European Union Risk Management Plan
JCOVDEN (VAC31518 [Ad26.COV2.S])

Data lock point for current RMP	03 July 2023	Version number	8.2

Final for Procedure EMEA/H/C/005737/II/0076 - Health Authority approval date 11 July 2024

Note: This document contains unblinded clinical trial data

CHMP Opinion Date = 11 July 2024

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QPPV Sign-off Date:	12 July 2024
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PPD

QPPV Name(s)[1]:	Dr. Laurence Oster-Gozet, PharmD, PhD
QPPV Signature:	The MAH QPPV has either reviewed and approved this RMP, or approved with an electronic signature appended to this RMP, as applicable.

Details of this RMP Submission	
Version Number	8.2
Rationale for submitting an updated RMP (if applicable)	Address the PRAC request for procedure EMEA/H/C/005737/II/0076 as included in the Request for Supplementary Information dated 11 April 2024.
Summary of significant changes in this RMP:	• Removal of trials COV2008 and COV3001 and study COV4002 as additional pharmacovigilance activities as the procedure EMEA/H/C/005737/II/0075/G is concluded. • Removal of a mechanistic study, ie, RNA transcriptome analysis after dosing with Ad26.COV2.S in Cynomolgus monkey, as additional pharmacovigilance activity as the study is completed and the nonclinical procedure EMEA/H/C/005737/II/0074/G is concluded. • Removal of trial COV3005 as additional pharmacovigilance activity as the trial is completed. • Inclusion of safety data of the extended cross-dose level pooling. • Removal of the missing information 'Interaction with other vaccines'.

Other RMP Versions Under Evaluation:

RMP Version Number	Submitted on	Procedure Number
Not applicable		

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[1] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu

Details of the Currently Approved RMP:

Version number of last agreed RMP:	7.1
Approved within procedure	EMEA/H/C/005737/II/0071/G
Date of approval (Competent authority opinion date)	08 June 2023

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PART I: PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name)	COVID-19 vaccine (Ad26.COV2-S [recombinant]), further referred to as Ad26.COV2.S
Pharmacotherapeutic group(s) (ATC Code)	COVID-19, viral vector, non-replicating (ATC code: J07BN02)
Marketing Authorisation Holder	Janssen-Cilag International NV
Medicinal products to which the RMP refers	1
Invented name(s) in the EEA	JCOVDEN
Marketing authorisation procedure	Centralized
Brief description of the product	Chemical class Ad26.COV2.S is a recombinant, replication-incompetent monovalent vaccine.
	Summary of mode of action Ad26.COV2.S is a monovalent vaccine composed of a recombinant, replication-incompetent human Ad26 vector that encodes a SARS-CoV-2 full-length S glycoprotein in a stabilized conformation. Following administration, the S glycoprotein of SARS-CoV-2 is transiently expressed, stimulating both neutralizing and other functional S-specific antibodies, as well as cellular immune responses directed against the S antigen, which may contribute to protection against COVID-19.
	Important information about its composition Ad26.COV2.S is produced in the PER.C6 TetR Cell Line and by recombinant DNA technology. Ad26.COV2.S contains genetically modified organisms. List of excipients: • 2-hydroxypropyl-β-cyclodextrin (HBCD) • Citric acid monohydrate • Ethanol • Hydrochloric acid • Polysorbate 80 • Sodium chloride • Sodium hydroxide • Trisodium citrate dihydrate • Water for injections
Reference to the Product Information	Module 1.3.1, Summary of Product Characteristics, Labeling and Package Leaflet

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Indication(s) in the EEA	Current: JCOVDEN is indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. JCOVDEN should be used in accordance with official recommendations.	
	Proposed: Not applicable	
Dosage in the EEA	Current: Primary vaccination JCOVDEN is administered as a single dose of 0.5 mL by IM injection only. Booster dose A booster dose (second dose) of 0.5 mL of JCOVDEN may be administered IM at least 2 months after the primary vaccination in individuals 18 years of age and older. A booster dose of JCOVDEN (0.5 mL) may be administered in individuals 18 years of age and older as a heterologous booster dose following completion of primary vaccination with an mRNA COVID-19 vaccine or an adenoviral vector-based COVID-19 vaccine. The dosing interval for the heterologous booster dose is the same as that authorized for a booster dose of the vaccine used for primary vaccination.	
	Proposed: Not applicable	
Pharmaceutical form(s) and strengths	Current: Ad26.COV2.S is a colorless to slightly yellow, clear to very opalescent suspension (pH 6-6.4). One dose (0.5 mL) of Ad26.COV2.S contains not less than 8.92 $\log_{10}$ infectious units.	
	Proposed: Not applicable	
Is/will the product be subject to additional monitoring in the EU?	☑ **Yes**	☐ **No**

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PART II: SAFETY SPECIFICATION

Module SI: Epidemiology of the Indication(s) and Target Population(s)

Considering the rapidly evolving situation, regular data updates on disease epidemiology are provided by the WHO (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports), ECDC (https://www.ecdc.europa.eu/en/covid-19/situation-updates), and Johns Hopkins Coronavirus Resource Center (https://coronavirus.jhu.edu/).

Regular updates on treatments and vaccines authorised in the European Union to treat or prevent COVID-19 are provided by the EMA (https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines-covid-19#authorised-medicines-section).

Indication:

JCOVDEN is indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

Incidence and Prevalence:

SARS-CoV-2 was first identified following reports of a cluster of acute respiratory illness cases in Wuhan, Hubei Province, China in December 2019 (Li 2020). It is a novel RNA virus from the family Coronaviridae, subgenus Sarbecovirus of the genus Betacoronavirus, and is most closely related (approximately 88% identical) to a group of SARS-like coronaviruses previously sampled from bats in China (Martin 2008, Wu 2020, Lu 2020).

The identification of SARS-CoV-2 follows the emergence of 2 other novel beta-coronaviruses capable of causing severe human disease over the past 18 years: SARS-CoV identified in Southern China in November 2002 and MERS-CoV isolated from a patient in Saudi Arabia who died of severe pneumonia and multi-organ failure in June 2012 (Lu 2020, WHO 2004, Zumla 2016).

SARS-CoV-2 has spread rapidly and globally since its emergence. The WHO declared that the outbreak constituted a public health emergency of international concern on 30 January 2020, and declared the outbreak to be a pandemic on 11 March 2020 (WHO 2020a, WHO 2020b).

As of 09 May 2022, over 516 million cases and over 6.3 million deaths from COVID-19 have been reported worldwide. Globally, over 4.0 million new cases and 16,734 deaths were reported during the week of 25 April through 01 May 2022 (WHO 2022a).

As of 01 May 2022, 138,908,085 cases and 1,087,139 deaths have been reported in the European Union/EEA (ECDC 2022a), and 22,328,784 cases and 189,251 deaths have been reported in the United Kingdom (Johns Hopkins 2022b). Ending 06 May 2022, the 14-day case notification rate for the European Union/EEA, based on pooled data collected by ECDC from official national sources from 29 countries, was 867.7 per 100,000 population (country range: 30.2-2,064) (ECDC 2022b).

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Over the course of the SARS-CoV-2 pandemic, there has been a continuous evolution of circulating SARS-CoV-2 variants. The reason why these strains seem to spread so quickly is poorly understood and is currently a topic of intensive research (Lauring 2021, Plante 2020, Tegally 2020, de Souza 2022). Vaccine effectiveness has been shown to be decreased with more recent variants, including Omicron (Ferdinands 2022, Natarajan 2022, Plumb 2022). As of 26 November 2021, the WHO declared Omicron a variant of concern, and by 22 December 2021, the Omicron variant was detected in 110 countries (WHO 2021). Since its identification, Omicron has continued to evolve, leading to variants with slightly different genetic constellations of mutations (WHO 2022b). As of 05 June 2022, the Omicron variant is the dominant variant of concern circulating globally according to the WHO (WHO 2022c).

Demographics of the Population within the Authorised Indication – Age, Sex, Racial and/or Ethnic Origin, and Risk Factors for the Disease

Age

SARS-CoV-2 infects people of all ages. However, people aged >60 years are at a higher risk of severe COVID-19 (ECDC 2023a). As of 13 May 2022, transmission continues to decline in most EU countries, as shown by decreases in both overall case notification rates and case rates among people aged 65 years and older. While decreasing, transmission in people aged 65 years and older is still at one of the highest levels in the pandemic (ECDC 2022c). In the European Union/EEA, the risk of hospitalization and death increases sharply with age (ECDC 2021).

Sex

Although there is no clear answer to the question of how much sex is influencing the health outcome of people diagnosed with COVID-19, in most countries with available data, mortality rates are consistently higher in men than in women (Global Health 50/50 2022). The ECDC reports previously included TESS (The European Surveillance System) analysis by demographics, noting that males had a higher risk of severe outcomes than females, particularly in the older age groups (ECDC 2021).

Racial and/or Ethnic Origin

Data on the characteristics of COVID-19 patients disaggregated by race/ethnicity remain limited. There is increasing evidence that some racial and ethnic minority groups are disproportionately affected by COVID-19 (Price-Haywood 2020, Millett 2020, CDC 2020a, CDC 2023a, ECDC 2020, Johns Hopkins 2022a). Inequities in the social determinants of health affecting these groups, such as occupation, education, income, healthcare access, and housing, are interrelated and influence a wide range of health and quality-of-life outcomes and risks (ECDC 2020, Johns Hopkins 2022a).

Risk Factors for the Disease

Risk factors increasing the risk for COVID-19 infection are the type of employment (public facing) and not using non-pharmaceutical prevention methods (distancing and masking) (Chu 2020, Hiironen 2022). Demographic factors increasing the risk for a severe disease course are older age,

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male sex, and postmenopausal state. The most common pre-existing comorbidities and risk factors in COVID-19 patients are hypertension, diabetes mellitus, cardiovascular diseases, chronic obstructive pulmonary disease, malignancy, chronic kidney disease, sickle cell disease, obesity, weakened immune system, and smoking (Dessie 2021, Wolff 2021, Emami 2020, CDC 2022b).

Main Existing Treatment and Prevention Options:

Prophylaxis

As of 01 December 2023, besides JCOVDEN, the following vaccines have received (conditional) marketing authorisation from EMA (EMA 2023): the mRNA-based BNT162b2 vaccine Comirnaty from Pfizer and BioNTech and adapted vaccines, the mRNA-1273 vaccine Spikevax from Moderna Inc and adapted vaccines, the ChAdOx1-S (recombinant) vaccine Vaxzevria from AstraZeneca, the (recombinant) vaccine Nuvaxovid from Novavax and adapted vaccine, the (recombinant) vaccine VidPrevtyn Beta from Sanofi Pasteur, and the (recombinant) vaccine Bimervax from HIPRA Human Health.

Therapeutics

As of 08 August 2022, the following treatments received (conditional) approval by the EMA for the treatment of COVID-19: remdesivir (Veklury), tixagevimab/cilgavimab (Evusheld), anakinra (Kineret), PF-07321332/ritonavir (Paxlovid), regdanvimab (Regkirona), tocilizumab (RoActemra), casirivimab/imdevimab (Ronapreve), and sotrovimab (Xevudy) (EMA 2023). In addition, EMA endorses the use of dexamethasone in COVID-19 patients on oxygen or mechanical ventilation (EMA 2020c).

Despite the ever growing number of available treatment options, an emphasis remains on disease prevention for global control of SARS-CoV-2. Since transmission of SARS-CoV-2 occurs primarily through respiratory secretions (droplets) and to a lesser extent via contact with contaminated surfaces, covering coughs and sneezes as well as social distancing (maintaining a distance of 1.5 m or 6 feet from others) can reduce the risk of transmission. Mouth and nose coverings, if properly pursued, may further reduce the spread of droplets from infectious individuals to others when social distancing is not possible. Furthermore, frequent handwashing and the use of hand sanitizer (>60% alcohol) are effective in reducing acquisition (CDC 2020b). Finally, frequent testing for SARS-CoV-2, contact tracing, and local quarantine measures have shown to be effective in reducing virus spread.

Natural History of the Indicated Condition in the Unvaccinated Population, Including Mortality and Morbidity:

SARS-CoV-2 can be transmitted from human to human by exposure to respiratory fluids carrying virus (CDC 2021). Contact tracing studies confirm that prolonged close contact is the main risk factor for transmission and that the risk of infection is much higher in household contacts compared to nonhousehold contacts (Bi 2020, Burke 2020, WHO 2020c). Transmission may also occur indirectly through infected surfaces or fomites.

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Approximately 40% to 45% of infected individuals will remain asymptomatic (Feehan 2021, Lavezzo 2020, Oran 2020). Respiratory symptoms of COVID-19 typically appear 5 to 6 days following exposure to the virus, but may appear from 2 to 14 days following exposure, with the clinical manifestations ranging from mild symptoms to severe illness or death (CDC 2022a, Guan 2020, Linton 2020, WHO 2020d). In a systematic review and meta-analysis of 148 studies, including 127 studies from China, which comprised 24,410 adults in 9 countries with laboratory confirmed COVID-19, the most prevalent symptoms were fever (78%), cough (57%), and fatigue (31%). Overall, 19% of hospitalized patients required non-invasive ventilation, 17% required intensive care, 9% required invasive ventilation, and 2% required extra-corporeal membrane oxygenation (Grant 2020). CDC descriptions of COVID-19 clinical case definitions and interviews with COVID-19-experienced clinicians sponsored by the MAH have included signs and symptoms of respiratory distress such as blue lips, extreme shortness of breath and dyspnea, persistent cough, deep vein thrombosis, discoloration of feet and toes, chills, shaking chills, loss of sense of taste and smell, signs of stroke, disorientation, inability to respond or understand verbal communication, among others. Other less common gastrointestinal symptoms have been reported by CDC (nausea, vomiting, diarrhea) (CDC 2022a). Although SARS-CoV-2 primarily affects the lungs, it has been found to damage the vascular endothelium of several other organs, resulting in complaints such as brain fog, palpitations, and fatigue. The extrapulmonary manifestations of COVID-19 vary, with the heart, brain, and kidneys being particularly susceptible to damage (EClinicalMedicine 2020). This vascular component of COVID-19 might help to explain the observed prolonged illness, also seen in young adults without underlying chronic medical conditions (Tenforde 2020).

For the week ending 13 May 2022, pooled data from 18 EU/EEA countries showed that the hospital occupancy rate was 15.1 COVID-19 patients per 100,000 population. The ICU admission rate for the European Union/EEA, based on data reported by 10 countries, was 0.5 per 100,000 population (country range: 0.1–1.0). The 14-day COVID-19 death rate for the European Union/EEA, based on data collected by ECDC from official national sources for 30 countries, was 16.2 (country range: 0.0-42.0) per million population (ECDC 2022c).

Important Comorbidities:

Important comorbidities for severe COVID-19 are hypertension, diabetes mellitus, cardiovascular diseases, chronic obstructive pulmonary disease, malignancy, chronic kidney disease, sickle cell disease, obesity, and weakened immune system.

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PART II: SAFETY SPECIFICATION

Module SII: Nonclinical Part of the Safety Specification

The nonclinical safety profile of Ad26.COV2.S was assessed in 2 pivotal GLP studies in NZW rabbits: a combined repeat-dose toxicity and local tolerance study and a combined EF-PPND toxicity study. Biodistribution studies (with 2 other Ad26-based vaccines) were conducted in NZW rabbits to assess the distribution, persistence, and clearance of the Ad26 vector. The nonclinical safety testing was consistent with applicable guidelines, including the WHO Guidelines on nonclinical evaluation of vaccines (WHO 2005), the EMA Guideline on quality, non-clinical and clinical aspects of live recombinant viral vectored vaccines (EMA 2010), the ICH-S5 Guideline on detection of toxicity to reproduction for human pharmaceuticals (EMA 2020a), and the FDA Guidance for Industry – Considerations for developmental toxicity studies for preventive and therapeutic vaccines for infectious disease indications (FDA 2006).

In line with the applicable guidelines, safety pharmacology, genotoxicity, and carcinogenicity studies have not been conducted with Ad26.COV2.S.

