <p>Later, headache left leg discomfort -> Deep venous thrombosis + Cerebral venous and sinus thrombosis and thrombopenia (120.000, other counts 90.000, 143.000)</p> <p>A post-vaccination thrombosis complication is most the likely explanation. Of note, nearly 30% of CT can be negative (FN) in a person with CVT.</p>
Case 5	<p>Cerebral venous and sinus thrombosis + Cerebral lobar haemorrhage + thrombopenia (126.000) 27-37-year-old healthy female (4months-postpartum). No other relevant background.</p> <p>+0-12D headache + blurred vision (likely due to papilledema) + nausea and vomiting (iIH). Diagnosis: CVST + Lobar (T) haemorrhage.</p> <p>A post-vaccination thrombo-haemorrhagic complication is the most likely explanation</p> <p>Blurred vision, nausea and vomiting (in particular if untreatable or without any other GI symptoms) are signs of intracranial hypertension and should be followed by neuroimaging to diagnosis a CVST or haemorrhage.</p>
Case 6	<p>Cerebral venous and sinus thrombosis + thrombocytopenia (64.000) in a 29-39 years old healthy female. No prior comorbidities or medications.</p> <p>Following the vaccine, she had a mild headache which she attributed to the vaccine. +15D severe headache + vomiting-> Neuroimaging confirmed CVST.</p> <p>A post-vaccination thrombosis complication is most the likely explanation.</p>

Case reference	Expert opinion
Case 7	<p>Mesenteric + thrombocytopenia (20.000) in a 31-41 years old obese <u>female with</u> alcohol use. Non smoking</p> <p>+7D abdominal pain -> Diagnosis of disseminated intravascular coagulation, superior mesenteric artery thrombosis.</p> <p>A post-vaccination thrombosis complication is most the likely explanation</p>
Case 8	<p>Pulmonary embolism + thrombopenia in 53-63 years old male with cancer and overall poor health.</p> <p>The gender and age-group are uncommon. The development of a PE and thrombopenia within 1 day post-vaccination is also uncommon but the prothrombotic state due to cancer (likely advanced as it is reported poor health status) may have had a key role here. A post-vaccination thrombo-haemorrhagic case cannot be formally ruled out but the prothrombotic state due to cancer is a strong confounder in this case.</p>
Case 9	<p>Cerebral sinus vein thrombosis + Cerebral haemorrhage <u>without</u> thrombocytopenia in a female aged 31-41 years with migraine (<u>without need for preventive medications</u>), background of allergies (seasonal, Sulpha) and sinus disorder. No hormonal contraception. Non-smoker. Alcohol use 2/month. Spironolactone (unknown indication-female acne considering hormonal contraception is contraindicated due in patients with migraine?).</p> <p>+18D Awoke with headache at 2.00. While a nurse told her, it was only a headache, she <u>insisted</u>, and a TC showed a cerebral haemorrhage confirmed by MRI (posterior bleeding) and MRA (dural venous sinus thrombosis).</p> <p>Very likely, the intense and abrupt headache awoke the patient during the night (most likely mass effect due to posterior haemorrhage). An abrupt onset of a severe headache MUST always prompt further exploration (CT mandatory to rule out bleeding) even in a patient with personal history of migraines as a migraine is rarely severe enough to awake the patient and it has not an abrupt onset.</p> <p>+23D and with platelets= 235.000, heparin was started (negative for heparin antibodies) but stopped +32D due to positive antibodies against heparin. At that day, platelet were lower 177.000 and Liver enzymes were increased (AST 78 ALT 89) suggesting haemolysis.</p> <p>A post-vaccination thrombo-haemorrhagic complication is the most likely explanation</p>
Case 10	<p>COVID-19 + cerebral sinus vein thrombosis + MCA ischemic stroke + pulmonary embolism + deep vein thrombosis + thrombocytopenia (100.000) in female, 32-42 -years old, with type II diabetes mellitus, hyperlipidaemia, obesity, idiopathic intracranial hypertension and vision loss, back pain. Previously, she has suffered acute respiratory failure, edema, and high BP. Allergy to Metformin.</p> <p>Concomitant medications: acetazolamide for iIH, tramadol, baclofen and gabapentin (back pain), insulin detemir (II DM & Obesity), lisinopril, amlodipine, furosemide and hydrochlorothiazide (BP and oedema), lactulose (constipation likely) and guaifenesin.</p>

Case reference	Expert opinion
	<p>+5D but binocular vision loss + headache of 1-month course. Neuroimaging negative. Treatment acetazolamide. This is typical course of an idiopathic intracranial hypertension in the typical patient (young female obese). Most likely, <u>vaccination triggered the consultation</u> of a previous syndrome unrelated with the vaccine.</p> <p>+18D COVID-19 infection confirmed by COVID-19 PCR and IgG tests were positive.</p> <ul style="list-style-type: none"> • Respiratory failure due to pneumonia further complicated with Pulmonary embolism. • Platelets 100.000 (+5D 366,000). • Intractable vomiting with nausea = Compression of area postrema in the medulla oblongata. In this case, due to increased intracranial pressure. On top of MCA ischemic stroke, the patient was diagnosed with dural venous sinus thrombosis. <p>Outcome: death by COVID-19 as reported.</p> <p>A thromboembolic complication due to COVID-19 in a person with comorbidities is the most likely scenario (thromboembolic complications are more frequently associated with COVID-19 than with vaccination) but a contributing effect of vaccination cannot be formally rule out. In any case, it would have been confounded due to COVID-19 and prior comorbidities.</p>
Case 11	<p>Cerebral venous and sinus thrombosis <u>without thrombopenia in female</u> 35-45 years healthy person without concomitant medications. No hormonal contraception. Smoking status unknown.</p> <p>+6D headache (only symptom)-> CT confirmed cerebral venous and sinus thrombosis. Treated with Apixaban. Good recovery.</p> <p>A post-vaccination thrombosis complication is the most likely explanation</p>

Table 3-3. Review by expert haematologist

Case Reference	Expert opinion
Case 1	36-46-yr-old female with prior history of obesity. 8 days after vaccination she developed CVST, severe thrombocytopenia (17), bilateral PE and stroke. Anti-PF4 was positive. Very suggestive of TTS
Case 2	28-38-yr-old female with prior history of migraine, depression and chronic immune thrombocytopenia. Some (unspecified) days after vaccination she presented with severe headache. CT scan was normal (i.e. no CVST) and platelets (114) consistent with her previous counts, given her prior history. Some days later, she came back with ocular headache, nausea, vomiting and photophobia, which improved with painkillers. 7 days after vaccination she developed intraparenchymal and subarachnoid haemorrhage with concomitant severe thrombocytopenia (10) and CVST. This case is very suggestive of TTS . What is very worrying about this case is that the patient consulted twice before the event and CT scans + platelet counts were unremarkable at the time. So, despite patient and physician awareness, nothing could be done to prevent this catastrophic event.
Case 3	45-55-yr-old female with unknown prior medical history. 7 days after vaccination she commenced with headache → 11 days after vaccination right hemiparesis + aphasia + seizures → multifocal haemorrhagic stroke + CVST + moderate thrombocytopenia (78). Very suggestive of TTS
Case 4	30-40-yr-old female with unknown prior medical history. 10 days after vaccination she developed headache → unremarkable CT scan → some days later she was found to have multiple thromboses (left leg DVT, CVST, jugular vein) + mild thrombocytopenia (122 later dropping to 90) → treatment with argatroban. Pending anti-PF4. Very suggestive of TTS

PRAC Rapporteur assessment comment

In addition to the previously reported 8 cases of concomitant thrombosis and thrombocytopenia in EudraVigilance (see 3.1.3 above), this update includes 11 additional case reports meeting Level 1-3 interim Brighton collaboration case definition, that reported concomitant thrombosis and thrombocytopenia following vaccination. There are two additional cases with CVST but without thrombocytopenia (one with negative anti-PF4-test and one with "heparin-resistance" and positive heparin antibodies (test not further specified).

Of the 11 additional cases, 7 reported CVST; platelet counts were from 10-126k. Eight were female and 3 were male. Two cases were fatal. Median age was 40.5 years (range: 34-58). Median TTO of first thromboembolic event was 11 days (range: 7-15 days). Median TTO of first symptom was 7 days (range: 1-15). One case appears to have had symptoms potentially compatible with thrombosis before vaccination; however, anti-PF4-antibodies were positive and platelet counts improved on IVIG treatment. In five of the cases, there was no apparent risk factor for thrombosis; in three cases, obesity was reported, one case had diabetes and one case was four months post-partum. Overall, the additional cases reported are considered largely similar to the previously assessed case reports. The majority occurred in females < 60 years of age, with similar TTO and clinical picture as previously noted.

As pointed out by one of the experts, it appears that in one case, despite awareness and medical attention early when symptoms started, events evolved rapidly with fatal outcome. It is noted that CVST was not diagnosed during the first medical visits; of note, standard CT is usually not sufficient to diagnose or rule out CVST; further investigations could be needed. In addition, despite additional

health care visits with more severe headache, no new CT was performed. Also, a late breaking case report for Vaxzevira, where a person came into primary care with headache and was found to have thrombocytopenia, but who was not further investigated, and sent home instead. The following day, she developed a very serious condition of thrombosis and thrombocytopenia, and shortly thereafter died. An additional warning (section 4.4) regarding particular attention and need for active further investigation of signs of thrombosis in case a person is diagnosed with thrombocytopenia relatively recently after vaccination, should therefore be added.

Since these symptoms are of relevance also for COVID-19 Vaccine Janssen and have been described in the case reports, a similar update is proposed for section 4.4.

3.2.2.1. Literature review

Literature findings pertain to clinical features and risk factors for thrombosis in HIT (Arepally G.M. et al 2021), concluding that clinical and biologic risk factors remain elusive. Pishko AM et al (2020) discussed the high incidence of major bleeding in patients with suspected HIT and found that median sGPVI (soluble glycoprotein VI) levels were significantly elevated in patients with major bleeding events compared with those without major bleeding events. A review of the association between platelet function and immune response by Kekomäki R (2003) discussed autoantibodies and drug-induced platelet antibodies. Key features of the human platelet FcγRIIa receptor were highlighted in a review by Qiao J et al (2015), including pathological consequences of engagement of this receptor in platelet-based autoimmune disorders.

Krauel K et al (2011) presented non-clinical data which demonstrates that PF4 binds to bacteria and forms antigenic complexes on bacterial surfaces; hypothesising that pre-immunisation by PF4-coated bacteria could potentially explain previous observations of natural anti-PF4 antibodies in non-heparin treated patients, and that PF4 may have a role in bacterial defence; HIT probably being a misdirected antibacterial host defence mechanism. Krauel K et al (2012) also identified the phosphate groups of the highly conserved lipid A as the binding site for PF4 on the surface of Gram-negative bacteria, further supporting the hypothesis that neoepitope formation on PF4 after binding to bacteria is an ancient host defence mechanism.

A non-clinical study by Jin Y et al (2014) demonstrated that human adenovirus may potentiate ADP and ristocetin-induced platelet aggregation. Shimony N et al (2009) characterised the attachment of Ad group C (serotype 5) to human platelets by employing a direct flow cytometry assay on human platelets using a FITC-labelled anti-Ad hexon antibody. Othman M et al (2007) assessed the influence of von Willebrand Factor (VWF) and P-selectin on the clearance of platelets following adenovirus administration, conclude that VWF and P-selectin are critically involved in a complex platelet-leukocyte-endothelial interplay, resulting in platelet activation and accelerated platelet clearance following adenovirus administration. Raddi N et al (2016) suggest that capsid fiber protein (and more precisely its shaft) of Ad serotype 5 triggers the cytokine production that leads to Ad-induced thrombocytopenia. Perdomo J et al (2019) showed that HIT immune complexes induce NETosis via interaction with FcγRIIa on neutrophils and through neutrophil-platelet association. Jaax M.E. et al (2013) demonstrated that nucleic acids, including aptamers, also bind to PF4 and enhance PF4 binding to platelets. Systematic assessment of RNA and DNA constructs, as well as 4 aptamers of different lengths and secondary structures, revealed that increasing length and double-stranded segments of nucleic acids augment complex formation with PF4, while single nucleotides or single-stranded polyA or polyC constructs do not, indicating that the formation of anti-PF4/heparin antibodies in postoperative patients may be augmented by PF4/nucleic acid complexes and that administration of therapeutic aptamers has the potential to induce anti-PF4/polyanion antibodies and a prothrombotic diathesis.

Nguyen TH et al (2017) showed that antibodies from autoimmune-HIT patients with high binding forces cluster PF4-molecules forming antigenic complexes which allow binding of polyanion-dependent anti-PF4/P-antibodies. The resulting immunocomplexes induce massive platelet activation in the absence of heparin.

A recent publication by Greinacher A et al (2021) concluded that the antibody responses to PF4 in SARS-CoV-2 infection and after vaccination with COVID-19 Vaccine AstraZeneca differ. Antibodies against SARS-CoV-2 spike protein do not cross-react with PF4 or PF4/heparin complexes through molecular mimicry, making it very unlikely that the intended vaccine-induced immune response against SARS-CoV-2 spike protein would itself induce antibody-mediated vaccine-induced thrombotic thrombocytopenia.

Brodard J et al (2021) tested 12 COVID-19 patients with suspected HIT; results indicate that COVID-19 patients could present with strong reactivity in PF4/heparin antigen tests without the presence of platelet-activating antibodies.

Clinical and laboratory findings in patients who developed thrombosis and thrombocytopenia following vaccination with COVID-19 Vaccine AstraZeneca were discussed by Greinacher A et al (2021), Schultz NH et al (2021) and Scully M et al (2021).

Brighton collaboration has developed an interim case definition of thrombosis and thrombocytopenia syndrome (TTS) following receipt of COVID-19 vaccines (2021).

Clinical guidance on COVID-19 vaccine induced thrombosis with thrombocytopenia has been presented by the British Society of Haematology (version 1.7 2021), the Society of Thrombosis and Haemostasis Research (GTH 2021).

PRAC Rapporteur comment

The literature findings are noted. Although it is currently not clear if or to what extent thrombosis in combination with thrombocytopenia after vaccination shares similarity with HIT, it is considered striking that no clear risk factors apart from the setting in which exposure to heparin occurs have been identified for HIT despite substantial efforts to find such risk factors. The findings that covid-19-infected patients with suspected HIT did not have platelet-activating antibodies are noted (Brodard 2021) and appear to be supported by the findings that antibody responses to PF4 differ in SARS-CoV-2 infection and after vaccination with Vaxzevria.

There are several findings of interest in literature regarding potential mechanisms; of note, the MAH is requested to include a thorough literature review when providing plans for future studies, see section 3.5.6.

3.2.3. Late-breaking additional cases

Three additional case reports were received on 28 April 2021:

- 1. This concerns a 29-39-year-old female, prescribed oral contraceptives (norethindrone-ethinyl oestradiol), sertraline, Wellbutrin; no chronic or long-standing health conditions. Vaccinated with COVID-19 Vaccine Janssen. Date and time adverse event started on day 8. Admitted with ischemic stroke and multiple thrombi in extremities with severe clotting diathesis (systemic and intracranial) causing severe stroke requiring craniotomy and thrombocytopenia. The adverse events include severe headache for about a week after receiving vaccine, which resulted in a collapse and emergently being brought to the emergency

room via ambulance where a CT revealed a stroke with emergent IR procedure with admittance to an ICU. This was complicated by an emergent craniotomy due to increased brain swelling and brain deviation/herniation, which was life threatening, which resulted in repeated intubation. Now currently in ICU with frequent checks and monitoring for life saving medical care. No laboratory data provided.

- Case 2. This concerns a 33-43-year-old female with a medical history of seasonal allergies, strain of cervical portion of right trapezius muscle and migraine headaches. Non-pregnant. Current prescriptions included acetaminophen; amoxicillin-clavulanate acid; Vitamin B12; methocarbamol; methylprednisolone; Vitamin K2. Date when adverse events started on day 6. On an unknown day after vaccination patient presents to emergency department with a headache that started seven days prior to arrival. Patient describes headache as different than normal headaches: worse with movement and episodes of dizziness. Patient also has rash/redness on right cheek of the face. Vital signs within normal ranges except blood pressure 141/96 mmHg. Patient admitted to hospital for further testing and management. Medical tests and laboratory results related to the adverse event(s): CTA chest: mild burden of acute pulmonary embolism with sub segmental filling defects in the right lower lobe. No right heart strain or lung infarct. CT venography head/brain: occlusive dural venous sinus thrombosis involving the left transverse and sigmoid sinuses. There is no associated infarct. Possible additional nonocclusive thrombus in the right internal jugular vein. Lower extremity ultrasound: negative for DVT. D-dimer: 27,150 FEU. Electrolytes: within normal ranges. CBC: platelets $20 \times 10^9/L$, rest within normal ranges. Liver function tests: alkaline phosphatase 25 U/L, AST 65 U/L, ALT 87 U/L, rest within normal ranges. PTT: 26.4 seconds, Dilute thrombin time: 14.9 seconds, Haptoglobin 208 mg/dL. At the time of the report, the patient had not recovered from the adverse events.
- Case 3. This report concerns a 72-82-year-old female with bipolar disorder, hypertension, mild asthma, depression, prescribed albuterol, amlodipine and venlafaxine, who was vaccinated with COVID-19 vaccine Janssen. Date when adverse events started reported at day 1 after vaccination. Pt felt poorly after vaccination. Presented to the ER with GI upset, diarrhoea, nausea, vomiting, fever, cough. She was sent home and presented again to be admitted on an unknown date with COVID pneumonia. She was on O2 by NC then worsening and admitted to ICU on hospital day 2. On an unknown date she developed arm weakness which progressed over days. She had a massive stroke and passed on an unknown date. Stroke did not show signs of haemorrhage. Distribution of stroke was multifocal and could suggest thrombosis. Pt developed thrombocytopenia in the last 24 hours of life. CT scan worsening large multi-focal left hemispheric stroke in multiple distributions. This was an acute development over previous CT that showed one area of focal stroke. CBC on an unknown date showed plts 157, dropped to 86 on an unknown date.