The nonclinical biodistribution and safety studies were conducted using the IM route, which is the route for use of Ad26.COV2.S in humans. The rabbit was considered a relevant toxicological species since Ad26.COV2.S was shown to elicit an immune response against the SARS-CoV-2 S protein encoded by the vaccine. The Ad26.COV2.S vaccine dose level and dosing volume (ie, $1x10^{11}$ vp, as a 1-mL injection) applied in the 2 pivotal nonclinical safety studies is 2-fold above the human dose level (ie, $5x10^{10}$ vp, as a 0.5-mL injection), hence the full human dose was covered. In addition, the number of Ad26.COV2.S doses administered in these studies (ie, 3 doses administered with a 14-day interval period between injections) exceeds the single-dose vaccine regimen as proposed in humans.

In nonclinical vaccine efficacy studies, VAED and VAERD were monitored after SARS-CoV-2 challenge of vaccinated NHP and Syrian hamsters. Clinical signs, viral load, and histopathology scores of respiratory tract tissues were determined in challenged animals to assess a theoretical risk of enhanced disease. Furthermore, immunogenicity was assessed in NHP, Syrian hamsters, mice, and rabbits to show induction of neutralizing antibodies and/or a Th1-polarized immune response; factors that are thought to minimize the occurrence of VAERD.

Additional nonclinical studies were performed to gain insights into potential mechanisms of (vaccine-induced) TTS. The studies addressed several hypotheses for the pathogenesis of TTS. The results obtained from these studies may separately or in combination also have relevance for the understanding of the pathogenesis of vaccine-associated thrombocytopenia, including ITP, and/or VTE.

Key findings from these nonclinical studies are presented in the table below.

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Key Safety Findings	Relevance to Human Usage
Toxicity	
Single & repeat-dose toxicity and local tolerance	
A single-dose toxicity study with Ad26.COV2.S was not conducted. Possible signs of acute toxicity were monitored following the first vaccination in the GLP combined repeat-dose toxicity and local tolerance study with Ad26.COV2.S in rabbits. In this study, IM administration of Ad26.COV2.S at $1x10^{11}$ vp/dose on 3 occasions with a 14-day interval period between injections was well tolerated. The observed changes were related to a normal, anticipated, (local and systemic) immunologic response to vaccination and consisted clinically of (rare) transient local injection site dermal reactions, with transient minimal hyperthermia and minimal body weight loss or lower body weight gain after injection. This was associated with a transient (acute phase/immune) response in clinical pathology parameters, characterized by increases in plasma proteins (C-reactive protein, fibrinogen, and globulins) and white blood cell counts (monocytes and lymphocytes). Microscopic pathology findings of minimal to slight inflammation and hemorrhage were observed at the injection sites, along with increased lymphoid cellularity of germinal centers in popliteal and iliac lymph nodes and the spleen, which is consistent with an immune response to the vaccine administration. Overall, the findings were considered non-adverse and were partially or completely reversible after a 3-week treatment-free period. There were no signs suggestive of an increased risk for thromboembolic events or coagulopathies. All vaccinated animals developed an antibody response against the SARS-CoV-2 S protein, confirming responsiveness of the rabbits to the vaccine.	The combined repeat-dose toxicity and local tolerance study with Ad26.COV2.S did not indicate any adverse vaccine-related effects. All vaccine-related effects noted were considered to reflect a normal, immunologic response to the vaccine. There were no findings observed that would raise a specific safety concern for the use of Ad26.COV2.S in humans. The Ad26.COV2.S vaccine dose level and dosing volume applied in the combined repeat-dose toxicity and local tolerance study with Ad26.COV2.S (ie, $1x10^{11}$ vp, as a 1-mL injection) is 2-fold above the human dose level ($5x10^{10}$ vp, as a 0.5-mL injection), hence the full human dose was covered. In addition, the number of Ad26.COV2.S doses administered (ie, 3 doses administered with a 14-day interval period between injections) exceeds the single-dose vaccine regimen as proposed in humans.
Reproductive toxicity	
In the EF-PPND toxicity study in female rabbits, administration of Ad26.COV2.S at $1x10^{11}$ vp during the premating (ie, 7 days prior to mating) and gestation period (ie, Day 6 and Day 20 of gestation) did not reveal any vaccine-related adverse effects on reproductive performance, fertility, ovarian and uterine examinations, or parturition. In addition, the repeat-dose toxicity and local tolerance study with Ad26.COV2.S did not reveal any effect on male sex organs that would impair male fertility.	The available toxicity studies with Ad26.COV2.S do not indicate any harmful effects with respect to reproductive toxicity or fertility. The Ad26.COV2.S vaccine dose level and dosing volume applied in the EF-PPND toxicity study (ie, $1x10^{11}$ vp, as a 1-mL injection) is 2-fold above the human dose level (ie, $5x10^{10}$ vp, as a 0.5-mL injection), hence the full human dose was covered.

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Key Safety Findings	Relevance to Human Usage
Developmental toxicity	
In the EF-PPND toxicity study in female rabbits, there was no adverse effect of vaccination on fetal body weights, external, visceral, and skeletal evaluations, or on postnatal development of the offspring. The parental females as well as their fetuses and offspring exhibited SARS-CoV-2 S protein-specific antibody titers, indicating that maternal antibodies were transferred to the fetuses during gestation.	The EF-PPND toxicity study with Ad26.COV2.S does not indicate any harmful effects with respect to embryofetal or postnatal development. The data indicate that maternal antibodies were transferred to the fetuses. This profile is expected to be similar in humans. The clinical significance of maternal antibody transfer to the fetus is unknown.
Genotoxicity	
In accordance with the WHO Guidelines on nonclinical evaluation of vaccines (WHO 2005), no genotoxicity studies were performed for Ad26.COV2.S. Adenoviral vectors are classified as nonintegrating because they lack the machinery to integrate their genome into the host chromosomes (EMA 2006, FDA 2020). As such, although adenoviral vector DNA is transferred to the nucleus of transduced cells, these vectors do not have the propensity to modify the host genome, hence reducing the risk of insertional mutagenesis (Feuerbach 1996, Lee 2017).	Ad26.COV2.S is not expected to be genotoxic in humans.
Carcinogenicity	
In accordance with the WHO Guidelines on nonclinical evaluation of vaccines (WHO 2005), no carcinogenicity testing was performed for Ad26.COV2.S.	Ad26.COV2.S is not expected to be carcinogenic in humans.
Juvenile toxicity	
Studies in juvenile animals were not performed.	There were no findings in the available (conventional) toxicity studies that would indicate a specific concern for the use of the vaccine in infants/children.
Safety pharmacology	
Safety pharmacology studies have not been conducted.	Data from the repeat-dose toxicity study (which included detailed clinical observations) do not suggest that Ad26.COV2.S affects physiological functions (eg, central nervous system, respiratory, and cardiovascular functions) other than those of the immune system.

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Key Safety Findings	Relevance to Human Usage
Other toxicity-related information or data	
Biodistribution	
Nonclinical biodistribution studies in NZW rabbits showed a limited distribution profile of the Ad26 vector following IM injection. In addition, clearance of the vector was observed within 90 to 180 days, reflected by a downward trend in the number of positive tissues and vector copies over time, to levels close to or below the detection limit. In addition, immunohistochemical evaluation showed the presence of S protein, with a similar distribution of S1 and S2 subunits, in the administration site and draining lymph node 1 day after IM injection of Ad26.COV2.S in NZW rabbits. Eleven days after injection, the S protein was no longer detectable in any of the examined tissues.	Ad26.COV2.S is neither expected to distribute widely, nor to replicate and/or persist in the tissues following IM injection.
Vaccine-associated enhanced respiratory disease	
Immunization with Ad26.COV2.S induced neutralizing antibody responses in all species tested (mice, rabbits, Syrian hamsters, and NHP) and elicited a Th1-polarized immune response in mice and NHP. Induction of neutralizing antibodies and a Th1-polarized immune response were confirmed in clinical study samples (Sadoff 2021, Stephenson 2021). In Ad26.COV2.S vaccinated and SARS-CoV-2 challenged NHP, no clinical or histopathological evidence of VAERD or VAED was observed at any vaccine dose level or for any vaccine regimen given, including animals with suboptimal immune responses that failed to protect against breakthrough SARS-CoV-2 infection. In Ad26.COV2.S vaccinated and SARS-CoV-2 challenged Syrian hamsters, no increased lung histopathology, viral load, or body weight loss was observed compared with the control group after SARS-CoV-2 challenge, including vaccinated animals showing breakthrough infection in the lung, indicating the absence of any signs of VAERD or VAED.	The available nonclinical data do not indicate any risk related to possible VAERD in humans.
Thrombosis with thrombocytopenia syndrome	
Presence of high levels of anti-PF4 antibodies appears to be a central mechanistic aspect of TTS pathogenesis. A possible interaction between PF4 and Ad26.COV2.S that has been hypothesized to lead to induction of anti-PF4 antibodies has been assessed using 3 different biophysical techniques: dynamic light scattering (DLS), biolayer interferometry (BLI), and surface plasmon resonance (SPR). In DLS and BLI experiments, no direct interactions between PF4 and Ad26.COV2.S were observed. SPR data demonstrated that the induced binding of PF4 to Ad26.COV2.S as published by Baker et al. (Baker 2021) is	The available (mechanistic) nonclinical data generated with Ad26.COV2.S do not allow to conclude on the potential mechanism of TTS.

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Key Safety Findings	Relevance to Human Usage
likely an experimental artefact. These findings are in line with findings of Michalik et al. (Michalik 2022) using DLS, showing no complex formation of PF4 with Ad26.COV2.S. Therefore, it is unlikely that binding of Ad26-vector particles to PF4 is driving the etiology of TTS. Characterization of the host cell protein (HCP) content and an overall safety assessment of the residual HCP identified in Ad26.COV2.S when produced from PER.C6 TetR cells, has shown that Ad26.COV2.S vaccine contains only trace levels of HCP and host cell DNA. HCP levels were significantly below levels of residual HCP reported for other commercial vaccines that are also produced on human cells. In the assessment of product quality attributes, no discrepancy regarding release and characterization data was found in Ad26.COV2.S vaccine batches associated with reported TTS case(s) compared with batches currently on the market with which no cases of TTS were reported. These data suggest that HCP, host cell DNA, any potential impurities and/or excipients of Ad26.COV2.S vaccine are not likely a contributing factor in the pathogenesis of TTS. An analysis of sequence homologies of the Ad26 Capsid proteins, TetR protein, and the SARS-CoV-2 S protein vaccine antigen with the human proteome and 4 selected human proteins potentially associated with TTS was performed and revealed only limited linear homologies. Linear epitope homology is unlikely to be the root cause to TTS. RNA sequencing of Ad26.COV2.S transduced cells in vitro to assess alternative splicing events leading to C-terminally truncated, soluble S protein variants was performed. No or very low frequency of aberrant splicing events were found that would affect the spike transgene encoded by Ad26.COV2.S, making it unlikely to contribute to TTS. Expression of S protein was assessed in the IM administration site, draining lymph nodes, and spleen by immunohistochemistry and in the blood by S-PLEX assay, on Days 1 and 11 following IM dosing in rabbits. A transient expression of the S protein was observed in the IM administration site, draining lymph nodes (iliac and/or popliteal), and blood on Day 1, with all tissues examined being negative for S protein expression on Day 11 post dosing. No adverse vaccine-related effects were noted. Overall, Ad26.COV2.S-induced S protein expression, including its bioavailability in blood, was not associated with a safety concern in this study, but does not allow S protein to be ruled out as a potential contributing factor in a multifactorial scenario of TTS induction following vaccination with Ad26.COV2.S in humans.	

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Key Safety Findings	Relevance to Human Usage
Vaccination with Ad26.COV2.S did not induce hPF4 binding antibodies in NHP and rabbits. In mice, hPF4 binding antibody responses were induced, however, responses were also seen with non-adeno-based vaccines not including or encoding the SARS-CoV-2 S antigen (eg, marketed influenza vaccine), hence indicative of an unspecific immune activation. In rabbits, IV administration of Ad26.COV2.S did not induce any additional changes in safety parameters, nor changes which were more pronounced to what was observed after IM administration of the same vaccine dose level (based on an evaluation of eg, clinical chemistry, coagulation and hematology endpoints including platelet counts, as well as S protein and Ad26 vector DNA distribution in the blood). Overall, a single dose IV administration of Ad26.COV2.S was well tolerated and did not induce any relevant changes in platelets, prothrombin time, or APTT clotting times, or gross or histopathological changes related to thrombosis, thromboembolic disease, or their sequelae. Although based on a limited number of animals, these data indicate that an accidental IV injection of Ad26.COV2.S may not represent an increased risk of TTS.	

Summary of Nonclinical Safety Concerns

Important identified risks	None
Important potential risks	None
Missing information	None

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PART II: SAFETY SPECIFICATION

Module SIII: Clinical Trial Exposure

SIII.1. Brief Overview of Development

The current clinical development plan of Ad26.COV2.S aims to develop a vaccine for the prevention of COVID-19 caused by SARS-CoV-2 in adults. In the course of the clinical development, different dose levels ($1x10^{10}$ vp, $1.25x10^{10}$ vp, $2.5x10^{10}$ vp, $3.5x10^{10}$ vp, $5x10^{10}$ vp, $7x10^{10}$ vp, $9x10^{10}$ vp, and $1x10^{11}$ vp), vaccination schedules (single dose with or without a second/booster dose[2]), and intervals between doses (2 to ≥6 months) are being assessed. The current clinical development plan includes 11 Company-sponsored interventional trials, including 5 trials that provide information on the efficacy and/or safety of booster doses for Ad26.COV2.S (ie, $5x10^{10}$ vp) (COV1001, COV1002, COV2001, COV2008, and COV3009). At the time of EU-RMP writing, all studies (except COV2004, COV3003, COV3006, and COV3009) are completed.

The first-in-human Phase 1/2a trial COV1001 performed an initial evaluation of the safety and immunogenicity of Ad26.COV2.S. This trial assessed the preselected $5x10^{10}$ vp and $1x10^{11}$ vp dose levels, both administered as a 1-dose and a 2-dose regimen in adults aged 18 to 55 years and ≥65 years.

A Phase 1 trial COV1002 was conducted in Japan, in parallel with trial COV1001, to evaluate the safety and immunogenicity of Ad26.COV2.S administered as a 2-dose regimen ($5x10^{10}$ vp, $1x10^{11}$ vp) in Japanese adults aged 20 to 55 years and ≥65 years.

A Phase 1 trial COV1003 was conducted to compare the safety and immunogenicity of Ad26.COV2.S at a single dose of $5x10^{10}$ vp in 2 different volumes (0.3 mL or 0.5 mL) in healthy adults aged 18 to ≤65 years.

A Phase 2a trial COV2001 in adults aged 18 to 55 years and ≥65 years evaluated the safety and immunogenicity of 2-dose ($5x10^{10}$ vp, $2.5x10^{10}$ vp, $1.25x10^{10}$ vp) and 1-dose ($5x10^{10}$ vp, $1x10^{11}$ vp) vaccination regimens, and safety and immunogenicity of 56- and 84-day vaccination intervals for the 2-dose regimen ($5x10^{10}$ vp). The trial also evaluated the safety and immunogenicity of Ad26.COV2.S in healthy adolescents aged 16 and 17 years, at a single dose of $2.5x10^{10}$ vp.

A Phase 2 trial COV2004 evaluates the safety and immunogenicity of Ad26.COV2.S in healthy pregnant participants aged 18 to 45 years, after a single dose of $5x10^{10}$ vp or 2 doses at $2.5x10^{10}$ vp.

A Phase 2 trial COV2008 in adults aged 18 years and older who have previously received vaccination with Ad26.COV2.S or BNT162b2 evaluated the safety and immunogenicity of

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[2] In this document, the terms "booster" and "second dose" are used interchangeably for participants who received a second dose of Ad26.COV2.S. As all participants had shown a response (both in ELISA and functional antibodies) after the first dose, and all showed a rapid rise of antibodies within a week after administration of the second dose, the second dose is effectively a booster.

Ad26.COV2.S administered as booster vaccination ($5x10^{10}$ vp, $2.5x10^{10}$ vp, $1x10^{10}$ vp), ≥6 months after the primary vaccination.