PRAC Rapporteur comment

The first two late-breaking cases concern thrombosis (ischaemic stroke in the first case and CVST + pulmonary embolism in the second case) with concomitant thrombocytopenia (no values provided for the first case, $20 \times 10^9/L$ for the second case) with adverse events starting approximately one week after vaccination. These are considered in line with the previously reported cases and found to be sufficiently well documented to support that an adverse event of thrombosis in combination with thrombocytopenia is the most likely explanation for these events. The third case concerns a 72-82-year-old female with COVID pneumonia who developed ischaemic stroke with subsequent decrease in

platelets. A relation to the vaccination is not clear given the concomitant COVID pneumonia ; this case is therefore not further discussed.

3.2.4. 2nd Updated Rapporteur's discussion

At the approval of the CMA for Covid-19 Vaccine Janssen on 11 March 2021, "Venous thromboembolism" was included as important potential risk in the RMP, due to a numerical imbalance of venous thromboembolism observed in the main clinical study, VAC31518COV3001.

On 12 March 2021, a signal procedure regarding thrombotic and embolic events was started for another adenovirus vector Covid-19 vaccine, which recently has been finalised⁸. During that assessment, very rare cases showing a combination of thrombosis and thrombocytopenia, and in some cases accompanied by bleeding, have gained particular attention.

For the Covid-19 Vaccine Janssen, a signal procedure was started at the PRAC meeting held on 6-9 April 2021, due to at that time in total four cases with such unusual clinical characteristics of thrombosis in combination with thrombocytopenia, occurring after vaccination with this vaccine.

On 15 April 2021, the MAH responded to questions, and the PRAC rapporteur also received further information from the EMA regarding data in Eudravigilance. The latter was updated on 17 April, 2021.

The PRAC Rapporteur assessment that was circulated on 19 April 2021, focused on the review of cases of unusual thrombosis in combination with thrombocytopenia, taking experience gained from a recently finalised signal evaluation⁹, and based on that, evaluated the need for updates of the product information, as well as the need for additional risk minimisation measures. For the AR sent out on 19 April, 17 April 2021 was the cut-off for new data. On 20 April 2021, the PRAC concluded on the need for new warnings and an update of section 4.8 of the SmPC, and subsequent updates of the package leaflet¹⁰.

Within this second step of assessment, a more in-depth evaluation of mechanistic aspects, as well as of the pharmacovigilance plan, and thereby the responses to previous Q7, has been undertaken. In addition, review of laboratory results from clinical studies and post-marketing on conditions not predominantly related to the combination of thrombosis and thrombocytopenia have been assessed in more depth, together with updates of the first response which the MAH has submitted. An update of current number of cases in EVDAS, as well as a literature review have also been included.

Quality of the submission from the MAH

Regarding quality of submissions, the MAH has in the most recent response clarified various mistakes including significant formatting errors, which had been included in the previous response. This has clarified certain issues. Regarding missing information for cases in clinical studies as well as from other sources, given the severity of events, additional actions to enhance follow-up on potential cases are of utmost importance, Overall, the MAH has ensured undertaking such efforts. New important data is expected to be provided to the regulatory authorities as soon as possible. Further information on e.g. case reports are expected in upcoming MSSRs.

Post marketing exposure

⁸ https://www.ema.europa.eu/en/documents/prac-recommendation/signal-assessment-report-embolic-thrombotic-events-smq-covid-19-vaccine-chadox1-s-recombinant_en.pdf

⁹ https://www.ema.europa.eu/en/documents/prac-recommendation/signal-assessment-report-embolic-thrombotic-events-smq-covid-19-vaccine-chadox1-s-recombinant_en.pdf

¹⁰ <https://www.ema.europa.eu/en/news/covid-19-vaccine-janssen-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood>

As of mid-day 7 April 2021, 4,183,424 doses of the COVID-19 Vaccine Janssen had been administered (source: direct Center of Disease Control (CDC) communication). Of these vaccinees, 54.3% were female and 45.7% were male. Divided by age groups, 40.8% were <50 years of age, 37.2% were administered to 50-64 -year-old vaccinees and 22% were \geq 65 years old. Thus, the distribution of vaccinees appears to not fully explain the young female predominance of cases of thrombosis in combination with thrombocytopenia.

Regarding cumulative (US) post-marketing exposure, the MAH refers to the CDC, which reports a total of 7,688,499 doses of the COVID-19 vaccine Janssen being used as of 15 April 2021.

The MAH has also specified the approximate number of individuals being within the 21-day post vaccination period as of 13 April; namely 2,489,153 individuals. Although not entirely clear what is meant, review of the cumulative presentation above, this exact number of subjects appear to have been more than three weeks ago, and thus possibly having past the main risk window for this unusual clinical event.

By end of March 2021, the clinical study exposure is estimated to about 286 000 subjects with the Covid-19 Vaccine Janssen, and more than 200 000 individuals with the Ad26 platform. In the evaluation supporting the CMA on 11 March 2021, approximately 27,200 vaccinated subjects had been assessed in clinical studies for death and SAEs ¹¹. Since the additional clinical study data referred to by the MAH have not been assessed by EMA, the safety data base within the CMA is the most relevant one.

Laboratory evaluations

Questions (Q2, Q3, parts of Q4) were raised regarding laboratory results from clinical studies and from post-marketing data, regarding e.g. thrombocytopenia. Based on the data presented, there was no clear imbalance of thrombocytopenia without thrombosis or bleeding in the clinical covid-19 studies. However, the platform data with a clear imbalance of low platelet counts in vaccines as compared to placebo is of concern. Therefore, the PRAC Rapporteur suggests that 'thrombocytopenia' should be included in the list of safety concerns as an important potential risk. It should, as feasible, therefore be actively followed up in ongoing PhV studies. The RMP should be updated accordingly.

Thrombosis

Cumulative reviews have also been presented with respect to thrombosis solely, from clinical studies as well as from post marketing experience. These show a numerical imbalance in the clinical trials with regards to overall thromboembolic events (35 individuals who received the vaccine, 27 placebo, 20 still blinded). In the phase 3b study in South Africa, five serious cases have been reported with thromboembolic events. There are currently 80 post-marketing case reports of thromboembolism. Laboratory data to conclude on any concomitant thrombocytopenia are however missing in the majority of cases.

Two additional post-marketing cases of CVST without concomitant thrombocytopenia were reported, one with negative HIT ELISA and one with a positive HIT-antibody test (however apparently after receiving heparin for treatment). As previously discussed, in heparin-induced thrombocytopenia, a decrease in platelet levels $>50\%$ from baseline is also considered suggestive of HIT, which could thus occur also with platelet levels within the normal range. It is considered possible that a similar clinical picture could occur also in thrombosis with thrombocytopenia after vaccination with COVID-19 Vaccine

¹¹ EPAR for [COVID-19 Vaccine Janssen, INN-Ad26.COV2-S, recombinant \(europa.eu\)](https://www.ema.europa.eu/en/medicines/humans/vaccines/COVID-19-Vaccine-Janssen-INN-Ad26.COV2-S-recombinant)

Janssen; however, the patient with positive HIT-antibodies had been treated with heparin before testing for these antibodies.

Thrombosis with thrombocytopenia

Regarding cases with thrombotic/ thromboembolic events and low platelets, there is a total of 21 well described cases (20 post-marketing including late-breaking FDA cases and 1 study case) and one additional potential study case. All the reported cases are from the US.

In the clinical covid-19 studies, one clear case of a 18-28-year-old male with CVST and thrombocytopenia was reported. One case of DVT and thrombocytopenia in a 56-66 male is considered potentially related to the vaccination. One case of CVA and thrombocytopenia in a 50-60 male is unclear since treatment assignment has not been unblinded, and one case of DVT in a 35-45 male does not have any laboratory values reported (neither of these two are included in the total of 21 cases). In addition to the 7 post-marketing reports described in the previous round, 11 additional sufficiently characterised post marketing cases have been reported in EudraVigilance (section 3.5.2), and 2 additional cases were received from the FDA (late-breaking information, section 3.5.3 above).

In total, 15 of the 21 cases had CVST; other thromboses include splanchnic vein thromboses, CVA, peripheral arterial thrombosis and DVT. Three cases were fatal. Age ranges from 18-63 years (excluding the potential clinical study case for whom very little information is given, age ranges from 18-59 years). Of the 21 cases, 17 are female (all post-marketing). Additional cases of thrombosis as well as concomitant thrombosis and thrombocytopenia have been reported post-marketing, but lack of information precludes any firm conclusion on these cases.

It is unclear if treatment with heparin could be used in cases with thrombotic thrombocytopenia following COVID-19 vaccination. The antibodies that are considered to be involved in this syndrome (anti-PF4) are different from those in HIT (heparin-induced thrombocytopenia). Currently, it is not considered sufficiently justified that heparin must be avoided (see Rapporteur's comment in section 3.1.2 for a more detailed discussion). Also, the Rapporteur does not find that there is sufficient evidence to contraindicate or warn against use of COVID-19 Vaccine Janssen in individuals with a history of HIT (see also assessment of Q13 above). Further, there are currently no clear findings that suggest that individuals with any history of thrombosis or thrombocytopenia are more at risk of developing the serious events of concomitant thrombosis and thrombocytopenia as compared to those without any history of thrombosis or thrombocytopenia. Therefore, the PRAC Rapporteur does not propose any warning or precautions in such individuals. Notably, any such warning could potentially lead to false reassurance, and also unjustified exclusion of individuals with a history of thrombosis or thrombocytopenia from being vaccinated.