A Phase 3 trial COV3003 in adults aged 18 to 55 years evaluates 6 dose levels (range: $1.25x10^{10}$ vp - $9x10^{10}$ vp) of Ad26.COV2.S administered as a 2-dose schedule.

The Phase 3 trials COV3001 (ENSEMBLE) and COV3009 (ENSEMBLE-2) evaluate(d) the efficacy, safety, and immunogenicity of Ad26.COV2.S in adults aged 18 to 59 years and ≥60 years, after administration of a single dose of study vaccine (COV3001) or 2 doses of study vaccine with an interval of 56 days (COV3009). Interim results from trial COV1001 led to the selection of the $5x10^{10}$ vp dose level for evaluation in these Phase 3 trials.

A Phase 3 trial COV3005 evaluated the safety and immunogenicity of Ad26.COV2.S co-administered with an influenza vaccine in adults aged 18 years and older.

All above clinical trials are randomized, placebo-controlled, and conducted in a double-blind fashion; except for COV1003 which was a randomized, observer-blind, parallel-group trial without placebo control, COV2004 which is an open-label study, and COV2008, COV3003, and COV3005 which are not placebo-controlled. During the course of the clinical development program, the placebo-controlled trials COV1001, COV1002, COV2001, COV3001, and COV3009 were unblinded and participants in the Placebo group were offered a single dose of Ad26.COV2.S (except for trial COV1002). The trials were continued in an open-label manner. In addition, the trial COV3001 protocol has been amended to offer all participants a booster vaccination with Ad26.COV2.S. Long-term safety follow-up post-booster continued for 1 year in COV3001 and will continue at least 6 months in COV3009. If a booster dose was required, other trial protocols were also amended to allow administration of a booster, either with Ad26.COV2.S or with another COVID-19 vaccine according to local recommendations.

A Phase 3b study COV3012 (Sisonke-1 [Together]) was a non-Company sponsored open-label, single-arm vaccine implementation study that monitored vaccine effectiveness and safety of a single dose of Ad26.COV2.S among healthcare workers aged ≥18 years in South Africa. This study was sponsored by the South African Medical Research Council. The Sisonke study was expanded to include an Ad26.COV2.S booster dose 6 to 9 months after the initial vaccination in healthcare workers (ie, study COV3021 [Sisonke-2/Sisonke Boost]).

A Phase 2 trial COV3006 evaluates the safety and immunogenicity of different dose levels of Ad26.COV2.S administered as a 1- or 2-dose regimen in healthy adolescents from 12 to 17 years inclusive.

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SIII.2. Clinical Trial Exposure

Company-sponsored Clinical Trials

The clinical trial exposure and safety data shown in this EU-RMP are based upon the pooled analyses of several Company-sponsored clinical trials.

Three sets of pooled data are presented in this EU-RMP, ie, the primary pooling, the cross-dose level pooling, and the extended cross-dose level pooling. Tables for the cross-dose level pooling are presented in Annex 7.7 and Annex 7.8.

1) Primary Pooling

The primary pooling served as the primary source for determining the safety and reactogenicity profile of Ad26.COV2.S in a randomized, double-blind, placebo-controlled manner.

Data from the following 5 trials were used for characterization of exposure and safety up to the cut-off dates for interim or primary analyses of the individual trials (02 August 2021 at the latest):

- 1 Phase 1/2a trial: COV1001 (unblinded data)
- 1 Phase 1 trial: COV1002 (unblinded data)
- 1 Phase 2a trial: COV2001 (adult cohort, unblinded data)
- 2 Phase 3 trials: COV3001 (unblinded data) and COV3009 (unblinded data)

The primary pooling includes exposure and safety data of Ad26.COV2.S at the approved dose level ($5x10^{10}$ vp), in adults aged ≥18 years. This pooling includes data from the double-blind phase of the above-mentioned double-blind, randomized, placebo-controlled trials and includes primary vaccination and homologous boosting with Ad26.COV2.S. Data from participants who received another COVID-19 vaccine outside the study were excluded from the analysis from the date of the other vaccination onwards.

The dataset used for the primary pooling safety analyses is the Full Analysis Set (FAS), which includes all participants with at least 1 documented vaccine (placebo or Ad26.COV2.S) administration, regardless of the occurrence of protocol deviations.

2) Cross-dose Level Pooling

Data of the cross-dose level pooling complements the findings of the primary pooling, providing extended data beyond the primary pooling cut-off dates, and supports risk characterization for risk management planning based on the current safety knowledge. The cross-dose level pooling includes clinical trial data that is not placebo-controlled and also groups for which the sequence of vaccination is not taken into account (mixed schedules).

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Data from the following 10 trials were used for characterization of exposure and safety up to the cut-off date of 24 February 2022:

- 1 Phase 1/2a trial: COV1001 (unblinded data)
- 2 Phase 1 trials: COV1002 (unblinded data) and COV1003 (unblinded data)
- 1 Phase 2a trial: COV2001 (adult cohort, unblinded data)
- 2 Phase 2 trials: COV2004 (open-label) and COV2008 (unblinded data)
- 4 Phase 3 trials: COV3001 (unblinded data), COV3003 (blinded data), COV3005 (blinded data), and COV3009 (unblinded data)

The cross-dose level pooling includes exposure and safety data of Ad26.COV2.S at any dose level (ranging from $1x10^{10}$ vp to $1x10^{11}$ vp), in adults aged ≥18 years. This pooling includes primary vaccination, as well as homologous booster and mixed schedules (encompassing a number of booster regimens of different COVID-19 vaccines, eg, Ad26.COV2.S followed by an mRNA vaccine). Data from participants who received another COVID-19 vaccine outside the study were included in the analysis of this pooling. Exposure data is presented by each Ad26.COV2.S dose level individually as well as for all dose levels combined (see Annex 7.7).

The dataset used for the cross-dose level pooling safety analyses is the FAS, which includes all participants with at least 1 documented vaccine (placebo, Ad26.COV2.S either alone or as part of a mixed schedule with another COVID-19 vaccine) administration, regardless of the occurrence of protocol deviations.

3) Extended Cross-dose Level Pooling

The extended cross-dose level pooling includes exposure and safety data from the 10 trials included in the cross-dose level pooling and from trial COV3006 (adolescents), up to the cut-off date of 03 July 2023.

Non-company Sponsored Studies

Data from the following 2 non-Company sponsored studies were also used for characterization of exposure and safety up to the cut-off date of 24 February 2023:

- 2 Phase 3b studies: COV3012 (open-label) and COV3021 (open-label)

These studies provide exposure and safety data of Ad26.COV2.S at the approved dose level ($5x10^{10}$ vp; primary vaccination and booster vaccination).

Exposure in the Primary Pooling

At the cut-off date of 02 August 2021, a total of 76,347 participants were included in the primary pooling, of which 38,538 participants received at least 1 dose of Ad26.COV2.S at the $5x10^{10}$ vp dose level and 9,199 participants received 2 doses. Overall, 47,737 doses of Ad26.COV2.S at the $5x10^{10}$ vp dose level were administered in the double-blind phase.

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Exposure to Ad26.COV2.S and matching placebo in the primary pooling is summarized in Tables SIII.1 through SIII.6 for all participants by dose, by age group, by sex, by race, by ethnicity, and by special populations (ie, participants with HIV infection, breastfeeding women at baseline, pregnant women at baseline, participants with comorbidities associated with increased risk for severe COVID-19, and participants who are SARS-CoV-2 seropositive at baseline). Any case of study vaccine exposure during pregnancy was included in the Company's Global Safety Database when reported during the trials.

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Table SIII.1: Exposure to Study Vaccine by Dose (Primary Pooling)

	Ad26.COV2.S	Placebo	Total
Number of participants receiving at least one dose, N	38538	37809	76347
Number of doses administered, N	47737	46212	93949
Participants receiving			
Dose 1 double blind	38538 (100.0%)	37809 (100.0%)	76347 (100.0%)
Dose 2 double blind	9199 (23.9%)	8340 (22.1%)	17539 (23.0%)
Dose 3 double blind	0	63 (0.2%)	63 (0.1%)

This table includes 5 trials: COV1001, COV1002, COV2001, COV3001 and COV3009. Only the primary dose ie $5x10^{10}$ vp dose level, regardless volume, is taken into account.
Total: Total number of participants with at least one dose (active or placebo) / Total number of doses (active or placebo).
If participants received Ad26.COV2.S before the placebo vaccination (e.g. randomized sequence Ad26.COV2.S-Placebo), then the placebo vaccination is not reported.
Note: Data cutoff for COV1001 of 21JUL2021, COV1002 of 02AUG2021, COV2001 of 11MAY2021, COV3001 of 09JUL2021, COV3009 of 25JUN2021

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Table SIII.2 Exposure to Study Vaccine by Age (Primary Pooling)

	Ad26.COV2.S	Placebo	Total
Age, N	38538	37809	76347
Age group I			
18-59 years	25278 (65.6%)	24723 (65.4%)	50001 (65.5%)
>=60 years	13259 (34.4%)	13086 (34.6%)	26345 (34.5%)
Missing	1 (<0.1%)	0	1 (<0.1%)
Age group II			
18-64 years	31145 (80.8%)	30514 (80.7%)	61659 (80.8%)
>=65 years	7392 (19.2%)	7295 (19.3%)	14687 (19.2%)
Missing	1 (<0.1%)	0	1 (<0.1%)
Age group III			
18-74 years	37257 (96.7%)	36594 (96.8%)	73851 (96.7%)
>=75 years	1280 (3.3%)	1215 (3.2%)	2495 (3.3%)
Missing	1 (<0.1%)	0	1 (<0.1%)

This table includes 5 trials ie COV1001, COV1002, COV2001, COV3001 and COV3009. Only the primary dose ie $5x10^{10}$ vp dose level, regardless concentration or volume, is taken into account.
Total: Total number of participants with at least one dose (active or placebo) / Total number of doses (active or placebo).
Note: Data cutoff for COV1001 of 21JUL2021, COV1002 of 02AUG2021, COV2001 of 11MAY2021, COV3001 of 09JUL2021, COV3009 of 25JUN2021

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Table SIII.3: Exposure to Study Vaccine by Sex (Primary Pooling)

	Ad26.COV2.S	Placebo	Total
Sex, N	38538	37809	76347
Female	17629 (45.7%)	17506 (46.3%)	35135 (46.0%)
Male	20903 (54.2%)	20296 (53.7%)	41199 (54.0%)
Undifferentiated	4 (<0.1%)	7 (<0.1%)	11 (<0.1%)
Unknown	1 (<0.1%)	0	1 (<0.1%)
Missing	1 (<0.1%)	0	1 (<0.1%)

This table includes 5 trials ie COV1001, COV1002, COV2001, COV3001 and COV3009. Only the primary dose ie $5x10^{10}$ vp dose level, regardless concentration or volume, is taken into account.
Total: Total number of participants with at least one dose (active or placebo) / Total number of doses (active or placebo).
Unknown: Not known, not observed, not recorded, or refused.
Note: Data cutoff for COV1001 of 21JUL2021, COV1002 of 02AUG2021, COV2001 of 11MAY2021, COV3001 of 09JUL2021, COV3009 of 25JUN2021
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Table SIII.4: Exposure to Study Vaccine by Race (Primary Pooling)

	Ad26.COV2.S	Placebo	Total
Race, N	38538	37809	76347
American Indian or Alaska Native	2482 (6.4%)	2456 (6.5%)	4938 (6.5%)
Asian	2245 (5.8%)	2091 (5.5%)	4336 (5.7%)
Black or African American	5580 (14.5%)	5520 (14.6%)	11100 (14.5%)
Native Hawaiian or other Pacific Islander	89 (0.2%)	90 (0.2%)	179 (0.2%)
White	25609 (66.5%)	25035 (66.2%)	50644 (66.3%)
Multiple	1433 (3.7%)	1466 (3.9%)	2899 (3.8%)
Unknown	413 (1.1%)	422 (1.1%)	835 (1.1%)
Not reported	644 (1.7%)	686 (1.8%)	1330 (1.7%)
Missing	43 (0.1%)	43 (0.1%)	86 (0.1%)

This table includes 5 trials ie COV1001, COV1002, COV2001, COV3001 and COV3009. Only the primary dose ie $5x10^{10}$ vp dose level, regardless concentration or volume, is taken into account.
Total: Total number of participants with at least one dose (active or placebo) / Total number of doses (active or placebo).
Not Reported: Not provided or available
Unknown: Not known, not observed, not recorded, or refused.
Note: Data cutoff for COV1001 of 21JUL2021, COV1002 of 02AUG2021, COV2001 of 11MAY2021, COV3001 of 09JUL2021, COV3009 of 25JUN2021
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Table SIII.5: Exposure to Study Vaccine by Ethnicity (Primary Pooling)

	Ad26.COV2.S	Placebo	Total
Ethnic, N	38538	37809	76347
Hispanic or Latino	12796 (33.2%)	12809 (33.9%)	25605 (33.5%)
Not Hispanic or Latino	24729 (64.2%)	23992 (63.5%)	48721 (63.8%)
Unknown	271 (0.7%)	271 (0.7%)	542 (0.7%)
Not reported	700 (1.8%)	695 (1.8%)	1395 (1.8%)
Missing	42 (0.1%)	42 (0.1%)	84 (0.1%)

This table includes 5 trials ie COV1001, COV1002, COV2001, COV3001 and COV3009. Only the primary dose ie $5x10^{10}$ vp dose level, regardless concentration or volume, is taken into account.
Total: Total number of participants with at least one dose (active or placebo) / Total number of doses (active or placebo).
Not Reported: Not provided or available
Unknown: Not known, not observed, not recorded, or refused.
Note: Data cutoff for COV1001 of 21JUL2021, COV1002 of 02AUG2021, COV2001 of 11MAY2021, COV3001 of 09JUL2021, COV3009 of 25JUN2021
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Table SIII.6: Exposure to Study Vaccine by Special Populations (Primary Pooling)

	Ad26.COV2.S	Placebo	Total
HIV infection, N	38538	37809	76347
Yes	817 (2.1%)	793 (2.1%)	1610 (2.1%)
No	14891 (38.6%)	14848 (39.3%)	29739 (39.0%)
Missing	22830 (59.2%)	22168 (58.6%)	44998 (58.9%)
Breastfeeding Women at Baseline*, N	17217	17340	34557
Yes	252 (1.5%)	423 (2.4%)	675 (2.0%)
No	6558 (38.1%)	6499 (37.5%)	13057 (37.8%)
Missing	10407 (60.4%)	10418 (60.1%)	20825 (60.3%)
Pregnant Women at baseline, N	17629	17506	35135
Yes	0	0	0
No	7007 (39.7%)	6876 (39.3%)	13883 (39.5%)
Missing	10622 (60.3%)	10630 (60.7%)	21252 (60.5%)
Comorbidities with increased risk for severe COVID-19, N	38538	37809	76347
Yes	15708 (40.8%)	15641 (41.4%)	31349 (41.1%)
No	21891 (56.8%)	21845 (57.8%)	43736 (57.3%)
Missing	939 (2.4%)	323 (0.9%)	1262 (1.7%)
SARS-CoV-2 seropositive at baseline, N	38538	37809	76347
Yes	3941 (10.2%)	3832 (10.1%)	7773 (10.2%)
No	34125 (88.5%)	33616 (88.9%)	67741 (88.7%)
Missing	472 (1.2%)	361 (1.0%)	833 (1.1%)

This table includes 5 trials ie COV1001, COV1002, COV2001, COV3001 and COV3009. Only the primary dose ie $5x10^{10}$ vp dose level, regardless concentration or volume, is taken into account.
Total: Total number of participants with at least one dose (active or placebo) / Total number of doses (active or placebo).
Missing: No information available in the CRF. Pregnancy was exclusion criteria in all studies. HIV status was not collected for participants with no co-morbidities.
*Trials included are COV3001 and COV3009.
Note: Data cutoff for COV1001 of 21JUL2021, COV1002 of 02AUG2021, COV2001 of 11MAY2021, COV3001 of 09JUL2021, COV3009 of 25JUN2021

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Exposure in the Cross-dose Level Pooling

At the cut-off date of 24 February 2022, a total of 80,462 participants had been included in the cross-dose level pooling, of which a total of 65,490 participants received at least 1 dose of Ad26.COV2.S at any dose level; 63,400 participants received at least 1 dose of Ad26.COV2.S at the $5x10^{10}$ vp dose level (unblinded or randomized to active vaccine). In total, 686 participants from trial COV3005 were still blinded. Overall, 107,088 doses of Ad26.COV2.S had been administered at any dose level (unblinded or randomized to active vaccine).

Exposure to Ad26.COV2.S and matching placebo in the cross-dose level pooling is summarized in the tables presented in Annex 7.7 for all participants by dose, by age group, by sex, by race, by ethnicity, and by special populations (ie, participants with HIV infection, breastfeeding women at baseline, pregnant women at baseline, participants with comorbidities associated with increased risk for severe COVID-19, and participants who are SARS-CoV-2 seropositive at baseline). Any case of study vaccine exposure during pregnancy was included in the Company's Global Safety Database when reported during the trials.

Exposure in the Extended Cross-dose Level Pooling

At the cut-off date of 03 July 2023, a total of 64,213 participants received at least 1 dose of Ad26.COV2.S only at any dose level. A total of 26,532 participants received at least 1 dose of Ad26.COV2.S at any dose level and administration of another COVID-19 vaccine (irrespective of vaccination sequence). Note that these numbers are not mutually exclusive and cannot be added up to obtain an overall number of participants who received Ad26.COV2.S. Four participants have an unknown vaccine administration.

Exposure in Study COV3012 (Sisonke-1)

A total of 496,424 participants had received a single dose of Ad26.COV2.S at the approved dose level (ie, $5x10^{10}$ vp) in the completed study COV3012.

Exposure in Study COV3021 (Sisonke Boost)

At the cut-off date of 24 February 2023, a total of 240,747 participants had received a booster dose of Ad26.COV2.S at the approved dose level (ie, $5x10^{10}$ vp) in study COV3021.

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PART II: SAFETY SPECIFICATION

Module SIV: Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table SIV.1: Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 1	**Known or suspected allergy or history of anaphylaxis or other serious adverse reactions to vaccines or their excipients (including specifically the excipients of the study vaccine)**
Reason for being an exclusion criterion	These individuals were excluded from clinical trials to avoid potentially severe and life-threatening allergic/hypersensitivity reactions. In addition, anaphylaxis is always considered a risk with foreign proteins administered by vaccination.
Considered to be included as missing information:	No
Rationale (if not included as missing information)	Standard medical practice for any vaccine includes contraindication of administration of the vaccines in case of known allergy to their components and for the vaccinator to be ready to immediately treat any possible severe allergic reaction such as anaphylaxis. The SmPC Section 4.3 states that JCOVDEN is contraindicated in individuals with hypersensitivity to the active substance or to any of the excipients. Section 4.4 states that events of anaphylaxis have been reported and appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine. Close observation for at least 15 minutes is recommended following vaccination.

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Table SIV.1: Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 2	**Immunocompromised participants**
Reason for being an exclusion criterion	These individuals were excluded from clinical trials to obtain unconfounded immunogenicity results. However, participants were not excluded from Stages 1b and 2b of trial COV3001 and from Stage 2 of trial COV3009 if they had a stable and well-controlled medical condition including comorbidities associated with an increased risk of progression to severe COVID-19 (eg, stable/well-controlled HIV infection[3]), or if they were receiving chronic low-dose (less than 20 mg of prednisone or equivalent) immunosuppressive therapy. Participants with clinical conditions stable under non-immunomodulator treatment (eg, autoimmune thyroiditis, autoimmune inflammatory rheumatic disease such as rheumatoid arthritis) could also be enrolled in trials COV3001 (Stages 1b and 2b) and COV3009 (Stage 2) at the discretion of the investigator. However, of all immunocompromised subgroups, only those participants with HIV infection were included at sufficient numbers to be able to provide meaningful data.
Considered to be included as missing information:	Yes
Rationale (if not included as missing information)	Not applicable
Criterion 3	**Receipt of licensed live attenuated vaccines within 28 days before or after planned administration of the first or subsequent study vaccinations, or receipt of any other licensed (not live) vaccine from 14 days before to 14 days after any study vaccine**
Reason for being an exclusion criterion	Concomitant vaccination could influence the individual's immune response to the vaccine and could confound the safety evaluation.
Considered to be included as missing information:	No
Rationale (if not included as missing information)	The SmPC Section 4.5 states that JCOVDEN can be administered concomitantly with seasonal standard dose inactivated influenza vaccine.

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[3] Defined as documented CD4 cell count ≥300 cells/μL and HIV viral load <50 copies or vp/mL within 6 months prior to screening, and on a stable antiretroviral treatment for 6 months.

Table SIV.1: Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 4	**A woman who is pregnant, or planning to become pregnant while enrolled in the trial or within 3 months after the last dose of study vaccine**
Reason for being an exclusion criterion	Per ICH guidelines, pregnant women should normally be excluded from clinical trials.
Considered to be included as missing information:	Yes
Rationale (if not included as missing information)	Not applicable
Criterion 5	**Breastfeeding women**
Reason for being an exclusion criterion	Breastfeeding women are usually excluded from clinical trials. However, they were not excluded from Phase 3 trials COV3001 and COV3009.
Considered to be included as missing information:	Yes
Rationale (if not included as missing information)	Not applicable
Criterion 6	**Chronic active HBV or HCV infection per medical history**
Reason for being an exclusion criterion	These individuals were excluded from clinical trials to obtain unconfounded immunogenicity results. However, they were not excluded from Stages 1b and 2b of trial COV3001 and Stage 2 of trial COV3009.
Considered to be included as missing information:	No
Rationale (if not included as missing information)	Ad26.COV2.S is a nonreplicating vaccine, therefore, there is no risk of infection leading to potential adverse clinical outcomes and the safety profile is not expected to be significantly different than in the general population. Recent studies suggest that patients with chronic HBV or HCV infection have an increased risk for morbidity and mortality from COVID-19 (Mirzaie 2021). Based on this assessment, it is considered that the potential benefit greatly outweighs the risk of vaccinating individuals with chronic HBV or HCV infection.

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SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, or adverse reactions with a long latency.

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program(s)

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Up to the cut-off date of 24 February 2022, 23 women who were pregnant at baseline received at least one dose of Ad26.COV2.S (cross-dose level pooling; all dose levels). Any case of study vaccine exposure during pregnancy was included in the Company's Global Safety Database when reported during the course of the trials. As of the cut-off date of 24 February 2023, 131 unique pregnancies following Ad26.COV2.S administration were retrieved from Company-sponsored clinical trials post-baseline. Of note, 1 participant reported a twin pregnancy during the trial.
Breastfeeding women	Up to the cut-off date of 24 February 2022, 718 women who were breastfeeding at baseline have received at least one dose of Ad26.COV2.S (cross-dose level pooling; all dose levels).
Pediatric population	Individuals aged <18 years were excluded from Phase 1 trials and only limited data are available from Phase 2 trials. In total, 33 adolescents (16-17 years) were vaccinated in trial COV2001 and 299 adolescents (12-17 years) were vaccinated in trial COV3006 in the pediatric development program. The use in pediatrics is not in scope of the indication.
Elderly	Of the 65,490 participants in the cross-dose level pooling who received at least one dose of Ad26.COV2.S (all dose levels), 21,323 (32.6%) participants were aged ≥60 years, 11,801 (18.0%) participants were aged ≥65 years, and 2,003 (3.1%) participants were aged ≥75 years.
Individuals with a disease severity different from inclusion criteria in clinical trials	Not applicable
Population with relevant different ethnic origin	Of the 65,490 participants in the cross-dose level pooling who received at least one dose of Ad26.COV2.S (all dose levels), 42,559 (65.0%) participants were white, 10,423 (15.9%) were black or African American, 4,204 (6.4%) were American Indian or Alaska Native (who were mainly enrolled in Latin America), 3,845 (5.9%) were Asian, 2,424 (3.7%) were of multiple race, and 149 (0.2%) were Native Hawaiian or other Pacific Islander. Overall, 22,804 (34.8%) participants were Hispanic or Latino.

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Type of Special Population	Exposure
Subpopulations carrying relevant genetic polymorphisms	Not applicable
Patients with relevant comorbidities:	
• Immunocompromised individuals	Of the 65,490 participants in the cross-dose level pooling who received at least one dose of Ad26.COV2.S (all dose levels), 1,440 (2.2%) participants had a stable/well-controlled HIV infection. Participants with other immunodeficiencies were included at low numbers.
• Individuals with comorbidities associated with increased risk for severe COVID-19	Of the 65,490 participants in the cross-dose level pooling who received at least one dose of Ad26.COV2.S (all dose levels), 25,737 (39.3%) participants had 1 or more comorbidities associated with an increased risk for severe COVID-19.
• Individuals with autoimmune or inflammatory disorders	Participants with clinical conditions stable under non-immunomodulator treatment (eg, autoimmune thyroiditis, autoimmune inflammatory rheumatic disease such as rheumatoid arthritis) were eligible for enrollment in Phase 3 trials COV3001 (Stages 1b and 2b) and COV3009 (Stage 2) at the discretion of the investigator. Of the 21,898 participants in the FAS of trial COV3001 who received Ad26.COV2.S ($5x10^{10}$ vp dose level), 552 participants had a medical history of at least 1 immune-mediated/autoimmune disorder at baseline. Of the 15,708 participants in the FAS of trial COV3009 who received at least 1 dose of Ad26.COV2.S ($5x10^{10}$ vp dose level), 458 participants had a medical history of at least 1 immune-mediated/autoimmune disorder at baseline.
• Frail individuals with comorbidities	Following a protocol amendment for trial COV3001 on 14 December 2020, calculation of a frailty index has been included to be applied to participants enrolled. Of the 19,577 participants in the Per Protocol set who received Ad26.COV2.S ($5x10^{10}$ vp dose level), 6 (<0.1%) were defined as frail and 2,147 (11.0%) were defined as pre-frail (COV3001 CSR Dec 2021).
• Individuals who are SARS-CoV-2 seropositive at baseline	Of the 65,490 participants in the cross-dose level pooling who received at least one dose of Ad26.COV2.S (all dose levels), 6,891 (10.5%) participants were SARS-CoV-2 positive at baseline (based on serology).

Rationale for not considering special populations as safety concerns

Use in pediatrics

Children and adolescents aged <18 years were excluded from Phase 1 trials and only limited data are available from Phase 2 trials. In total, 33 adolescents (16-17 years) were vaccinated in trial COV2001 and 299 adolescents (12-17 years) were vaccinated in trial COV3006 in the pediatric development program. The safety and efficacy of Ad26.COV2.S in children and adolescents (<18 years of age) have not yet been established. The available data from the completed trial COV2001 suggest that Ad26.COV2.S administered at the 2.5×10^{10} vp dose level in adolescents aged 16 to 17 years had an acceptable safety and reactogenicity profile. The trial COV3006

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protocol has been amended to reduce the trial sample size. Besides this study, for which enrollment and vaccinations have been completed, no other pediatric studies are ongoing or planned.

On 30 December 2022, EMA granted a product specific waiver for all subsets of the pediatric population on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for pediatric patients.

Use in pediatrics is not considered missing information as it is not in scope of the indication.

Use in elderly

The risk for severe illness with COVID-19 increases with age, with elderly being at highest risk.

The primary pooling included 13,259 (34.4%) participants aged ≥60 years, 7,392 (19.2%) participants aged ≥65 years, and 1,280 (3.3%) participants aged ≥75 years who received Ad26.COV2.S.

During the primary pooling, the overall frequency of solicited local and systemic AEs post any dose in the Ad26.COV2.S group was lower in participants aged ≥60 years (42.6% and 49.7%, respectively) compared to participants aged ≥18 to 59 years (69.5% and 70.8%, respectively). This lower frequency in participants aged ≥60 years was reported for all selected solicited local and systemic AEs.

The potential benefit of receiving Ad26.COV2.S in elderly populations outweighs the risks. This age group is one of the primary targets of vaccination worldwide. Based on the number of elderly participants and the primary pooling results, use in elderly is not considered missing information.

Individuals with comorbidities associated with increased risk for severe COVID-19

Individuals with comorbidities that are or might be associated with an increased risk of progression to severe COVID-19 were included in trials COV2008, COV3001 (Stages 1b and 2b), and COV3009 (Stage 2). These included individuals with respiratory comorbidities, ie, moderate to severe asthma; chronic lung diseases such as COPD, pulmonary fibrosis, and cystic fibrosis; and individuals with other comorbidities, ie, type 1 and type 2 diabetes mellitus; serious heart conditions (including heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension); moderate to severe hypertension; obesity; liver disease; sickle cell disease; thalassemia; cerebrovascular disease; neurologic conditions such as dementia; chronic kidney disease; cancer; immunocompromised state from solid organ transplant; immunocompromised state from blood or bone marrow transplant, immune deficiencies, use of corticosteroids, or use of other immune weakening medicines; and HIV.

Of the 38,538 participants in the primary pooling who received at least one dose of Ad26.COV2.S, 15,708 (40.8%) participants had 1 or more comorbidities associated with an increased risk for severe COVID-19.

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During the primary pooling, the overall frequency of solicited local and systemic AEs post any dose in the Ad26.COV2.S group was lower in participants with one or more comorbidities at baseline (51.7% and 57.0%, respectively) compared to participants without comorbidities at baseline (62.6% and 65.3%, respectively). This lower frequency in participants with one or more comorbidities was reported for most selected solicited local and systemic AEs.

Use in individuals with comorbidities associated with increased risk for severe COVID-19 is not considered missing information.

The safety and efficacy of individuals who are frail and also have comorbidities associated with increased risk for severe COVID-19 has not yet been assessed and is considered missing information (see Module SVII.1.2).

Individuals who are SARS-CoV-2 seropositive at baseline

The extent to which pre-existing antibodies to SARS-CoV-2 could impact the safety and immunogenicity of Ad26.COV2.S is not yet known.

A positive serological test result for SARS-CoV-2 infection was not an exclusion criterion in trials COV3001 and COV3009.

Of the 38,538 participants in the primary pooling who received at least one dose of Ad26.COV2.S, 3,941 (10.2%) participants were SARS-CoV-2 positive at baseline, based on serology. Based on serology or RT-PCR assessment, a total of 10.6% of participants were SARS-CoV-2 positive at baseline.

During the primary pooling, no clinically relevant differences in the frequency of solicited local and systemic AEs were observed in participants receiving Ad26.COV2.S who were SARS-CoV-2 sero- and PCR-negative at baseline (58.9% and 62.9%, respectively) compared to participants who were SARS-CoV-2 sero- and/or PCR-positive at baseline (59.7% and 58.9%, respectively).

Use in individuals who are SARS-CoV-2 seropositive at baseline is not considered missing information.

Summary of Missing Information Due to Limitations of the Clinical Trial Program

Use in pregnancy and while breastfeeding
Use in immunocompromised patients
Use in patients with autoimmune or inflammatory disorders
Use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)
Long-term safety

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PART II: SAFETY SPECIFICATION

Module SV: Post-authorisation Experience

SV.1. Post-authorisation Exposure

A conditional Marketing Authorisation was granted by the European Commission for Ad26.COV2.S on 11 March 2021 and vaccination of the EU/EEA population was initiated on 14 April 2021. Additionally, the WHO granted Ad26.COV2.S vaccine emergency use listing on 12 March 2021. On 16 December 2021, the European Commission authorized (as part of the conditional Marketing Authorisation) Ad26.COV2.S as homologous or heterologous booster following completion of primary vaccination with an approved mRNA COVID-19 vaccine. On 11 November 2022, the European Commission authorized (as part of the conditional Marketing Authorisation) Ad26.COV2.S as heterologous booster following completion of primary vaccination with an adenoviral vector-based COVID-19 vaccine. On 09 January 2023, the European Commission converted the conditional marketing authorization for the Ad26.COV2.S vaccine into a standard marketing authorization. Post-authorisation exposure in the European Union/EEA and worldwide from launch up to 28 February 2023[4] is presented below.

SV.1.1. Method used to Calculate Exposure

Post-authorisation exposure in the European Union/EEA is based on the number of administered doses reported on the ECDC COVID-19 Vaccine Tracker website (ECDC 2023b).