However, an additional warning (section 4.4) regarding particular attention and need for active further investigation of signs of thrombosis, in case a person is diagnosed with thrombocytopenia relatively recently after vaccination should be added. The reason is a late breaking case report for Vaxzevria, where a person came into primary care with headache and was found to have thrombocytopenia, but who was not further investigated, and sent home instead. The following day, she developed a very serious condition of thrombosis and thrombocytopenia, and shortly thereafter died. There is also one fatal case report from EudraVigilance after COVID-19 Vaccine Janssen (section 3.6.2) in which thrombosis appears not to have been sufficiently investigated early after onset of symptoms.

Since these symptoms have been described and are of relevance also for COVID-19 Vaccine Janssen, a similar update is proposed for section 4.4 (see 3.6.5).

O/E analyses

The O/E analysis submitted by the MAH is based on very limited data since CVST in combination with thrombocytopenia is an extremely rare medical condition, and reported cases so far are few. The MAH has updated the analyses with the most recent and corrected data as requested. The picture of an increased incidence of CVST, as well as CVST in combination with thrombocytopenia in women below 55 years of age who have been vaccinated compared to the expected incidences remains.

Causality discussion

Across the non-clinical studies with Ad26.COV2.S and other Ad26-based vaccines there were no observations indicating an adverse vaccine-related effect on thrombosis and/or thrombocytopenia. The study findings were generally limited to mild and transient effects expected from a local and general inflammatory reaction subsequent to vaccination. Given the very low incidence of the thromboembolic events or coagulopathies associated with Ad26.COV2.S, likely of multifactorial aetiology, it is not unexpected that no signals are observed in healthy animals.

Taken together, the non-clinical data with Ad26.COV2.S and other Ad26-based vaccines provide no further understanding on potential causal relationship between vaccination with Covid-19 vaccine Janssen and the events of thrombosis and thrombocytopenia.

In the first response (15 April), the MAH concluded that the number of thrombotic events with thrombocytopenia are low and there is insufficient data to conclude a definitive causal association with the Ad26.COV2.S vaccine. Nevertheless, following further PRAC discussions, the MAH agreed to update also section 4.8 of the PI, and thus that there is at least a reasonable possibility of causality. As concluded in the AR of 19 April, the PRAC Rapporteur considers that a causal association is sufficiently supported based on the following:

- The observed cases with CVST and concomitant thrombocytopenia represent clinical entities that are extremely rare in an overall population. Although CVST is well-known to occur predominantly in younger females, often related to hormonal factors such as pregnancy, puerperium or estrogen-containing medications, concomitant thrombocytopenia is not part of any usual clinical picture for CVST.
- The findings of positive anti-PF4-antibodies in several cases, in one case with documented non-existing anti-PF4-antibodies before vaccination, suggest that the clinical picture is likely due to these antibodies. A similarity with HIT (heparin-induced thrombocytopenia) is evident based on the clinical picture; however, there is no known exposure to heparin before the events of thrombosis and thrombocytopenia in any of the reported cases, and in one case, a screening test for anti-PF4/heparin antibodies by latex-enhanced immunoassay was negative whereas results of a PF4/polyanion ELISA were strongly positive.
- In several cases, there was no apparent risk factor for CVST or other thrombosis or for thrombocytopenia. For a picture of thrombotic thrombocytopenia with positive anti-PF4-antibodies, this is similar to "spontaneous HIT" which is characterized by a similar clinical and laboratory picture in patients without exposure to heparin; however, some trigger is warranted in such cases (such as surgery, infectious disease etc). The only common trigger in these cases is the vaccination with the Ad26.COV2.S vaccine.
- The timing of events is congruent for all the cases, with symptoms of thrombosis and/or thrombocytopenia occurring within three weeks from the vaccination. This is also in line with what is known for HIT type II and spontaneous HIT as well as for the thrombotic thrombocytopenia related to another adenoviral vector COVID-19 vaccine.

- Extensive work-up excluding other potential causes of thrombosis and/or thrombocytopenia has been provided for two of the cases. This includes antiphospholipid antibodies, homocysteine, Factor VIII, antithrombin, protein C, protein S, Factor V Leiden, prothrombin gene mutation, hepatitis/HIV, ADAMTS 13, PNH and JAK2. The only abnormality that could explain the clinical picture in these cases was positive anti-PF4-antibodies.

Based on the above, the product information section 4.4 and 4.8 were updated in the previous round.

Further regulatory action and additional studies

Product information

No risk groups for thrombosis in combination with thrombocytopenia have been identified with regards to previous thrombosis, thrombocytopenia or both. None of the reported cases have a history suggestive of HIT (heparin-induced thrombocytopenia) or have described exposure to heparin prior to vaccination. At present, no contraindication, warning or precaution is considered well-founded enough to be included in the product information.

However, an additional warning (section 4.4) regarding particular attention and need for active further investigation of signs of thrombosis, in case a person is diagnosed with thrombocytopenia relatively recently after vaccination should be added. The reason is a late breaking case report for Vaxzevria, where a person came into primary care with headache and was found to have thrombocytopenia, but who was not further investigated, and sent home instead. The following day, she developed a very serious condition of thrombosis and thrombocytopenia, and shortly thereafter died. Also, there is one fatal case report from EudraVigilance (section 3.6.2) in which thrombosis appears not to have been sufficiently investigated early after onset of symptoms.

Since these symptoms are of relevance also for COVID-19 Vaccine Janssen and have been described in the case reports, a similar update is proposed for section 4.4.

RMP

There was no clear imbalance of thrombocytopenia without thrombosis or bleeding in the clinical studies. However, based on platform data with an imbalance of low platelet counts in vaccinees as compared to placebo, the PRAC Rapporteur suggests that 'thrombocytopenia' should be included in the list of safety concerns as an important potential risk.

Currently, the COVID-19 Vaccine Janssen RMP includes 'thromboembolism' as an important potential risk. This should be maintained. The PRAC Rapporteur also proposes that 'Thrombosis in combination with thrombocytopenia' should be included as an important identified risk (similar to Vaxzevria).

The MAH has addressed questions regarding additional research and studies, as raised by the PRAC on 9 April. Based on the response the following is concluded:

- No interaction studies of the JanssenCovid-19 vaccine with blood components have been provided. The MAH is exploring whether suitable and valuable in vitro models are available and are planning to collaborate with experts in the field. This is agreed. The MAH should provide a more detailed plan on this work within 30 days. (RSI).
- From a non-clinical perspective, no discussion has been provided on how additional studies can provide further data regarding potential effects of the i) Ad26 vector; ii) the spike

protein on the coagulation system, including potential triggers of platelet activation and subsequent thrombotic effects. The MAH plans to collaborate with experts and will seek regulatory advice on possible investigative non-clinical study proposals. Gaining further clinical data from the rare cases of thrombosis in combination with thrombocytopenia is endorsed prior to design of meaningful hypothesis-driven in vitro or in vivo non-clinical studies. This is agreed. The MAH should provide a more detailed plan on this work within 90 days, which should include a thorough literature review,

- A discussion on the putative cell surface receptors for AD26 viral cell entry, based on literature, has been provided. In vitro experiments have shown that Ad26 can use CAR (coxsackievirus B and adenovirus receptor), CD46 (membrane cofactor protein or cluster of differentiation 46), sialic acid and $\alpha\beta 3$ integrin as cell surface receptors for infecting target cells. The main receptor of human adenovirus type 26 seems not fully established, but current knowledge appears to identify sialic acid-bearing glycans as a primary entry receptor and that this interaction can form a productive infection. These cell surface receptors are all reported to be expressed on human platelets (Gupalo 2011; Seya 1988; Baker 2019; Kasirer-Friede 2007).
- While putative cell surface receptors of Ad26 are discussed, whether Ad26 and cell surface interaction may activate platelets has not been touched upon. In the literature, it is reported that adenoviral vectors of serotype 5 can activate platelets and cause a transient thrombocytopenia following intravenous administration in monkeys (Wolins 2003), rabbits (Cichon 1999), and mice (Varnavski 2005; Othman 2009). In mice, it has been described that after intravenous administration, Ad5 rapidly binds to circulating platelets, which causes their activation/aggregation and subsequent entrapment in liver sinusoids whereafter virus-platelet aggregates are taken up by Kupffer cells and degraded (Stone 2007).
- Finally, no discussion addressing whether the AD26 vector may affect the structure of PF4 has been provided.

In order to further establish the mechanism for this adverse event, the most critical information is a thorough collection of clinical and laboratory data from the affected individuals, including all relevant previous clinical experience. It can be assumed that so far unidentified risk factors are needed for developing this rare condition. A genome analysis of the affected individuals for the potential identification of genetic associations would be highly informative and should be performed if feasible. Based on the collected knowledge, testable hypotheses for the mechanism of the condition should be set up and further mechanistic studies aiming at testing these hypotheses should be designed. A time plan for the mechanistic studies should be provided.

The RMP should be updated accordingly, and the current PhV activities should be revised to reflect data collection also for these safety concerns, as feasible.

Updates in Monthly safety summary reports (MSSRs)

Any updates on cases reports so far, as well as of coming case, should be provided in upcoming MSSR. Furthermore, a literature review on new key clinical data in relation to thrombosis in combination with thrombocytopenia should be included, together with updates on number of cases reported post marketing, presented also based on geographical region.

3.2.5. 2nd Updated Rapporteur's recommendation

The PRAC rapporteur recommends updates of section 4.4 of the SmPC, and of sections 2, 4 and 6 of the Package leaflet.

The following wording is proposed (new text in **bold italics**):

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 COVID-19 Vaccine Janssen. This includes severe cases of venous thrombosis at unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis as well as arterial thrombosis concomitant with thrombocytopenia. Fatal outcome has been reported. These cases occurred within the first three weeks following vaccination, and mostly in women under 60 years of age. Healthcare professionals should be alert to the signs and symptoms of thromboembolism and/or thrombocytopenia. Those vaccinated should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, **leg pain**, leg swelling, or persistent abdominal pain following vaccination. Additionally, anyone with neurological symptoms including severe or persistent headaches, **seizures, confusion** 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. Thrombosis in combination with thrombocytopenia requires specialised clinical management. Healthcare professionals should consult applicable guidance and/or consult specialists (e.g., haematologists, specialists in coagulation) to diagnose and treat this condition.

In individuals diagnosed with thrombocytopenia after vaccination with COVID-19 Vaccine Janssen, a high clinical suspicion is warranted, and patients should be actively investigated for signs of thrombosis.

Package leaflet

Section 2

[...]

As with any vaccine, vaccination with COVID-19 Vaccine Janssen may not fully protect all those who receive it. It is not known how long you will be protected.

Blood disorders

A combination of blood clots and low levels of 'platelets' (cells that help blood to clot) in the blood has been observed very rarely following vaccination with COVID-19 Vaccine Janssen. This includes severe cases with blood clots, including in unusual locations such as the brain, liver, bowel and spleen, in some cases in combination with bleeding. These cases occurred within the first three weeks following vaccination and occurred mostly in women below 60 years of age. Fatal outcome has been reported.

Seek immediate medical attention if you experience severe or persistent headaches, **seizures, confusion** or blurred vision, unexplained skin bruising beyond the site of vaccination which appear a few days after vaccination, **pinpoint round spots beyond the site of vaccination**, develop shortness of breath, chest pain, **leg pain**, leg swelling, or persistent abdominal pain. Inform your health care provider that you have recently received COVID-19 Vaccine Janssen.

Section 4

PRAC rapporteur comment: It is proposed that this section is started highlighting the very rare, serious ADR of thrombosis in combination with thrombocytopenia.

Introducing the section with:

Like all vaccines, COVID-19 Vaccine Janssen can cause side effects, although not everybody gets them. Most of the side effects occur in the 1 or 2 days of getting the vaccination.

Blood clots often in unusual locations (e.g. brain, liver, bowel, spleen) in combination with low level of blood platelets (thrombocytopenia) have been observed very rarely (may affect up to 1 in 10,000 vaccinated individuals).

Get urgent medical attention if from a few days following vaccination you get any of the following symptoms:

- ***experience a severe or persistent headache, blurred vision, confusion or seizures (fits)***
- ***develop shortness of breath, chest pain, leg swelling, leg pain or persistent abdominal pain***
- ***notice unusual skin bruising or pinpoint round spots beyond the site of vaccination***

Get urgent medical attention if you get symptoms of a severe allergic reaction. //...

...//...

Section 6

The following information is intended for healthcare professionals only:

[...]

- 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 pain**, leg swelling, or persistent abdominal pain following vaccination. Additionally, anyone with neurological symptoms including severe or persistent headaches, **seizures, confusion** 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. Thrombosis in combination with thrombocytopenia requires specialised clinical management. Healthcare professionals should consult applicable guidance and/or consult specialists (e.g., haematologists, specialists in coagulation) to diagnose and treat this condition.
- ***In individuals diagnosed with thrombocytopenia after vaccination with COVID-19 Vaccine Janssen, a high clinical suspicion is warranted, and patients should be actively investigated for signs of thrombosis.***

RMP

1. 'Thrombosis in combination with thrombocytopenia' should be included as an important identified risk based on the observed case reports and that a causal association is considered sufficiently supported. 'Thromboembolism' is currently included as an important potential risk. This should be maintained.

2. 'Thrombocytopenia' should be included in the list of safety concerns as an important potential risk, based on the imbalance of decreased platelet counts in the platform data.
3. The current PhV activities should be revised to reflect data collection also for these safety concerns, as feasible. Furthermore, the following should be addressed in the RMP:
 - a. The MAH should provide a more detailed plan on interaction studies of the JanssenCovid-19 vaccine with blood components within 30 days
 - b. The MAH should provide a more detailed plan on how additional studies can provide further data regarding potential effects of the i) Ad26 vector; ii) the spike protein on the coagulation system, including potential triggers of platelet activation and subsequent thrombotic effects. Gaining further clinical data from the rare cases of thrombosis in combination with thrombocytopenia is endorsed prior to design of meaningful hypothesis-driven in vitro or in vivo non-clinical studies. This plan should be provided within 90 days. A thorough literature review should be included, and this should also be taken into account for the expected plan for further research in this topic.

As revised RMP should be submitted, to reflect the points above.

3.2.6. Comments from other PRAC members

Supportive comments were received from **Member states**.

Member state 1:

We fully agree with the PRAC Rapporteur. We have some comments on the proposed amendments of the SmPC and PL:

Section 4.4

- Use of the term 'Thrombosis with Thrombocytopenia Syndrome (TTS) may be considered in this section.
- For the addition of '**confusion**': it is suggested to use 'mental status change', as mental status changes (including confusion) is a presenting symptom in CVST in 22% (Capecchi et al. 2018) and this would also cover other symptoms of alert such as confusion, behaviour disorders, amnesia, delirium etc.
- For the additional warning regarding high clinical suspicion, the following may be considered:
As Thrombosis with Thrombocytopenia Syndrome may initially present with symptoms or signs of either thrombosis or thrombocytopenia, patients who are diagnosed with unexplained thrombocytopenia following vaccination even in the absence of signs and symptoms of thrombosis should be actively investigated for evidence of thrombosis. Similarly, patients who present with thromboembolism following vaccination should be evaluated for thrombocytopenia.

The proposed addition in section 6 of the PL is not supported. Following input from EMA (QRD) may be considered:

"According to QRD template 10.2, this section should include practical information specially for parenteral preparations relevant for healthcare professionals, such as on preparation and/or handling, incompatibilities, posology of the medicine, overdose or monitoring measures and laboratory

investigations, where relevant. Therefore, I don't think that this is the best place to include information on the safety warning on thrombocytopenia and coagulation disorders that could happen within the first fourteen days following vaccination. Moreover, please also note that no information on the anaphylactic reactions that could happen even sooner than the thrombocytopenia disorders following the administration of the vaccine have been included in this section for any of the other authorised COVID-19 vaccines. Therefore, I would not be in favour of including this information to keep consistency with the information included so far."

PRAC Rapporteur Comment

For section 4.4, we consider that the initial part of the first proposed sentence ('As Thrombosis with Thrombocytopenia Syndrome may initially present with symptoms or signs of either thrombosis or thrombocytopenia') is not warranted (also to avoid naming this 'TTS' at present). We fully agree to change 'confusion' to 'mental status change'. Also, not only 'unexplained' thrombocytopenia but any thrombocytopenia should warrant active investigation for evidence of thrombosis (notably, thrombocytopenia is not uncommon after other vaccinations). Further, we do not think that patients without any signs or symptoms of thrombosis should be actively investigated for thrombosis – it is not clear what this means and could cause confusion among prescribers and potentially lead to unnecessary radiological investigations.

For our amended proposal for section 4.4, see section 3.6.8 below.

For section 6, this section was updated within the previous round of this procedure.

3.2.7. Response from MAH (submitted 30 April 2021)

SUMMARY OF PRODUCT CHARACTERISTICS

Section 4.4. Thrombocytopenia and coagulation disorders

The Company agrees with the Rapporteur to include a paragraph to highlight the importance of active investigation and proposes to move the proposed new text to the end of the second paragraph under "Thrombocytopenia and coagulation disorders" as an extension of the existing signs and symptoms that physicians should be aware of. The Company also proposes to include a timeframe "within three weeks" during which physicians should remain vigilant and also proposes to replace patients with "vaccine recipients".

PACKAGE LEAFLET

Section 2. What you need to know before you are given COVID-19 Vaccine Janssen

The Company agrees to move the following sentence "As with any vaccine, vaccination with COVID-19 Vaccine Janssen may not fully protect all those who receive it. It is not known how long you will be protected." under Warnings and precautions (ie, above the blood disorders paragraph).

The Company proposes to include the patient friendly term "fits" after "seizures" to align with the Rapporteur proposal in Section 4, when describing when to seek immediate medical attention under Blood disorders in the context of the following paragraph:

"Seek immediate medical attention, if you experience severe or persistent headaches **seizures (fits), confusion** or blurred vision, unexplained skin bruising beyond the site of vaccination which appear a few days after vaccination, **pinpoint round spots beyond the site of vaccination**, develop

shortness of breath, chest pain, **leg pain**, leg swelling, or persistent abdominal pain. Inform your healthcare provider that you have recently received COVID-19 Vaccine Janssen."

Section 4. Possible side effects

The Company agrees to add the proposed text relating to possible side effects.

Section 6 Contents of the package and other information

The Company agrees with the Rapporteur to include a paragraph to highlight the importance of active investigation and proposes to move the proposed new text to the end of the 6th bullet point under "The following information is intended for healthcare professionals only" as an extension of the existing signs and symptoms that physicians should be aware of.