Estimates of worldwide post-authorisation exposure are based upon the number of administered doses reported from CDC for the US (CDC 2023b), ECDC for EEA countries, Korea Disease Control and Prevention Agency for South Korea (KDCA 2023), Ministério da Saúde for Brazil (Ministério da Saúde 2021), and National Department of Health for South Africa (NDH 2023).

The vaccine exposure figures described in this section are an overall estimation with some uncertainties regarding the lack of exposure information received from many countries.

SV.1.2. Exposure

European Union/EEA

Cumulative postmarketing exposure from the European Union/EEA according to the ECDC as of 28 February 2023, is a total of 19,781,050 primary doses of Ad26.COV2.S.

The ECDC publishes the Ad26.COV2.S vaccine doses administered by age group (ECDC 2023c). The age group numbers in this report currently cover 29 EEA countries, ie, all EEA countries excluding France. In addition, the French age group breakdown for the Ad26.COV2.S vaccine is published on a regular basis by ANSM in France (ANSM 2023), which is combined with the age group data for the other 29 countries. Therefore, the overall EEA age group distribution is based on the number of Ad26.COV2.S vaccine doses administered in all EEA countries.

[4] Note: The data for the distributed/delivered doses is available for whole months only, therefore the exposure data was cumulatively provided until 28 February 2023, instead of the postmarketing DLP of 24 February 2023.

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The age group distribution from launch up to 24 February 2023 is shown in the table below. Note that the last update with Company-specific exposure numbers was on 30 December 2021. Linear extrapolation was used to estimate exposure post 30 December 2021.

Distribution of Ad26.COV2.S Administered Doses in EEA Countries by Age Group

Age Group	18-29	30-39	40-49	50-64	65-74	75+
Distribution	21.5%	18.8%	18.8%	27.5%	8.9%	4.3%

Worldwide

An estimate of 53,047,996 primary doses of Ad26.COV2.S vaccine were administered worldwide from launch to 28 February 2023.

A total of 3,132,632 subjects were administered the homologous Ad26.COV2.S vaccine booster dose in South Africa, South Korea, and the US from launch to 28 February 2023.

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PART II: SAFETY SPECIFICATION

Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

Vaccines in general are not considered to present a risk for abuse potential, and this is also applicable to Ad26.COV2.S. The potential for misuse of Ad26.COV2.S is negligible given its composition, mechanism of action, and availability only through prescription and administration by healthcare personnel.

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PART II: SAFETY SPECIFICATION

Module SVII: Identified and Potential Risks

In accordance with EMA's 'Consideration on core requirements for RMPs of COVID-19 vaccines' guidance (EMA 2020b), the below factors were taken into consideration for the generation of the safety specifications and are not determined to be identified or potential risks.

- The vaccine construct and the formulation.

  Ad26.COV2.S is a monovalent vaccine composed of a recombinant, replication-incompetent human Ad26 vector that encodes a SARS-CoV-2 full length S protein in a stabilized conformation. The S protein on the surface of SARS-CoV-2 binds to the ACE2 receptor of a host cell, allowing the virus to infect the cell. Vaccination with Ad26.COV2.S leads to humoral and cellular immune responses directed against the S protein. The production of neutralizing and other functional S-specific antibodies may block binding of the viral S protein to the ACE2 receptor, thereby inhibiting viral entry into host cells, and mediate cellular effector mechanisms via Fc function, leading to clearance of SARS-CoV-2 virus particles and infected cells. Cellular immune responses may further contribute to protection by clearing SARS-CoV-2-infected cells via cytotoxic mechanisms. Ad26.COV2.S is produced in PER.C6 TetR cells.

- The non-pathogenicity of the vector.

  Ad26.COV2.S is replication-incompetent as it only encodes the S protein of SARS-CoV-2 and is not capable of replicating in human cells. As such, it is not capable of causing infection/disease.

- The vaccine does not contain an adjuvant.

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

Summary of Safety Concerns	
Important identified risks	Anaphylaxis
Important potential risks	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)
	Venous thromboembolism
Missing information	Use in pregnancy and while breastfeeding
	Use in immunocompromised patients
	Use in patients with autoimmune or inflammatory disorders
	Use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)
	Interaction with other vaccines
	Long-term safety

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SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not all potential or identified risks for the vaccine are considered to meet the level of importance necessitating inclusion in the list of safety concerns in the RMP.

Reason for not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

Risks not Included in the List of Safety Concerns in the RMP
Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):
Risk 1: Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation, or stress-related reactions Risk 2: Nervous system disorders: Headache, Tremor Risk 3: Respiratory, thoracic and mediastinal disorders: Cough, Sneezing, Oropharyngeal pain, Exacerbation of chronic pulmonary disorders (ie, asthma and COPD) Risk 4: Gastrointestinal disorders: Nausea Risk 5: Skin and subcutaneous tissue disorders: Rash, Hyperhidrosis Risk 6: Musculoskeletal and connective tissue disorders: Myalgia, Arthralgia, Muscular weakness, Pain in extremity, Back pain Risk 7: General disorders and administration site conditions: Fatigue, Injection site pain, Pyrexia, Injection site erythema, Injection site swelling, Chills, Asthenia, Malaise (See below for more information on reactogenicity, anxiety-related reactions, and exacerbation of chronic pulmonary disorders [ie, asthma and COPD])
Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:
None
Known risks that require no further characterization and are followed up via routine pharmacovigilance and for which the risk minimization messages in the product information are adhered by prescribers (eg, actions being part of standard clinical practice in each EU Member state where the product is authorised):
None
Known risks that do not impact the risk-benefit profile:
None
Other reasons for considering the risks not important for inclusion in the list of safety concerns:
Immunization errors (see below for more information)

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Reactogenicity

In acknowledgment of EMA's 'Consideration on core requirements for RMPs of COVID-19 vaccines' guidance (EMA 2020b), the reactogenicity profile of Ad26.COV2.S is discussed below. The reactogenicity profile does not impact the overall safety profile of the vaccine and is not proposed to be included in the list of safety concerns, rather it is discussed for completeness here.

Frequencies were calculated based on the Safety Subset of trial COV3001 (primary analysis). The most common local adverse reaction reported was injection site pain (48.6%). The most common systemic adverse reactions were headache (38.9%), fatigue (38.2%), myalgia (33.2%), and nausea (14.2%). Pyrexia (defined as body temperature ≥38°C) was observed in 9% of participants. Most adverse reactions occurred within 1 to 2 days following vaccination and were mild to moderate in severity and of short duration (1 to 2 days).

Adverse drug reactions observed during trial COV3001 in adults aged ≥18 years are listed below, organized by SOC, with their corresponding frequency categories in order of decreasing seriousness. Frequency categories are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000), not known (cannot be estimated from the available data).

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Adverse Reactions Reported Following Vaccination With Ad26.COV2.S (Based on Safety Subset of COV3001, Primary Analysis)

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Not known (cannot be estimated from the available data)
Immune system disorders				Hypersensitivity[a]; Urticaria	Anaphylaxis[b]
Nervous system disorders	Headache		Tremor		
Respiratory, thoracic and mediastinal disorders		Cough	Sneezing; Oropharyngeal pain		
Gastrointestinal disorders	Nausea				
Skin and subcutaneous tissue disorders			Rash; Hyperhidrosis		
Musculoskeletal and connective tissue disorders	Myalgia	Arthralgia	Muscular weakness; Pain in extremity; Back pain		
General disorders and administration site conditions	Fatigue; Injection site pain	Pyrexia; Injection site erythema; Injection site swelling; Chills	Asthenia; Malaise		

[a] Hypersensitivity refers to allergic reactions of the skin and subcutaneous tissue.
[b] Cases received from an ongoing open-label study in South Africa.

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Solicited AEs were recorded in an e-Diary from the day of vaccination until 7 days after each vaccination. The frequencies of solicited local and systemic AEs by age (≥18 to <60 years and ≥60 years), comorbidities, and SARS-CoV-2 serostatus at baseline are presented in Annex 7.6. A summary of the results is presented below.

Overall, no clinically relevant differences in the reactogenicity profile of Ad26.COV2.S were observed across comorbidities and SARS-CoV-2 serostatus at baseline. The frequency of solicited local and systemic AEs was lower in participants aged ≥60 years compared to participants aged ≥18 to <60 years. No overall differences in safety were observed between older adults ≥65 years and ≥75 years of age and younger adults (≥18 to <60 years of age). Furthermore, participants with one or more comorbidity (ie, asthma, cerebrovascular disease, chronic kidney disease, COPD, serious heart conditions, hypertension, and obesity) at baseline had higher frequencies of solicited AEs in the Ad26.COV2.S group compared to placebo.

Solicited Local Adverse Events

In the Ad26.COV2.S group, the frequency of solicited local AEs was lower in participants aged ≥60 years compared to participants aged ≥18 to <60 years. In general, this lower frequency was reported for all selected solicited local AEs, including the most frequent solicited local AE, ie, vaccination site pain (33.3% of participants aged ≥60 years compared to 58.6% of participants aged ≥18 to <60 years).

In general, no clinically relevant differences in the frequency of solicited local AEs were observed in participants with one or more comorbidities compared to participants without comorbidities after vaccination with Ad26.COV2.S. The most frequent solicited local AE, ie, vaccination site pain, was reported in the Ad26.COV2.S group with a lower frequency in participants with one or more comorbidities compared to those without comorbidities (40.9% versus 52.7%). In general, a similar frequency for all other selected solicited local AEs was reported in participants with and without comorbidities.

The frequency of solicited local AEs was similar in participants who were seronegative for SARS-CoV-2 at baseline compared to participants who were seropositive for SARS-CoV-2 at baseline (50.1% and 54.5%, respectively) in the Ad26.COV2.S group.

In the Ad26.COV2.S group, no clinically relevant differences in median duration and the median time to onset for solicited local AEs were reported within the subgroups by age (≥18 to <60 years and ≥60 years), comorbidities, and SARS-CoV-2 serostatus at baseline. Median duration and median time to onset never exceeded 3 days in any of these subgroups.

Solicited Systemic Adverse Events

In the Ad26.COV2.S group, the overall frequency of solicited systemic AEs was lower in participants aged ≥60 years compared to participants aged ≥18 to <60 years. In general, this lower frequency in participants aged ≥60 years was reported for all selected solicited systemic AEs, including the most frequent solicited systemic AE, ie, headache (30.5% of participants aged ≥60 years compared to 44.5% of participants aged ≥18 to <60 years).

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Pyrexia (fever defined as body temperature ≥38.0°C, as recorded by the participants) was reported in the Ad26.COV2.S group in 3.1% of participants aged ≥60 years compared to 12.8% of participants aged ≥18 to <60 years. Grade 3 pyrexia was reported in 1 (0.1%) participant aged ≥60 years (67 years of age) compared to 7 (0.3%) participants aged ≥18 to <60 years (all <35 years of age).

No clinically relevant differences in the frequency of solicited systemic AEs were observed in the Ad26.COV2.S group in participants with one or more comorbidities (49.6%) compared to participants without comorbidities (58.1%) and in participants who were seronegative for SARS-CoV-2 at baseline (55.4%) compared to participants who were seropositive for SARS-CoV-2 at baseline (50.6%).

In the Ad26.COV2.S group, no clinically relevant differences were observed in the median duration and median time to onset for solicited systemic AEs, with specifically pyrexia being similar across subgroups by age (≥18 to <60 years and ≥60 years), comorbidities, and SARS-CoV-2 serostatus at baseline.

Per protocol, prophylactic antipyretic use was not encouraged. However, antipyretics were recommended post-vaccination for symptom relief as needed and were used more frequently in the Ad26.COV2.S group compared to the Placebo group. Of the 302 participants who experienced pyrexia in the Ad26.COV2.S group, 202 (66.9%) used antipyretics. Overall, in the FAS, 1,128/21,895 (5.2%) participants in the Ad26.COV2.S group used analgesics or antipyretics up to 7 days post-vaccination.

Anxiety-related reactions

Individuals can react in anticipation of, or as a result of, an injection of any kind. These reactions are not related to the vaccine, but to fear of the injection (WHO 2019). The most common manifestations of anxiety-related reactions to immunization are:

- Fainting (syncope and presyncope): the most commonly reported anxiety-related reaction, especially in older children, adolescents, and older adults. It does not require any additional measures other than to prevent injury from fainting.
- Hyperventilation: increased breathing rate may cause dizziness and tingling sensation. It will typically recede shortly after vaccination has been completed.
- Vomiting: more commonly observed in children, typically following extended periods of crying and apnea. Regular measures to avoid broncho-aspiration are sufficient.
- Convulsions: might occur in very rare instances, especially in children and in adolescents, and it may be accompanied by fainting. The individual should recover without any sequelae.

As stated in the SmPC Section 4.4, anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation, or stress-related reactions, may occur in association with vaccination as a psychogenic response to the needle injection. It is important that precautions are in place to avoid injury from fainting.

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Anxiety-related reactions are not considered an important potential risk as they do not require further characterization by additional pharmacovigilance activities, or risk minimization beyond standard clinical practice. The routine risk minimization measures included in the SmPC and PL are part of standard clinical practice for vaccines in general and are considered sufficient for purposes of risk communication.

Exacerbation of chronic pulmonary disorders (ie, asthma and COPD)

An increased risk for severe COVID-19 outcomes has been reported in individuals with chronic lung diseases including COPD (Schultze 2020). Asthma patients are also at an increased risk for severe COVID-19; however, the disease burden in these patients is less evident for SARS-CoV-2 compared to influenza and other viruses (Izquierdo 2021). Therefore, these populations are a priority for vaccination against COVID-19.

Vaccines against other respiratory diseases, including influenza, have been associated with exacerbations of both asthma and COPD (Duffy 2017). Two possible mechanistic pathways have been proposed: viral infection (ie, lack of efficacy) and IgE hypersensitivity. Evidence for such association, however, remains weak (Committee to Review Adverse Effects of Vaccines; Institute of Medicine 2012).

A numerical imbalance has been observed in trial COV3001 regarding exacerbations of asthma and COPD in participants in the Ad26.COV2.S group compared to placebo (8 versus 1). The median time to onset was 11 days after vaccination. A single event was reported as serious (exacerbation of COPD), which occurred 39 days after vaccination. All events were assessed as not related by the investigator and were recovered at the time of reporting.

Despite the numerical imbalance in the Ad26.COV2.S group versus placebo, a causal link cannot be established based on the currently available data. All reported events occurred later than 72 hours after vaccination, which does not support a causal mechanism of reactive airway disease due to vaccine hypersensitivity. In addition, the onset of these episodes could have been confounded by other triggers such as infection. Since patients with asthma and COPD are at an increased risk for severe COVID-19 outcomes, exacerbation of chronic pulmonary disorders is considered a risk but not a safety concern.

Immunization errors

Large-scale public health approaches for mass vaccination may represent changes to the standard vaccine treatment process, thereby potentially introducing the risk of immunization errors related to administration, vaccination scheme, storage conditions, errors associated with a multidose vial, and confusion with other COVID-19 vaccines.

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Anticipated undesirable clinical outcomes arising from immunization errors include:

- Insufficient immunogenicity of the vaccine(s) in case of 'failure to vaccinate' (due to immunization error) leading to lack of anticipated clinical benefit (related to efficacy).
- Increased reactogenicity in case of overdosing (due to the use of multidose vial). Higher doses (up to 2-fold, ie, $1x10^{11}$ vp) administered in Phase 1/2 trials were well tolerated, but an increased reactogenicity was reported.

Other potential undesirable clinical outcomes of immunization errors are unknown. Immunization errors are not expected to result in any safety concerns. Any AE arising as a consequence of an immunization error will be monitored via routine pharmacovigilance activities and will be presented in each PBRER/PSUR.

At the time of initial cMAA submission, the Company considered the following situations as potential sources of immunization errors:

- As the majority of other COVID-19 vaccine regimens are administered as a 2-dose schedule, there is a possibility for Ad26.COV2.S to be erroneously administered twice.
- As multidose vials (>5 mL) will be used for vaccination, there is the possibility of administering a higher dose than the selected dose level of $5x10^{10}$ vp of Ad26.COV2.S.
- Ad26.COV2.S is indicated in individuals aged ≥18 years. As the indication of other manufacturer's COVID-19 vaccines includes the use in adolescents aged 16 and 17 years, there is a risk for Ad26.COV2.S being erroneously administered in this age group.
- Currently, no safety data exist regarding the use of Ad26.COV2.S in combination with any other COVID-19 vaccine as part of a mixed schedule. There is a risk for the vaccine unwittingly being administered to an individual already vaccinated with another COVID-19 vaccine or vice versa.