The Company also proposes to include a timeframe "within three weeks" during which physicians should remain vigilant and also proposes to replace patients with "vaccine recipients".

RISK MANAGEMENT PLAN (RMP)

RECOMMENDATION 1

Thrombosis in combination with thrombocytopenia should be included as an important identified risk based on the observed case reports and that a causal association is considered sufficiently supported. 'Thromboembolism' is currently included as an important potential risk. This should be maintained.

APPLICANT RESPONSE

The Company agrees to include thrombosis in combination with thrombocytopenia as an important identified risk in the EU-RMP, based on a plausible association. The Company would like to clarify that Venous Thromboembolism (and not all forms of Thromboembolism) is currently included as an important potential risk.

RECOMMENDATION 2

'Thrombocytopenia' should be included in the list of safety concerns as an important potential risk, based on the imbalance of decreased platelet counts in the platform data.

APPLICANT RESPONSE

The Company respectfully disagrees with the proposed inclusion of thrombocytopenia as an important potential risk, considering:

- The late breaking cases reported following vaccination with the AstraZeneca vaccine Vaxzevria are cases within the spectrum of thrombosis in combination with thrombocytopenia, which will be included as an important identified risk.
- Thrombocytopenia is commonly reported as an Adverse Event following immunization, especially following immunization with live attenuated viral vaccines. The mechanistic evidence is considered weak to establish a causal relationship. In most cases, such events of thrombocytopenia are either asymptomatic or mild (IOM, 2012).
- The reports of low platelets / thrombocytopenia observed within 28 days following study vaccination during clinical development of other Ad26-based vaccines were determined to be transient in nature and not associated with a thrombotic or embolic event: Platelet count decrease was observed following 70 out of 4,105 Ad26 doses (1.7%) and 7 out of 719 placebo doses (1.0%). In total, 18 cases of Grade 3 platelet count decrease cases were reported within 28 days following Ad26 vaccination (mostly coinciding with the 8 days post-vaccination visit). Except one case for which the safety laboratory assessment was not repeated, all Grade 3 platelet count decrease cases returned to normal range upon retesting in the days following the Grade 3 event. A single case of persistent (duration 40 days), grade 3 thrombocytopenia was reported in a 54-64-year-old female following

vaccination with Ad26.RSV.preF (study VAC18193RSV1004, RSV adult program). The subject remained asymptomatic throughout the duration of the event and had normal physical exams (no bruising and/or petechiae reported). This is described in further detail in the response to the PRAC meeting of 07 April, Question 4.3 (Ad26 Platform Data). Based on the above, the Company considers that standalone thrombocytopenia does not meet the criteria to be considered an important potential risk. The Company considers the proposed wording in the SmPC Warnings and Precautions section to be adequate (with amendments, see response to SmPC recommendations) appropriate. However, the Company considers this to be a risk minimization measure for thrombosis with thrombocytopenia not for thrombocytopenia alone.

RECOMMENDATION 3

The current PhV activities should be revised to reflect data collection also for these safety concerns, as feasible. Furthermore, the following should be addressed in the RMP: a. The MAH should provide a more detailed plan on interaction studies of the Janssen COVID-19 vaccine with blood components within 30 days. b. The MAH should provide a more detailed plan on how additional studies can provide further data regarding potential effects of the i) Ad26 vector; ii) the spike protein on the coagulation system, including potential triggers of platelet activation and subsequent thrombotic effects. Gaining further clinical data from the rare cases of thrombosis in combination with thrombocytopenia is endorsed prior to design of meaningful hypothesis driven in vitro or in vivo non-clinical studies. This plan should be provided within 90 days. A thorough literature review should be included, and this should also be taken into account for the expected plan for further research in this topic.

APPLICANT RESPONSE

The Company agrees to provide more detailed proposed study plans as requested above but would appreciate clarification on how to address this in the EU-RMP.

PRAC Rapporteur Comment

For the SmPC, the addition of a timeframe for thrombocytopenia of "within three weeks" during which physicians should be vigilant, see updated proposed recommendation in section 3.6.8 below.

It is not considered appropriate to replace patients with "vaccine recipients" for those who are diagnosed with either thrombocytopenia or thrombosis, since they would normally be considered patients if they have required a work-up for either thrombocytopenia or thrombosis.

For the PL, the MAH proposed amendments regarding fits (section 2) and timeframe (section 6) are accepted, see revised proposal in section 3.6.8 below.

For the RMP, it has been clarified in the recommendations that the current important potential risk (to be maintained) pertains to venous thromboembolism only.

The Rapporteur maintains that 'thrombocytopenia' should be listed as an important potential risk. The imbalance in the platform data is sufficiently clear to support this, and therefore, it is considered to classify thrombocytopenia as an important potential risk. The case in the platform data reiterated by the MAH (54-64-year-old female with grade 3 thrombocytopenia for more than 40 days) is not considered to support that this cannot be clinically relevant.

Regarding how to address this in the RMP; all parts of the RMP should be updated to reflect the new safety concerns. Furthermore, the PhV-plan should be updated with revised / new proposals for additional data collection including studies.

It is anticipated that a revised RMP is submitted within another procedure, within a relatively short time frame. This needs further confirmation with the EMA.

3.2.8. 3rd Updated Rapporteur's proposed recommendation

The PRAC rapporteur recommends updates of section 4.4 of the SmPC, and of sections 2, 4 and 6 of the Package leaflet.

The following wording is proposed (new text in ***bold italics, changes from 2nd recommendation highlighted***):

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 COVID-19 Vaccine Janssen. This includes severe cases of venous thrombosis at unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis as well as arterial thrombosis concomitant with thrombocytopenia. Fatal outcome has been reported. These cases occurred within the first three weeks following vaccination, and mostly in women under 60 years of age. Healthcare professionals should be alert to the signs and symptoms of thromboembolism and/or thrombocytopenia. Those vaccinated should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, ***leg pain***, leg swelling, or persistent abdominal pain following vaccination. Additionally, anyone with neurological symptoms including severe or persistent headaches, ***seizures, mental status change*** 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. Thrombosis in combination with thrombocytopenia requires specialised clinical management. Healthcare professionals should consult applicable guidance and/or consult specialists (e.g., haematologists, specialists in coagulation) to diagnose and treat this condition.

In individuals diagnosed with thrombocytopenia within 3 weeks after vaccination with COVID-19 Vaccine Janssen, a high clinical suspicion is warranted, and patients should be actively investigated for signs of thrombosis. Similarly, patients who present with thromboembolism following vaccination should be evaluated for thrombocytopenia.

Package leaflet

Section 2

[...]

As with any vaccine, vaccination with COVID-19 Vaccine Janssen may not fully protect all those who receive it. It is not known how long you will be protected.

Blood disorders

A combination of blood clots and low levels of 'platelets' (cells that help blood to clot) in the blood has been observed very rarely following vaccination with COVID-19 Vaccine Janssen. This includes severe cases with blood clots, including in unusual locations such as the brain, liver, bowel and spleen, in some cases in combination with bleeding. These cases occurred within the first three weeks following vaccination and occurred mostly in women below 60 years of age. Fatal outcome has been reported.

Seek immediate medical attention if you experience severe or persistent headaches, **seizures (fits)**, **mental status change** or blurred vision, unexplained skin bruising beyond the site of vaccination which appear a few days after vaccination, **pinpoint round spots beyond the site of vaccination**, develop shortness of breath, chest pain, **leg pain**, leg swelling, or persistent abdominal pain. Inform your health care provider that you have recently received COVID-19 Vaccine Janssen.

Section 4

PRAC rapporteur comment: It is proposed that this section is started highlighting the very rare, serious ADR of thrombosis in combination with thrombocytopenia.

Introducing the section with:

Like all vaccines, COVID-19 Vaccine Janssen can cause side effects, although not everybody gets them. Most of the side effects occur in the 1 or 2 days of getting the vaccination.

Blood clots often in unusual locations (e.g. brain, liver, bowel, spleen) in combination with low level of blood platelets (thrombocytopenia) have been observed very rarely (may affect up to 1 in 10,000 vaccinated individuals).

Get urgent medical attention if from a few days following vaccination you get any of the following symptoms:

- ***experience a severe or persistent headache, blurred vision, **mental status change** or seizures (fits)***
- ***develop shortness of breath, chest pain, leg swelling, leg pain or persistent abdominal pain***
- ***notice unusual skin bruising or pinpoint round spots beyond the site of vaccination***

Get urgent medical attention if you get symptoms of a severe allergic reaction. //...

...//...

Section 6

The following information is intended for healthcare professionals only:

[...]

- 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 pain**, leg swelling, or persistent abdominal pain following vaccination. Additionally, anyone with neurological symptoms including severe or persistent headaches, **seizures, mental status change** 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. Thrombosis in combination with thrombocytopenia requires specialised clinical management. Healthcare professionals should consult applicable guidance and/or consult specialists (e.g., haematologists, specialists in coagulation) to diagnose and treat this condition.
- ***In individuals diagnosed with thrombocytopenia **within 3 weeks** after vaccination with COVID-19 Vaccine Janssen, a high clinical suspicion is warranted, and patients should be actively investigated for signs of thrombosis. **Similarly, patients who*****

present with thromboembolism following vaccination should be evaluated for thrombocytopenia.

RMP

4. 'Thrombosis in combination with thrombocytopenia' should be included as an important identified risk based on the observed case reports and that a causal association is considered sufficiently supported. 'Venous Thromboembolism' is currently included as an important potential risk. This should be maintained.
5. 'Thrombocytopenia' should be included in the list of safety concerns as an important potential risk, based on the imbalance of decreased platelet counts in the platform data.
6. The current PhV activities should be revised to reflect data collection also for these safety concerns, as feasible. Furthermore, the following should be addressed in the RMP:
 - a. The MAH should provide a more detailed plan on interaction studies of the JanssenCovid-19 vaccine with blood components within 30 days
 - b. The MAH should provide a more detailed plan on how additional studies can provide further data regarding potential effects of the i) Ad26 vector; ii) the spike protein on the coagulation system, including potential triggers of platelet activation and subsequent thrombotic effects. Gaining further clinical data from the rare cases of thrombosis in combination with thrombocytopenia is endorsed prior to design of meaningful hypothesis-driven in vitro or in vivo non-clinical studies. This plan should be provided within 90 days. A thorough literature review should be included, and this should also be taken into account for the expected plan for further research in this topic.

All parts of the RMP should be updated to reflect the new safety concerns. Furthermore, the PhV-plan should be updated with revised / new proposals for additional data collection including studies. It is anticipated that a revised RMP is submitted within another procedure, within a relatively short time frame. This needs further confirmation with the EMA.

3.2.9. Adopted PRAC Recommendation

The PRAC has reviewed additional evidence concerning thromboembolic events in association with Covid-19 Janssen vaccine, with particular focus on cases with combination of thrombosis and thrombocytopenia. Recently, this condition has been named 'thrombosis with thrombocytopenia syndrome (TTS)'. The updated review has included data ascertained from newly identified spontaneously reported cases both in EudraVigilance and other sources, clinical, pre-clinical and literature data and data from the marketing authorisation holder (MAH).

Based on review of the available evidence the PRAC considers that further updates to the product information are required including information to outline that patients who are diagnosed with thrombocytopenia within three weeks of vaccination should be actively investigated for signs of thrombosis. Similarly, updates have been included in order to reflect that patients who present with thrombosis within 3 weeks of vaccination should be evaluated for thrombocytopenia. Furthermore, the condition should be renamed 'thrombosis with thrombocytopenia syndrome'.

The PIL should be updated to include information at the start of section 4, concerning the signs and symptoms of thrombosis with thrombocytopenia.

The PRAC has also reviewed preclinical and literature data concerning possible pathophysiological mechanisms. A plan concerning additional pharmacovigilance activities, aimed to further elucidate potential pathophysiological mechanism(s) for TTS, and for quantification of the magnitude of the risk, should be submitted.

Following further consideration, the text regarding TTS which was added to section 6 of the package leaflet following the extraordinary PRAC meeting on 20 April 2021, should be removed. The reason is that it is not considered to fulfil the purpose of the information to be added to that section of the package leaflet, as per the requirements specified in QRD template 10.2.

The PRAC recommends that the MAH for Covid-19 Vaccine Janssen (Janssen-Cilag International NV) should submit a variation to amend the product information as described below (new text underlined/text to be removed with strikethrough):

Section 4.4

~~Thrombocytopenia and coagulation disorders~~ **Thrombosis with thrombocytopenia syndrome**

A combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with COVID-19 Vaccine Janssen. This includes severe cases of venous thrombosis at unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis as well as arterial thrombosis concomitant with thrombocytopenia. Fatal outcome has been reported. These cases occurred within the first three weeks following vaccination, and mostly in women under 60 years of age.

Healthcare professionals should be alert to the signs and symptoms of thromboembolism and/or thrombocytopenia. Those vaccinated should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg pain, leg swelling, or persistent abdominal pain following vaccination. Additionally, anyone with neurological symptoms including severe or persistent headaches, seizures, mental status change 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.

Thrombosis in combination with thrombocytopenia requires specialised clinical management. Healthcare professionals should consult applicable guidance and/or consult specialists (e.g., haematologists, specialists in coagulation) to diagnose and treat this condition.

Individuals diagnosed with thrombocytopenia within 3 weeks after vaccination with COVID-19 Vaccine Janssen should be actively investigated for signs of thrombosis. Similarly, individuals who present with thrombosis within 3 weeks of vaccination should be evaluated for thrombocytopenia.

Package leaflet

Section 2

[...]

Blood disorders

A combination of blood clots and low levels of 'platelets' (cells that help blood to clot) in the blood has been observed very rarely following vaccination with COVID-19 Vaccine Janssen. This includes severe

cases with blood clots, including in unusual locations such as the brain, liver, bowel and spleen, in some cases in combination with bleeding. These cases occurred within the first three weeks following vaccination and occurred mostly in women below 60 years of age. Fatal outcome has been reported.

Seek immediate medical attention if you experience severe or persistent headaches, seizures (fits), mental status change or blurred vision, unexplained skin bruising beyond the site of vaccination which appear a few days after vaccination, pinpoint round spots beyond the site of vaccination, develop shortness of breath, chest pain, leg pain, leg swelling, or persistent abdominal pain. Inform your health care provider that you have recently received COVID-19 Vaccine Janssen.

Section 4

Like all vaccines, COVID-19 Vaccine Janssen can cause side effects, although not everybody gets them. Most of the side effects occur in the 1 or 2 days of getting the vaccination.

Get medical attention immediately if within 3 weeks of vaccination you get any of the following symptoms:

- experience a severe or persistent headache, blurred vision, mental status changes or seizures (fits)
- develop shortness of breath, chest pain, leg swelling, leg pain or persistent abdominal pain
- notice unusual skin bruising or pinpoint round spots beyond the site of vaccination

Get urgent medical attention if you get symptoms of a severe allergic reaction. **...//**

Section 6

The following information is intended for healthcare professionals only:

[...]

- 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 pain, leg swelling, or persistent abdominal pain following vaccination. Additionally, anyone with neurological symptoms including severe or persistent headaches, seizures, mental status change 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. Thrombosis in combination with thrombocytopenia requires specialised clinical management. Healthcare professionals should consult applicable guidance and/or consult specialists (e.g., haematologists, specialists in coagulation) to diagnose and treat this condition.

Risk management plan (RMP)

The RMP needs to be revised to reflect the outcome of this signal review. This should be undertaken in steps.

For the **first step**, the marketing authorisation holder (MAH) should submit a variation within 14 days. In this variation the safety specification should be updated as follows:

- Add “Thrombosis with thrombocytopenia syndrome” to the list of safety concerns as an important identified risk. All parts of the RMP should be updated accordingly.
- Add “Thrombocytopenia” to the list of safety concerns as an important potential risk. All parts of the RMP should be updated accordingly.

Furthermore, in **ongoing clinical studies**, the following should be addressed:

1. The MAH should ensure that all reported thrombotic events with thrombocytopenia and/or bleeding events are investigated by exploring within planned/ongoing studies an in-depth exploration of platelet function as needed, as well as investigation of the patient’s immunological background. The following tests should be considered but not limited to:
 - a. Measurements of platelet levels, D-dimer and fibrinogen levels;
 - b. Additional laboratory testing: Complete blood count (haemoglobin levels, white blood cells with complete formula, thrombocyte levels), haemolysis parameters (schistocytes, reticulocytes, haptoglobin levels), ADAMTS13 activity, PTT, TCA, fibrinogen, D-dimers, lupus anti-coagulant research (including cardiolipin antibodies IgG and IgM) and anti B2GPI antibodies IgG and IgM;
 - c. In case of low levels of platelets: titration of anti-PF4 antibodies;
 - d. Additional search for anti-platelets antibodies (with specific target to identify) and deep exploration of platelet function;
 - e. Investigation of patient “immune background” (e.g. anti-nuclear factor, ANCA, rheumatoid factor, HLA B27, hypersensitivity markers).
 - f. COVID-19 testing, including PCR and serology: with regard to relevant cases, information on the type of testing performed, the timing of such testing, and the site from which the PCR swabs were taken should also be provided.
 - g. Other analysis to consider include:
 - i. Factor V Leiden; Factor II (prothrombin) variant; Inflammatory markers: TNF α , IL-1, IL-4, IL-6, IL-10, IL-13;
 - ii. Platelet activation markers: sCD40L, soluble glycoproteins, degranulation markers (PF4, vWF, P-selectin, annexin V);
 - iii. Cell adhesion molecules;
 - iv. Immunology: C3, C4, antinuclear IgG, anti-double stranded DNA IgG, anti-Smith IgG, anti-SSA IgG, anti-SSB IgG, anti-Jo1 IgG, anti-MPO IgG, anti-PR3 IgG, anti-glomerular basement membrane IgG;
 - v. Complement activation markers: Complement Complex C5b-9, C5a;
 - vi. Adeno virus serology;
 - vii. Tissue type (genetics)
 - viii. Serology to be considered: Cytomegalovirus (IgG and IgM,) Epstein-Barr virus (IgG and IgM),

Finally, in ongoing /planned **post-authorisation observational studies**, the following should be addressed:

The protocols of existing post-authorisation observational studies (i.e. VAC31518COV4003, VAC31518COV4001) should be modified to include the AESIs of concern, as described below. The Brighton Collaboration Interim Case Definition for Thrombosis with Thrombocytopenia Syndrome should also be considered for case finding algorithms.