Potential immunization errors are mitigated through the information in the SmPC Sections 4.1, 4.2, and 6.6, which contain instructions regarding the therapeutic indication, posology, method of administration, and storage conditions of Ad26.COV2.S.

In addition, a Janssen COVID-19 vaccine-specific Contact Center will be available to support vaccination providers (eg, healthcare professionals and individuals who administer the vaccine) and recipients by providing a straightforward and streamlined way for them to ask unsolicited requests for medical information.

These available resources will provide information on the proper preparation and administration of the vaccine and reduce the potential for immunization errors in the context of a mass vaccination campaign.

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List of AESIs

There were no pre-specified AESIs for Ad26.COV2.S early clinical development. The Company follows a dynamic medical review of incoming SAEs to identify potential safety issues.

For the purpose of the EU-RMP and monthly summary safety reports, a set of AESIs has been identified taking into consideration the available lists of AESIs from the following expert groups and regulatory authorities:

- Brighton Collaboration (SPEAC) (Law 2020)
- ACCESS protocol (2020)
- US CDC (preliminary list of AESI for VAERS surveillance) (Shimabukuro 2020)
- MHRA (unpublished guideline)

These AESIs are taken in consideration for routine and additional pharmacovigilance activities. The list is considered dynamic and may be customized following the evolving safety profile of the vaccine.

Medical conditions covered by the list of AESIs include:

- Immune-mediated and (neuro-)inflammatory disorders.
- Thrombotic and thromboembolic events.
- Major organ disorders, including neurological, cardiovascular, hepatic, and respiratory.
- Events associated with COVID-19.

The detailed list of AESIs is available in Annex 7.4.

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SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety Concerns for Inclusion in the RMP	Risk-Benefit Impact
Important identified risks	
Anaphylaxis	Allergic reactions, including possibly severe reactions (eg, hypersensitivity reactions and anaphylaxis), are known to occur with any injectable vaccine. Most individuals fully recover with treatment, but serious complications can occur. Reporting from selected healthcare organizations in the United States found an overall rate of anaphylaxis after vaccination of 1.3 cases per million doses administered to both children and adults. The estimated rate of anaphylaxis reported to VAERS from 1990 to 2016 was 0.6 per 1 million doses distributed after measles, mumps, and rubella vaccine, and 0.2 per 1 million doses distributed after pneumococcal polysaccharide vaccine; from 2006 to 2016, the estimated rate was 1.2 per 1 million doses distributed after varicella vaccine. From 2010 to 2016, the median estimated annual rate after influenza vaccine (all types) among persons aged 1 to 84 years was 0.2 (range: 0.1-0.4) per 1 million doses administered (Su 2019). Available data seem to suggest a particular patient profile for individuals who experience anaphylaxis after vaccination: the vast majority has a history of atopy (history of atopic disease, such as asthma, allergic rhinitis, atopic dermatitis, or food or drug allergy) but anaphylaxis can occur among individuals with no known history of hypersensitivity. Ad26.COV2.S contains ingredients with known potential to cause allergic reactions, including polysorbate 80.
Important potential risks	
Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)	VAERD was first seen in the 1960s in infants with RSV infection after receiving a vaccine against RSV that led to markedly worse respiratory disease as compared to non-vaccinated infants. Subsequently, reports of VAED were reported in individuals without prior exposure to Dengue who received tetravalent Dengue vaccines. Nonclinical experience with SARS-CoV- and MERS CoV-based vaccines also indicated a risk for VAERD, however, this risk could not be confirmed in humans due to the lack of efficacy studies. For candidate SARS-CoV-2 vaccines, no evidence of VAED or VAERD after IM immunization has been reported to date in nonclinical studies or clinical trials. Nevertheless, in the absence of long-term safety and efficacy data, the evidence is not yet sufficient to fully dismiss VAED, including VAERD as a safety concern, and it remains an important potential risk. If VAED, including VAERD was to be identified as a true risk, depending on its incidence and severity, it could negatively impact the overall risk-benefit balance of Ad26.COV2.S for certain individuals.

Medicinal product no longer authorised

Safety Concerns for Inclusion in the RMP	Risk-Benefit Impact
Venous thromboembolism	Natural infection with SARS-CoV-2 has shown to be associated with hypercoagulability, pulmonary intravascular coagulation, microangiopathy, and VTE or arterial thrombosis. The occurrence of thrombotic and thromboembolic events in context of COVID-19 is associated with a poor outcome. The hypercoagulable state observed in patients with severe COVID-19 is thought to be related to the high-grade systemic inflammatory response, although other mechanisms such as the higher incidence of severe COVID-19 in individuals with risk factors for thrombotic and thromboembolic events have been proposed. It is unknown whether these proposed mechanisms linking COVID-19 and thromboembolic events could also be applicable for vaccines against COVID-19. The available evidence from the clinical trial development program does not suggest that VTE is an important identified risk in participants vaccinated with Ad26.COV2.S. Nevertheless, due to the observed numerical imbalance and its potential life-threatening nature, the risk of VTE resulting from vaccination with Ad26.COV2.S, especially in participants with comorbidities associated with DVT and PE, cannot be entirely ruled out. Therefore, venous thromboembolism is considered an important potential risk.
Missing information	
Use in pregnancy and while breastfeeding	As being pregnant or planning to become pregnant is an exclusion criterion in all clinical trials being conducted to date, the safety profile of Ad26.COV2.S in pregnant women has not been established and the risk in this population has not yet been defined. Breastfeeding women were excluded from all clinical trials, except from Phase 3 trials COV3001 and COV3009. Up to the DLP of the EU-RMP that was part of the initial cMAA submission (22 January 2021), 128 breastfeeding women have received Ad26.COV2.S in trial COV3001, but no data are currently available from these trials in this subpopulation. Therefore, the safety profile of Ad26.COV2.S in breastfeeding women has not been established and the risk in this population has not yet been defined.
Use in immunocompromised patients	The safety profile of Ad26.COV2.S is not known in immunocompromised patients, including those receiving immunosuppressant therapy, due to their exclusion from the clinical development program. Only individuals with a stable/well-controlled HIV infection, those receiving chronic low-dose (less than 20 mg of prednisone or equivalent) immunosuppressive therapy were included in trials COV3001 and COV3009. Given the fact that Ad26.COV2.S is a replication-incompetent vaccine, the safety profile of Ad26.COV2.S when used in immunocompromised individuals is not expected to differ from that in the general population, with no specific safety concerns.

Medicinal product no longer authorised

Safety Concerns for Inclusion in the RMP	Risk-Benefit Impact
Use in patients with autoimmune or inflammatory disorders	There is limited information on the safety of Ad26.COV2.S in individuals with autoimmune or inflammatory disorders and a theoretical concern that the vaccine may exacerbate their underlying disease.
Use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)	There is limited information on the safety of Ad26.COV2.S in frail patients with comorbidities. These comorbidities may compromise their immune response and the safety profile of Ad26.COV2.S in this subpopulation could vary from that seen in healthy adults, with a potentially higher risk of severe COVID-19.
Interaction with other vaccines	Ad26.COV2.S will be used in individuals who may also receive other vaccines. Trials to determine if concomitant administration of Ad26.COV2.S with other vaccines may affect the efficacy or safety of either vaccine have not been performed. This applies also to mixed schedules with other COVID-19 vaccines.
Long-term safety	There are no available data on the long-term safety of Ad26.COV2.S. Further data are being collected for at least 2 years in ongoing trials COV3001 and COV3009 following administration of Ad26.COV2.S, and for up to 1 year in studies COV4003 and COV4001. Based on long-term safety data from other Ad26-based vaccines (at least 6 months up to 4.5 years post-vaccination in clinical trials), no long-term safety issues have been identified (Adenoviral Vaccine Safety Database V5.0 2020).

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

The missing information 'Interaction with other vaccines' has been removed from the list of safety concerns, based on the following rationale:

Trial COV3005, a randomized, double-blind, Phase 3 study evaluated the safety, reactogenicity, and immunogenicity of coadministration of Ad26.COV2.S and seasonal quadrivalent influenza vaccines in healthy adults. The reactogenicity following administration of Ad26.COV2.S with seasonal quadrivalent influenza vaccine was higher than following administration of the vaccines separately. Individuals with various vaccination history showed an acceptable safety profile range when receiving Ad26.COV2.S coadministered with seasonal influenza vaccine. Ad26.COV2.S coadministered with influenza vaccine demonstrated a safety profile in line with the profile observed in previous studies. Overall, study results indicated that the safety profile of coadministration was considered acceptable.

These findings support that JCOVDEN can be administered concomitantly with seasonal standard dose inactivated influenza vaccine. This is reflected in Section 4.5 of the SmPC.

Medicinal product no longer authorised

As no further additional pharmacovigilance activities are ongoing or planned, interaction with other vaccines is no longer considered as missing information in the EU-RMP. Interaction with other vaccines will continue to be discussed in the PSUR, in line with applicable GVP guidance.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

Important identified risks

1. Thrombosis with thrombocytopenia syndrome
2. Guillain-Barré syndrome
3. Thrombocytopenia, including immune thrombocytopenia
4. Venous thromboembolism
5. Myocarditis and pericarditis

Important potential risks

1. Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)

Missing information

1. Use in pregnancy and while breastfeeding
2. Use in immunocompromised patients
3. Use in patients with autoimmune or inflammatory disorders
4. Use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)
5. Long-term safety

MedDRA version 24.1 was used to classify the clinical trials AE information that is summarized in this Section, unless specified otherwise. MedDRA version 26.0 was used for the extended cross-dose level pooling. MedDRA terms used in the database search for each important identified risk and important potential risk are detailed in Annex 7.3.

Medicinal product no longer authorised

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: Thrombosis with thrombocytopenia syndrome

Potential Mechanisms:

The exact mechanism of thrombosis with thrombocytopenia syndrome (TTS) following vaccination with Ad26.COV2.S is unknown. Several hypothetical biological mechanisms have been proposed to explain the pathophysiology of vaccine-induced TTS, including vaccine-mediated induction of platelet-activating antibodies directed against the cationic platelet chemokine PF4 (CXCL4), subsequently referred to as anti-PF4 antibodies (Greinacher 2021).

The MAH assessed a possible interaction between PF4 and Ad26.COV2.S (for details see Module SII) and does not have conclusive evidence for binding of Ad26.COV2.S to PF4 in vitro. Several research teams in the TTS field are pursuing to investigate the potential binding of different Adenovirus vectors or other components in the formulation of the COVID-19 vaccines to PF4. The MAH will continue to follow the research developments regarding the potential binding to PF4 and support those activities wherever possible.

Besides the adenovirus vector, a potential role of the S protein as well as of a predisposition of the patient should be considered. The SARS-CoV-2 S protein has been associated with endothelial inflammation, leukocyte adhesion, release of PF4, hypercoagulation, and thrombosis (Robles 2022, Lei 2021, Perico 2022, Zhang 2020, Grobbelaar 2021, Zheng 2021, Lee 2023), and is hypothesized to be related to adverse effects after COVID-19 vaccination (Trougakos 2022).

PF4 binding data and a potential role of the S protein were presented by the MAH at the virtual workshop on 27 June 2022, hosted by the EMA to review the current understanding of the pathophysiology of TTS (EMA 2022b, Buoninfante 2022).

With the remaining ongoing additional pharmacovigilance activities included in Part III.2, the MAH aims to further understand what the potential causes of TTS might be and to gain insights into possible anti-PF4 antibody induction in the context of post-vaccination TTS.

Evidence Source(s) and Strength of Evidence:

Thrombosis in combination with thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with Ad26.COV2.S and is an adverse drug reaction described in the SmPC.

Characterization of the Risk:

A combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with Ad26.COV2.S. This includes severe cases of venous thrombosis at unusual sites such as cerebral venous sinus thrombosis (CVST), splanchnic vein thrombosis as well as arterial thrombosis concomitant with thrombocytopenia.

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Fatal outcomes have been reported. These cases occurred within the first 3 weeks following vaccination, and mostly in individuals <60 years of age.

In this EU-RMP, for purposes of TTS risk characterization and presentation of cases, the PRAC case definition, which is based on the one proposed by the UK's National Institute for Health and Care Excellence (NICE) [NICE 2022] is used (Annex 7.5.1).

Clinical Trial Data

A table presenting the data for the 28-day post any dose period of the primary pooling is provided in this section. A table presenting data for the entire study follow-up period and by each post-dose period (including the follow-up period beyond 28 days of vaccination) of the primary pooling is provided in Annex 7.8.1. A table presenting data for the cross-dose level pooling is provided in Annex 7.8.2.

Cases of thrombosis with concurrent thrombocytopenia in clinical trials are identified and reviewed as described in Annex 7.3. Cases that were qualified for TTS assessment and classified according to PRAC case definition are presented below.

Medicinal product no longer authorised

Frequency, Seriousness, Outcomes and Severity of Thrombosis with Thrombocytopenia Qualified for TTS Assessment in Primary Pooling; Full Analysis Set

	Double Blind Ad26.COV2.S	Double Blind Placebo
Post Any Dose Period		
Number of participants exposed	38538	37809
PY follow-up	3608	3490
n (%)	4 (<0.1%)	2 (<0.1%)
95% CI (%)	(0.00%;0.03%)	(0.00%;0.02%)
Incidence per PY follow-up	0.11%	0.06%
95% CI (%) for Incidence rate	(0.034%;0.258%)	(0.010%;0.177%)
Number of Thrombosis with thrombocytopenia qualified for TTS assessment AEs	5	2
Seriousness		
Was serious	4 (80.0%)	1 (50.0%)
Outcomes		
Resulted in Death	0	0
Recovered with sequelae	0	0
Recovered without sequelae	4 (80.0%)	1 (50.0%)
Did not recover (Persisted)	0	1 (50.0%)
Recovering/Resolving	1 (20.0%)	0
Unknown	0	0
Severity		
Grade 1	0	0
Grade 2	1 (20.0%)	0
Grade 3	1 (20.0%)	2 (100.0%)
Grade 4	3 (60.0%)	0
Relatedness		
Related	1 (20.0%)	0
Not related	4 (80.0%)	2 (100.0%)
PRAC requested criteria		
Confirmed, Probable, Possible	4 (80.0%)	2 (100.0%)
Confirmed	1 (20.0%)	0
Possible	3 (60.0%)	2 (100.0%)
Unlikely	1 (20.0%)	0

Adverse events are coded using MedDRA version 24.1
This table includes 5 trials ie COV1001, COV1002, COV2001, COV3001 and COV3009. Only the primary dose ie $5x10^{10}$ vp dose level, regardless volume, is considered.
Person*Years (PY) follow-up for Entire Double-blind Phase is defined as time participant was followed up from first randomized dose datetime till the double-blind end datetime defined as earliest of unblinding datetime, open label vaccination datetime, other COVID-19 vaccination datetime or EoS* datetime (whichever comes first).
*EoS = earliest of End of study date, early discontinuation date, cut-off date.
Post-Dose 1, 2 etc, is the period from the day of the vaccination 1, 2, etc. (Day 1) until Day 29 ie Day 1+28 or earlier because of discontinuation, unblinding, open label vaccination, taking another COVID-19 vaccine or cut-off. Post any dose is combination of all post-doses (post dose 1, 2, etc.).
n (%): number (percentage) of participants with 1 or more events. 95% CI= 95% Confidence Interval.
The 95% CI for the percentage of participants is the Clopper-Pearson 95% CI; the 95% CI for the incidence rate is the exact Poisson 95% CI.
If participants received Ad26.COV2.S before the placebo vaccination (e.g. randomized sequence Ad26.COV2.S-Placebo), then the placebo vaccination is not reported. For these participants, time to onset of adverse events of interests (AEI) is linked to active dose received by the participant.
Note: Data cutoff for COV1001 of 21JUL2021, COV1002 of 02AUG2021, COV2001 of 11MAY2021, COV3001 of 09JUL2021, COV3009 of 25JUN2021
At time of database releases classifications for thrombosis with thrombocytopenia qualified for TTS assessment were not yet available in the database. AEs which were present in database and were later identified as 'Qualified for TTS Assessment' and classified per PRAC criteria, are presented in the table (latest classification at the time of RMP cut-off date 24 February 2022 was used). When there is a thromboembolic event with a concurrent thrombocytopenia and/or a low platelet count (both defined as platelet count below 150,000/µL) within 42 days of the thromboembolic event, the case is labeled as "qualified for assessment" and is being discussed and classified by the TTS Assessment Committee.