List: Preferred Terms for embolic and thrombotic events

'Embolic and thrombotic events, arterial'	'Embolic and thrombotic events, venous'	'Embolic and Thrombotic events, vessel type unspecified and mixed arterial and venous'
Acute aortic syndrome ³ Acute myocardial infarction ³ Arterial thrombosis Cerebellar artery occlusion Cerebellar artery thrombosis Cerebral artery embolism Cerebral artery occlusion Cerebral artery thrombosis Coronary artery embolism ³ Coronary artery occlusion ³ Coronary artery reocclusion ³ Coronary artery thrombosis ³ Coronary vascular graft occlusion ³ Embolism arterial Femoral artery embolism Hepatic artery embolism Hepatic artery occlusion Hepatic artery thrombosis Iliac artery embolism Iliac artery occlusion Ischaemic cerebral infarction ² Ischaemic stroke ² Mesenteric arterial occlusion Mesenteric arteriosclerosis Mesenteric artery embolism Mesenteric artery thrombosis Myocardial infarction ³ Myocardial necrosis ³ Papillary muscle infarction ³ Peripheral artery occlusion Peripheral artery thrombosis Peripheral embolism Post procedural myocardial infarction ³ Pulmonary artery occlusion Pulmonary artery thrombosis Renal artery occlusion Renal artery thrombosis Renal embolism Retinal artery embolism Retinal artery occlusion Retinal artery thrombosis Silent myocardial infarction ³ Spinal artery embolism Spinal artery thrombosis Splenic artery thrombosis Splenic embolism Subclavian artery embolism Subclavian artery occlusion Subclavian artery thrombosis Thromboembolectomy Thrombotic microangiopathy	Budd-Chiari syndrome Cavernous sinus thrombosis Cerebral venous sinus thrombosis Cerebral venous thrombosis ² Deep vein thrombosis ² Embolism venous ² Hepatic vein occlusion Hepatic vein thrombosis Iliac vein occlusion Inferior vena caval occlusion Jugular vein occlusion Jugular vein thrombosis Mesenteric vein thrombosis Mesenteric venous occlusion Ophthalmic vein thrombosis Pelvic venous thrombosis Portal vein occlusion Portal vein thrombosis Pulmonary embolism ² Pulmonary infarction Pulmonary microemboli Pulmonary thrombosis Pulmonary vein occlusion Pulmonary venous thrombosis Renal vein occlusion Renal vein thrombosis Retinal vein occlusion Retinal vein thrombosis Splenic vein occlusion Splenic vein thrombosis Superior sagittal sinus thrombosis Superior vena cava occlusion Transverse sinus thrombosis Venous thrombosis	Basal ganglia stroke ² Brain stem infarction ² Brain stem stroke ² Cerebellar infarction ² Cerebral infarction ² Cerebral ischaemia Cerebral microembolism Cerebral microinfarction ² Cerebral thrombosis Cerebral vascular occlusion Cerebrovascular accident ² Choroidal infarction ² Coronary bypass thrombosis ³ Disseminated intravascular coagulation ¹ Embolic cerebellar infarction ² Embolic cerebral infarction ² Embolic stroke ² Haemorrhagic adrenal infarction Haemorrhagic cerebral infarction Haemorrhagic infarction ² Haemorrhagic stroke ² Haemorrhagic transformation stroke ² Heparin-induced thrombocytopenia Microembolism Pituitary infarction ² Post procedural stroke ² Spinal stroke ² Stroke in evolution ² Strokectomy ² Thrombotic stroke ²

Thrombotic thrombocytopenic purpura Transient ischaemic attack Vertebral artery occlusion Vertebral artery thrombosis		
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Codes: 1 – PT already listed for AESI 'Vaccine associated-disease'; 2 – PT already listed for AESI 'Stroke and other cerebrovascular events, Venous thromboembolism'; 3 – PT already listed for AESI 'Myocardial infarction', no code = selection by PRAC RAP expert

As a **second step**, another variation should be submitted within 90 days in order to further update the pharmacovigilance plan (part III) of the RMP. The variation should present a plan aimed at further characterisation of the important identified risk of "thrombosis with thrombocytopenia syndrome". This should include proposals of **new studies**. The following should be addressed:

Ascertainment and evaluation of further clinical data from rare cases of TTS will be a critical part in designing proposals for hypothesis-driven in vitro or in vivo non-clinical studies. Furthermore, a thorough literature review should also be taken into account for the proposals of further mechanistic work. These pieces of background material should be submitted within the variation. Based on that, the MAH should present:

- A detailed plan on interaction studies of the Janssen Covid-19 vaccine with blood components (e.g. erythrocytes, thrombocytes, leucocytes etc., coagulation factors, natural IgM antibodies) both in the presence and absence of pre-existing immunity to Ad26.CoV2-S.
- A detailed plan on how additional studies can provide further data regarding potential effects of the i) Ad26 vector; ii) the spike protein on the coagulation system, including potential triggers of platelet activation and subsequent thrombotic effects.
- The MAH should address the feasibility of conducting pharmacogenomic analyses in cases of TTS, as part of further evaluation of possible underlying biological mechanisms behind TTS following use of the Covid-19 vaccine Janssen.

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The MAH has included the following references in their response on 22nd of April 2021:

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5. Annex

DHPC agreed at the extraordinary PRAC on 20 April 2021.

COVID-19 Vaccine Janssen: link between the vaccine and the occurrence of thrombosis in combination with thrombocytopenia

Dear Healthcare Professional,

Janssen-Cilag International NV in agreement with the European Medicines Agency and the <National Competent Authority > would like to inform you of the following:

Summary

- **A combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with COVID-19 Vaccine Janssen. A causal relationship with the vaccine is considered plausible.**
- **These cases occurred within the first three weeks following vaccination, and mostly in women under 60 years of age.**
- **No specific risk factors have been identified at this stage.**
- **Healthcare professionals should be alert to the signs and symptoms of thromboembolism and/or thrombocytopenia.**
- **Those being vaccinated should be instructed to seek immediate medical attention if they develop symptoms of thromboembolism and, or thrombocytopenia following vaccination.**

- **Thrombosis in combination with thrombocytopenia requires specialised clinical management. Consult applicable guidance and/or specialists (e.g., haematologists, specialists in coagulation) to diagnose and treat this condition.**

Background on the safety concern

COVID-19 Vaccine Janssen suspension for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older.

A combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with COVID-19 Vaccine Janssen. This includes severe cases of venous thrombosis at unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis concomitant with thrombocytopenia. Fatal outcome has been reported. These cases occurred within the first three weeks following vaccination, and mostly in women under 60 years of age.

Healthcare professionals should be alert to the signs and symptoms of thromboembolism and/or thrombocytopenia. Those vaccinated should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg swelling, or 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.

In several of the cases with concomitant thrombosis and thrombocytopenia, testing for anti-platelet factor (PF) 4-antibodies was positive or strongly positive. Extensive work-up for other potential mechanisms that could cause thrombosis and/or thrombocytopenia has been provided for a minority of these cases; however, no other abnormalities have been found that are considered to explain the observed events. However, the exact pathophysiological mechanism for the occurrence of these thrombotic events is not defined yet. No specific risk factors have been identified at this stage.

Thrombosis in combination with thrombocytopenia requires specialised clinical management. Healthcare professionals should consult applicable guidance and/or consult specialists (e.g., haematologists, specialists in coagulation) to diagnose and treat this condition.

The Pharmacovigilance Risk Assessment Committee, PRAC, one of EMA's scientific committees, has performed a thorough investigation including a review of case reports of blood clots and thrombocytopenia in individuals who received the vaccine and has also evaluated an observed to expected analysis.

Based on the current evidence, the PRAC has recommended an update to the product information to reflect the current knowledge of this safety issue. This comprises an update of the warning section, as well as inclusion of thrombosis in combination with thrombocytopenia as an adverse reaction with a frequency of very rare.

Call for reporting

Healthcare professionals should report any suspected adverse reactions associated with the use of COVID-19 Vaccine Janssen in accordance with the national spontaneous reporting system *<include the details (e.g. name, postal address, fax number, website address) on how to access the national spontaneous reporting system>*.

▼ This product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Company contact point

<Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address (company contact point in the concerned EU MS should be included, respectively)>

Yours Faithfully

Medical Director of Janssen-Cilag International B.V.

Communication plan

Communication Plan for Direct Healthcare Professional Communication

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	COVID-19 Vaccine Janssen suspension for injection (Ad26.COVID-S [recombinant])
Marketing authorisation holder(s)	Janssen-Cilag International N.V.
Safety concern and purpose of the communication	Information on the risk of thrombosis in combination with thrombocytopenia.
DHPC recipients	General practitioners, specialists in internal medicine, haematology, emergency medicine and vaccination centres. The target group should be further defined at national level, in agreement with the respective national competent authority.
Member States where the DHPC will be distributed	All EU member states where COVID-19 Vaccine Janssen is authorised.
Timetable	Date

DHPC and communication plan (in English) agreed by PRAC	Tue 20/04/2021
DHPC and communication plan (in English) agreed by CHMP	Wed 21/04/2021
Submission of translated DHPCs to the national competent authorities for review	Thu 22/04/2021
Agreement of translations by national competent authorities	Fri 23/04/2021
Dissemination of DHPC	Mon 26/04/2021