Modified from [TSFAE1P2.RTF] [PROD/VAC31518/Z_RMP/DBR_ADHOC_JAN22/RE_ADHOC_JAN22_BLA/TSFAE1P2.SAS] 20JUL2022, 00:48

Medicinal product no longer authorised

In the primary pooling, within 28 days post any dose, 5 cases in 4 (<0.1%) participants were qualified for TTS assessment, following Ad26.COV2.S administration. Of the 5 cases that were qualified for TTS assessment, 1 case (considered related to the study vaccine by both the Company and the investigator) met the PRAC case definition of confirmed TTS and 3 cases met possible PRAC case definition.

Similar incidences were observed in the cross-dose level pooling analysis and in the extended cross-dose level pooling analysis within 28 days post any dose following Ad26.COV2.S administration.

No new information to further characterize this safety concern was identified from clinical trials evaluating an Ad26.COV2.S booster dose as compared with the first dose of Ad26.COV2.S.

COV3012 (Sisonke-1) and COV3021 (Sisonke Boost)

One non-fatal case was qualified for TTS assessment in study COV3012. This case was classified as a possible TTS case according to the PRAC case definition.

Up to 24 February 2023, no TTS cases were reported in study COV3021.

Postmarketing Experience

Cumulatively, from launch to 24 February 2023, a total of 310 primary dose cases received from postmarketing experience were qualified for TTS assessment. Of these cases, 267 cases met confirmed (n=37), probable (n=17), or possible (n=213) PRAC case definition. This represents a reporting rate of 4.73 spontaneous cases per million primary doses administered. The outcome was fatal in 43 out of these 267 cases.

Cumulatively, from launch to 24 February 2023, a total of 5 heterologous booster dose cases received from postmarketing experience were qualified for TTS assessment. Of these cases, 5 cases met possible PRAC case definition. This represents a reporting rate of 0.32 spontaneous cases per million booster doses administered. One heterologous case had a fatal outcome. No homologous booster dose cases were reported.

Risk Factors and Risk Groups:

Although no clear risk factors have been identified, the cases of thrombosis in combination with thrombocytopenia reported in the postmarketing setting more commonly occurred in individuals aged <60 years.

Preventability:

TTS requires specialized clinical management. Healthcare professionals should consult applicable guidance and/or consult specialists (eg, hematologists, specialists in coagulation) to diagnose and treat this condition (SmPC Section 4.4).

Medicinal product no longer authorised

The SmPC Section 4.3 states that JCOVDEN is contraindicated in individuals with a history of confirmed TTS following vaccination with any COVID-19 vaccine. The SmPC Section 4.4 makes reference to this contraindication and states that 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 changes, or blurred vision after vaccination, or who experiences spontaneous bleeding, skin bruising (petechia) beyond the site of vaccination after a few days, should seek prompt medical attention. Individuals diagnosed with thrombocytopenia within 3 weeks after vaccination with JCOVDEN should be actively investigated for signs of thrombosis. Similarly, individuals who present with thrombosis within 3 weeks of vaccination should be evaluated for thrombocytopenia.

Impact on the Risk-Benefit Balance of the Product:

Thrombosis in combination with thrombocytopenia after vaccination with Ad26.COV2.S is a very rare event which is potentially life-threatening, especially if improperly managed. Adequate risk minimization that raises public awareness and supports education of healthcare professionals may lead to earlier diagnosis and appropriate treatment, which may improve the prognosis of TTS. Based on current information, the overall risk-benefit balance for Ad26.COV2.S is considered to remain positive for the indicated target populations.

Public Health Impact:

The occurrence of thrombosis with thrombocytopenia syndrome is very rare following vaccination with Ad26.COV2.S. Therefore, the impact on public health is expected to be low.

Annex 1 MedDRA Term:

PT Thrombosis with thrombocytopenia syndrome

Medicinal product no longer authorised

Important Identified Risk: Guillain-Barré syndrome

Potential Mechanisms:

The mechanism of Ad26.COV2.S-related GBS has not been established. However, as with other vaccines, immune activation is believed to play a role in the development of the disease (Sejvar 2011).

Evidence Source(s) and Strength of Evidence:

GBS has been observed very rarely following vaccination with Ad26.COV2.S both in clinical trials and in the postmarketing setting. Similar AEs have also been described following administration of other COVID-19 vaccines. Despite no clear biological mechanism being identified, the MAH considers the increase in observed versus expected ratios since authorisation to be sufficient evidence for a plausible association between Ad26.COV2.S and GBS.

Guillain-Barré syndrome is an adverse drug reaction described in the SmPC.

Characterization of the Risk:

Clinical Trial Data

A table presenting the data for the 28-day post any dose period of the primary pooling is provided in this section. A table presenting data for the entire study follow-up period and by each post-dose period (including the follow-up period beyond 28 days of vaccination) of the primary pooling is provided in Annex 7.8.1. A table presenting data for the cross-dose level pooling is provided in Annex 7.8.2.

Medicinal product no longer authorised

Frequency, Seriousness, Outcomes, and Severity of Guillain-Barré Syndrome in Primary Pooling; Full Analysis Set

	Double Blind Ad26.COV2.S	Double Blind Placebo
Post Any Dose Period		
Number of participants exposed	38538	37809
PY follow-up	3608	3490
n (%)	1 (<0.1%)	1 (<0.1%)
95% CI (%)	(0.00%;0.01%)	(0.00%;0.01%)
Incidence per PY follow-up	0.03%	0.03%
95% CI (%) for Incidence rate	(0.002%;0.122%)	(0.002%;0.126%)
Number of Guillain-Barré syndrome AEs	1	1
Seriousness		
Was serious	1 (100.0%)	1 (100.0%)
Outcomes		
Resulted in Death	0	0
Recovered with sequelae	0	0
Recovered without sequelae	0	1 (100.0%)
Did not recover (Persisted)	0	0
Recovering/Resolving	1 (100.0%)	0
Unknown	0	0
Severity		
Grade 1	0	0
Grade 2	0	1 (100.0%)
Grade 3	0	0
Grade 4	1 (100.0%)	0
Relatedness		
Related	1 (100.0%)	0
Not related	0	1 (100.0%)

Adverse events are coded using MedDRA version 24.1
This table includes 5 trials ie COV1001, COV1002, COV2001, COV3001 and COV3009. Only the primary dose ie $5x10^{10}$ vp dose level, regardless volume, is considered.
Person*Years (PY) follow-up for Entire Double-blind Phase is defined as time participant was followed up from first randomized dose datetime till the double-blind end datetime defined as earliest of unblinding datetime, open label vaccination datetime, other COVID-19 vaccination datetime or EoS* datetime (whichever comes first).
*EoS = earliest of End of study date, early discontinuation date, cut-off date.
Post-Dose 1, 2 etc. is the period from the day of the vaccination 1, 2, etc. (Day 1) until Day 29 ie Day 1+28 or earlier because of discontinuation, unblinding, open label vaccination, taking another COVID-19 vaccine or cut-off. Post any dose is combination of all post-doses (post dose 1, 2, etc.).
n (%): number (percentage) of participants with 1 or more events. 95% CI= 95% Confidence Interval.
The 95% CI for the percentage of participants is the Clopper-Pearson 95% CI; the 95% CI for the incidence rate is the exact Poisson 95% CI.
If participants received Ad26.COV2.S before the placebo vaccination (e.g. randomized sequence Ad26.COV2.S-Placebo), then the placebo vaccination is not reported. For these participants, time to onset of adverse events of interests (AEI) is linked to active dose received by the participant.
Note: Data cutoff for COV1001 of 21JUL2021, COV1002 of 02AUG2021, COV2001 of 11MAY2021, COV3001 of 09JUL2021, COV3009 of 25JUN2021

Modified from [TSFAE1P3.RTF] [PROD/VAC31518/Z_RMP/DBR_ADHOC_JAN22/RE_ADHOC_JAN22_BLA/TSFAE1P3.SAS] 20JUL2022, 00:48

Medicinal product no longer authorised

In the primary pooling, within 28 days post any dose, 1 event of GBS was reported in 1 (<0.1%) participant following Ad26.COV2.S administration. The event was reported post-dose 1 and assessed as related to the study vaccine by the investigator. Within the 42-day risk window after vaccination for GBS, as well as during the rest of the double-blind phase, no additional events of GBS were reported.

There were no new events observed in the cross-dose level pooling analysis within 28 days post any dose following Ad26.COV2.S administration. No additional events were reported within the 42-day risk window after vaccination for GBS and 7 additional events were reported in the Ad26.COV2.S group with an onset within Day 102 – Day 284 post-vaccination, of which 1 was considered to be related to the study vaccine by the investigator.

Between the cut-off date of the cross-dose level pooling analysis (24 February 2022) and of the extended cross-dose level pooling analysis (03 July 2023), no additional events of GBS were reported within 28 days post any dose in the Ad26.COV2.S group, nor within the 42-day risk window, as well as during the rest of the study period.

No new information to further characterize this safety concern was identified from clinical trials evaluating an Ad26.COV2.S booster dose as compared with the first dose of Ad26.COV2.S.

COV3012 (Sisonke-1) and COV3021 (Sisonke Boost)

Two cases of GBS were identified in study COV3012 (of which none were fatal).

Up to 24 February 2023, no cases of GBS were reported in study COV3021.

Postmarketing Experience

Cumulatively, from launch to 24 February 2023, a total of 576 primary dose cases of GBS meeting at least Brighton Collaboration Level 4 of diagnostic certainty have been received from postmarketing experience. This represents a reporting rate of 10.84 spontaneous cases per million primary doses administered. The outcome was fatal in 14 out of these 576 cases.

Cumulatively, from launch to 24 February 2023, a total of 15 booster dose cases (8 homologous and 7 heterologous) of GBS meeting at least Brighton Collaboration Level 4 of diagnostic certainty have been received from postmarketing experience. This represents a reporting rate of 4.47 spontaneous cases per million booster doses administered. The outcome was fatal in 2 out of these 15 cases.

A recent large cohort study using data from the US Vaccine Safety Datalink (VSD) showed an unadjusted incidence rate for GBS of 32.4 (95% CI: 14.8-61.5) per 100,000 person-years (1 to 21 days following Ad26.COV2.S administration), which was significantly higher than the background rate. The adjusted risk ratio was 6.03 (95% CI: 0.79-147.79) (1 to 21 days vs 22 to 42 days following Ad26.COV2.S administration). Nearly all patients presenting GBS after Ad.26.COV2.S administration, identified in this surveillance, had facial weakness or paralysis, in addition to weakness and decreased reflexes in the limbs.

Medicinal product no longer authorised

Risk Factors and Risk Groups:

There are no known risk factors for the development of GBS following Ad26.COV2.S vaccination. Based mainly on data from North America and Europe, it has been shown in literature that the GBS incidence increased by 20% for every 10-year increase in age; GBS is usually more frequent in males, with the highest incidence between 50 to 70 years of age (Van Doorn 2020).

Preventability:

The SmPC Section 4.4 states that healthcare professionals should be alert of GBS signs and symptoms to ensure correct diagnosis, in order to initiate adequate supportive care and treatment and to rule out other causes.

Impact on the Risk-Benefit Balance of the Product:

Although GBS is a serious event that has been reported following vaccination with Ad26.COV2.S, it has been reported at a very low incidence and adequate risk minimization via the SmPC is considered sufficient to manage this risk. Therefore, the impact on the risk-benefit balance for the vaccine is considered to be low.

Public Health Impact:

GBS associated with vaccines typically occurs at a low incidence, resulting in a low public health impact. Although the potential clinical consequences of GBS are serious, this is a risk known to healthcare professionals, with negligible public health impact.

Annex 1 MedDRA Term:

SMQ (narrow) Guillain-Barré syndrome

Medicinal product no longer authorised

Important Identified Risk: Thrombocytopenia, including immune thrombocytopenia

Potential Mechanisms:

The mechanistic evidence for vaccine-derived thrombocytopenia is not very well understood. It is suspected to have a strong immune component such as immunostimulation causing alterations in cytokines that abrogate platelet production from megakaryocyte precursors and antigenic mimicry between virus and platelet antigens, giving rise to cross-reactive anti-platelet antibodies (anti-IIb/IIIa) and/or activation of cytotoxic T cells that decrease platelet survival (Wise 2007). Similar to other autoimmune disorders, molecular mimicry with bacterial or viral proteins might be one reason for the pathogenesis of immune thrombocytopenia (ITP) (Marini 2019).

The SARS-CoV-2 S protein has been associated with endothelial inflammation, leukocyte adhesion, release of PF4, hypercoagulation, and thrombosis (Robles 2022, Lei 2021, Perico 2022, Zhang 2020, Grobbelaar 2021, Zheng 2021), and is hypothesized to be related to adverse effects after COVID-19 vaccination (Trougakos 2022).

Recent mechanistic studies (nonclinical studies, and studies using clinical trial samples) conducted by the MAH to study the pathogenesis of (vaccine-induced) TTS with potential relevance to thrombocytopenia (including ITP), did not elucidate a clear mechanism of action for thrombocytopenia (including ITP) following Ad26.COV2.S administration.

Evidence Source(s) and Strength of Evidence:

Cases of ITP with very low platelet levels (<20,000 per µL) have been reported very rarely after vaccination with Ad26.COV2.S, usually within the first 4 weeks after receiving Ad26.COV2.S. This included cases with bleeding and cases with fatal outcome. Some of these cases occurred in individuals with a history of ITP.

Based on the observed imbalance in postmarketing events, ITP is an adverse drug reaction described in the SmPC.

Characterization of the Risk:

Clinical Trial Data

A table presenting the data for the 28-day post any dose period of the primary pooling is provided in this section. A table presenting data for the entire study follow-up period and by each post-dose period (including the follow-up period beyond 28 days of vaccination) of the primary pooling is provided in Annex 7.8.1. A table presenting data for the cross-dose level pooling is provided in Annex 7.8.2.

Medicinal product no longer authorised

Frequency, Seriousness, Outcomes, and Severity of Thrombocytopenia, Including Immune Thrombocytopenia in Primary Pooling; Full Analysis Set

	Double Blind Ad26.COV2.S	Double Blind Placebo
Post Any Dose Period		
Number of participants exposed	38538	37809
PY follow-up	3608	3490
n (%)	3 (<0.1%)	2 (<0.1%)
95% CI (%)	(0.00%;0.02%)	(0.00%;0.02%)
Incidence per PY follow-up	0.08%	0.06%
95% CI (%) for Incidence rate	(0.021%;0.216%)	(0.010%;0.177%)
Number of Thrombocytopenia, including immune thrombocytopenia Aes	3	2
Seriousness		
Was serious	0	1 (50.0%)
Outcomes		
Resulted in Death	0	0
Recovered with sequelae	0	0
Recovered without sequelae	2 (66.7%)	0
Did not recover (Persisted)	1 (33.3%)	1 (50.0%)
Recovering/Resolving	0	1 (50.0%)
Unknown	0	0
Severity		
Grade 1	1 (33.3%)	1 (50.0%)
Grade 2	1 (33.3%)	0
Grade 3	1 (33.3%)	1 (50.0%)
Grade 4	0	0
Relatedness		
Related	0	0
Not related	3 (100.0%)	2 (100.0%)

Adverse events are coded using MedDRA version 24.1
This table includes 5 trials ie COV1001, COV1002, COV2001, COV3001 and COV3009. Only the primary dose ie $5x10^{10}$ vp dose level, regardless volume, is considered.
Person*Years (PY) follow-up for Entire Double-blind Phase is defined as time participant was followed up from first randomized dose datetime till the double-blind end datetime defined as earliest of unblinding datetime, open label vaccination datetime, other COVID-19 vaccination datetime or EoS* datetime (whichever comes first).
*EoS = earliest of End of study date, early discontinuation date, cut-off date.
Post-Dose 1, 2 etc. is the period from the day of the vaccination 1, 2, etc. (Day 1) until Day 29 ie Day 1+28 or earlier because of discontinuation, unblinding, open label vaccination, taking another COVID-19 vaccine or cut-off. Post any dose is combination of all post-doses (post dose 1, 2, etc.).
n (%): number (percentage) of participants with 1 or more events. 95% CI= 95% Confidence Interval.
The 95% CI for the percentage of participants is the Clopper-Pearson 95% CI; the 95% CI for the incidence rate is the exact Poisson 95% CI.
If participants received Ad26.COV2.S before the placebo vaccination (e.g. randomized sequence Ad26.COV2.S-Placebo), then the placebo vaccination is not reported. For these participants, time to onset of adverse events of interests (AEI) is linked to active dose received by the participant.
Note: Data cutoff for COV1001 of 21JUL2021, COV1002 of 02AUG2021, COV2001 of 11MAY2021, COV3001 of 09JUL2021, COV3009 of 25JUN2021

Modified from [TSFAE1P8.RTF] [PROD/VAC31518/Z_RMP/DBR_ADHOC_JAN22/RE_ADHOC_JAN22_BLA/TSFAE1P8.SAS] 20JUL2022, 00:48

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In the primary pooling, within 28 days post any dose, 3 events of thrombocytopenia were reported in 3 (<0.1%) participants following Ad26.COV2.S administration; no events of ITP, as reported by the investigator, were reported in the Ad26.COV2.S group. None of the events of thrombocytopenia were assessed as related to the study vaccine.

Events of thrombocytopenia were observed at an increased frequency in the Ad26.COV2.S group in the cross-dose level pooling analysis within 28 days post any dose when compared to the primary pooling analysis. Within 28 days post any dose, 285 events of thrombocytopenia were reported in 277 (0.4%) participants in the Ad26.COV2.S group; no events of ITP, as reported by the investigator, were reported in the Ad26.COV2.s group. Thirty-two (11.2%) of the thrombocytopenia events were considered related to the study vaccine.

The observed increased frequency in events of thrombocytopenia in the Ad26.COV2.S group in the cross-dose level pooling (0.4%) compared to the primary pooling (<0.1%), is primarily driven by the implementation of protocol amendments that defined the follow-up of AESIs (thrombocytopenia and/or thrombosis). After the implementation of these amendments, a prospective pre-vaccination blood sample collection for platelet count assessment was required at the time of Ad26.COV2.S (or blinded) vaccine administration. As a result, an increased rate of thrombocytopenia was observed as compared to the double-blind phase of trials where this requirement was not in place. The majority of these were thrombocytopenias on the day of vaccination, suggesting some events may have had an onset pre-vaccination.

Between the cut-off date of the cross-dose level pooling analysis (24 February 2022) and of the extended cross-dose level pooling analysis (03 July 2023), thrombocytopenia was reported in 152 additional participants within 28 days post any dose in the Ad26.COV2.S group; no events of ITP, as reported by the investigator, were reported in the Ad26.COV2.S group. The frequency of thrombocytopenia in the Ad26.COV2.S group further increased in the extended cross-dose level pooling (0.7% of participants) compared to the cross-dose level pooling (0.4% of participants). Similar to the cross-dose level pooling, the observed increased frequency in events of thrombocytopenia is primarily driven by the requirement of pre-vaccination blood sampling for platelet count assessment at the time of vaccine administration.

No new information to further characterize this safety concern was identified from clinical trials evaluating an Ad26.COV2.S booster dose as compared with the first dose of Ad26.COV2.S.

COV3012 (Sisonke-1) and COV3021 (Sisonke Boost)

A total of 3 cases of thrombocytopenia were received from study COV3012. Two cases met the diagnostic criteria for ITP, of which 1 was fatal.

Up to 24 February 2023, no cases of thrombocytopenia were reported in study COV3021.

Postmarketing Experience

Cumulatively, from launch to 24 February 2023, a total of 829 primary dose cases of thrombocytopenia were received from postmarketing experience, of which 81 were fatal. This represents a reporting rate of 15.17 spontaneous cases per million primary doses administered. Of these 829 cases, 414 met the diagnostic criteria for ITP, of which 9 were fatal.

Cumulatively, from launch to 24 February 2023, a total of 21 booster dose cases (7 homologous and 14 heterologous) of thrombocytopenia were received from postmarketing experience, of which 1 was fatal. This represents a reporting rate of 4.79 spontaneous cases per million booster doses

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administered. Of these 21 cases, 11 (5 homologous, 5 heterologous, and 1 unknown primary dose followed by Ad26.COV2.S booster) met the diagnostic criteria for ITP, of which none were fatal.

Risk Factors and Risk Groups:

Limited data from postmarketing experience with Ad26.COV2.S, including literature, suggest that individuals with chronic or recurrent ITP may be at increased risk of developing ITP following vaccination with Ad26.COV2.S.

Preventability:

The SmPC Section 4.4 provides guidance to healthcare professionals to be alert to signs and symptoms of thrombocytopenia and includes a caution for bleeding following IM injection in individuals diagnosed with thrombocytopenia or any coagulation disorder.

In addition, Section 4.4 states that if an individual has a history of ITP, the risks of developing low platelet levels should be considered before vaccination with JCOVDEN, and platelet monitoring is recommended following vaccination with JCOVDEN.

Impact on the Risk-Benefit Balance of the Product:

ITP is a potentially life-threatening event, and if not recognized or managed appropriately, may result in persistent or significant disability or incapacity, and hence requires immediate medical intervention. ITP has been reported very rarely following vaccination with Ad26.COV2.S and adequate risk minimization via the SmPC is considered sufficient to manage this risk. Based on current clinical trial and postmarketing data and the information in the SmPC, the risk-benefit balance for the vaccine is considered to remain favorable for the indicated target populations.

Public Health Impact:

Based on the currently available information on the known frequency, clinical characteristics, and outcome of ITP events reported after Ad26.COV2.S vaccination, the public health impact is expected to be low.

Annex 1 MedDRA Term:

PT Immune thrombocytopenia

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Important Identified Risk: Venous thromboembolism

Potential Mechanisms:

A potential mechanism for the occurrence of VTE includes a hypercoagulable state due to an increased pro-inflammatory response to vaccination. Activation of endothelial cells, platelets, and leukocytes with subsequent formation of microparticles can trigger the coagulation system through the induction of tissue factor (Branchford 2018). An underlying mechanism for VTE without thrombocytopenia has not been confirmed. Natural infection with SARS-CoV-2 has shown to be associated with hypercoagulability, pulmonary intravascular coagulation, microangiopathy, and VTE or arterial thrombosis (Ribes 2020).

The SARS-CoV-2 S protein has been associated with endothelial inflammation, leukocyte adhesion, release of PF4, hypercoagulation, and thrombosis (Robles 2022, Lei 2021, Perico 2022, Zhang 2020, Grobbelaar 2021, Zheng 2021), and is hypothesized to be related to adverse effects after COVID-19 vaccination (Trougakos 2022).

Recent mechanistic studies (nonclinical studies, and studies using clinical trial samples) conducted by the MAH to study the pathogenesis of (vaccine-induced) TTS with potential relevance to VTE, did not elucidate a clear mechanism of action for VTE following Ad26.COV2.S administration. However, in the context of the MAH's mechanistic work on TTS, the hypothesis was tested if TTS and other thrombotic events could have a common mechanism with TTS being the most severe manifestation. Obtained data suggest that a common mechanism is unlikely.

Evidence Source(s) and Strength of Evidence:

VTE has been observed rarely following vaccination with Ad26.COV2.S in clinical trials and in the postmarketing setting. While a higher proportion of cases of VTE was observed within the Ad26.COV2.S group versus the Placebo group in trial COV3001, there was no increase in VTE events among individuals who received Ad26.COV2.S in trial COV3009.

VTE is an adverse drug reaction described in the SmPC.

Characterization of the Risk:

Clinical Trial Data

A table presenting the data for the 28-day post any dose period of the primary pooling is provided in this section. A table presenting data for the entire study follow-up period and by each post-dose period (including the follow-up period beyond 28 days of vaccination) of the primary pooling is provided in Annex 7.8.1. A table presenting data for the cross-dose level pooling is provided in Annex 7.8.2.

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Frequency, Seriousness, Outcomes, and Severity of Venous Thromboembolism in Primary Pooling; Full Analysis Set

	Double Blind Ad26.COV2.S	Double Blind Placebo
Post Any Dose Period		
Number of participants exposed	38538	37809
PY follow-up	3608	3490
n (%)	10 (<0.1%)	7 (<0.1%)
95% CI (%)	(0.01%;0.05%)	(0.01%;0.04%)
Incidence per PY follow-up	0.28%	0.20%
95% CI (%) for Incidence rate	(0.139%;0.486%)	(0.086%;0.388%)
Number of Venous thromboembolism AEs	10	7
Seriousness		
Was serious	4 (40.0%)	3 (42.9%)
Outcomes		
Resulted in Death	0	0
Recovered with sequelae	0	0
Recovered without sequelae	9 (90.0%)	3 (42.9%)
Did not recover (Persisted)	1 (10.0%)	2 (28.6%)
Recovering/Resolving	0	2 (28.6%)
Unknown	0	0
Severity		
Grade 1	0	1 (14.3%)
Grade 2	6 (60.0%)	2 (28.6%)
Grade 3	0	2 (28.6%)
Grade 4	4 (40.0%)	2 (28.6%)
Relatedness		
Related	3 (30.0%)	0
Not related	7 (70.0%)	7 (100.0%)

Adverse events are coded using MedDRA version 24.1
This table includes 5 trials ie COV1001, COV1002, COV2001, COV3001 and COV3009. Only the primary dose ie $5x10^{10}$ vp dose level, regardless volume, is considered.
Person*Years (PY) follow-up for Entire Double-blind Phase is defined as time participant was followed up from first randomized dose datetime till the double-blind end datetime defined as earliest of unblinding datetime, open label vaccination datetime, other COVID-19 vaccination datetime or EoS* datetime (whichever comes first).
*EoS = earliest of End of study date, early discontinuation date, cut-off date.
Post-Dose 1, 2 etc. is the period from the day of the vaccination 1, 2, etc. (Day 1) until Day 29 ie Day 1+28 or earlier because of discontinuation, unblinding, open label vaccination, taking another COVID-19 vaccine or cut-off. Post any dose is combination of all post-doses (post dose 1, 2, etc.).
n (%): number (percentage) of participants with 1 or more events. 95% CI= 95% Confidence Interval.
The 95% CI for the percentage of participants is the Clopper-Pearson 95% CI; the 95% CI for the incidence rate is the exact Poisson 95% CI.
If participants received Ad26.COV2.S before the placebo vaccination (e.g. randomized sequence Ad26.COV2.S-Placebo), then the placebo vaccination is not reported. For these participants, time to onset of adverse events of interests (AEI) is linked to active dose received by the participant.
Note: Data cutoff for COV1001 of 21JUL2021, COV1002 of 02AUG2021, COV2001 of 11MAY2021, COV3001 of 09JUL2021, COV3009 of 25JUN2021

Modified from [TSFAE1P4.RTF] [PROD/VAC31518/Z_RMP/DBR_ADHOC_JAN22/RE_ADHOC_JAN22_BLA/TSFAE1P4.SAS] 20JUL2022, 00:48

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In the primary pooling, within 28 days post any dose, 10 (<0.1%) participants reported each 1 event of VTE following Ad26.COV2.S administration. Of these 10 VTE events, 4 were reported as DVT and 3 were reported as PE. The majority of these VTE events had an onset within 28 days post-dose 1 (9 events) and 3 events were considered related to the study vaccine. The majority of VTE events were reported more than 28 days post-vaccination (any dose). Minor numerical imbalances between the Ad26.COV2.S group and the placebo group were observed beyond 28 days post any dose. However, data should be interpreted with caution as some participants had confounding risk factors for VTE, which may contribute to the observed risk imbalance between both groups.

Similar incidences were observed in the cross-dose level pooling analysis and in the extended cross-dose level pooling analysis within 28 days post any dose. The majority of events in both groups had an onset after 28 days post-vaccination. For the entire follow-up period, more events were observed in the Ad26.COV2.S group.

No new information to further characterize this safety concern was identified from clinical trials evaluating an Ad26.COV2.S booster dose as compared with the first dose of Ad26.COV2.S.

COV3012 (Sisonke-1) and COV3021 (Sisonke Boost)

A total of 28 cases of VTE were identified during study COV3012. Of these, 9 reported DVT, 19 reported PE, and 2 reported CVST. Two cases (both PE) had a fatal outcome.

Up to 24 February 2023, a total of 3 cases of VTE were identified during study COV3021. Of these, 2 reported PE and 1 reported portal vein thrombosis. None of them were fatal.

Postmarketing Experience

Cumulatively, from launch to 24 February 2023, a total of 2,195 primary dose cases of venous embolic and thrombotic events have been received from postmarketing experience, of which 159 cases had a fatal outcome. This represents a reporting rate of 40.91 spontaneous cases per million primary doses administered. Of these, 799 reported DVT, 972 reported PE, and 179 reported CVST.

Cumulatively, from launch to 24 February 2023, a total of 70 booster dose cases (43 homologous and 27 heterologous) of venous embolic and thrombotic events have been received from postmarketing experience, of which 5 cases had a fatal outcome. This represents a reporting rate of 21.07 spontaneous cases per million booster doses administered. Of these, 31 reported DVT, 22 reported PE, and 4 reported CVST.

Risk Factors and Risk Groups:

In trials COV3001 and COV3009, underlying risk factors have been identified in participants with VTE such as COVID-19, male gender, old age (>65 years), long-haul travel, thrombophilia, obesity, active malignancy, trauma, previous venous thrombosis, hypertension, and COPD.

Medicinal product no longer authorised

Preventability:

The SmPC Section 4.4 provides guidance to healthcare professionals to be alert to signs and symptoms of thromboembolism and advises to take the occurrence of VTE into consideration for individuals at increased risk for VTE.

Impact on the Risk-Benefit Balance of the Product:

VTE is a potentially life-threatening event, and if not recognized or managed appropriately, may result in persistent or significant disability or incapacity, and hence requires immediate medical intervention. Adequate risk minimization via the SmPC is considered sufficient to manage this risk. Based on current information, the overall risk benefit balance for JCOVDEN is considered to remain positive for the indicated target populations.

Public Health Impact:

Based on the currently available information on the known frequency, clinical characteristics, and outcome of VTE events reported after Ad26.COV2.S vaccination, the public health impact is expected to be low.

Annex 1 MedDRA Term:

SMQ Embolic and thrombotic events, venous

Medicinal product no longer authorised

Important Identified Risk: Myocarditis and pericarditis

Potential Mechanisms:

Infectious diseases account for the majority of cases of myocarditis or pericarditis in previously healthy patients, mainly due to either a direct viral infection or post-viral immune-mediated reaction and myocardial inflammation (Friedrich 2009) and is more frequent in young males. Also viral infection with SARS-CoV-2 can result in acute myocarditis, yet COVID-19 vaccination (including mRNA vaccines and Ad26.COV2.S) was associated with decreased risk of myocarditis, myocardial infarction, and ischemic stroke after COVID-19 (Jiang 2023, Kim 2022, Patone 2022).

The mechanism of action for vaccine-induced myopericarditis remains to be elucidated. Given the increased incidence among males, differences in hormone signaling might be involved in the pathophysiology (Heymans 2022). It has been proposed that vaccines triggering an intense immune response could be associated with a higher risk of myocarditis (Karlstad 2022). Also, a possible association of circulating S protein with the occurrence of myocarditis has been described (Yonker 2023). Molecular mimicry between the S protein of SARS-CoV-2 and cardiac self-antigens is another possible mechanism. However, only limited experimental evidence supporting this hypothesis exists (Vojdani 2020, Vojdani 2021). The delivery of the Spike gene by different vaccine delivery platforms may result in a different expression pattern of the S protein, thus potentially affecting parameters like levels, kinetics, location and/or post-translational modifications. There are also differences in the biosynthesis, structural features, and presentation of the S protein in current COVID-19 vaccines (Heinz 2021) that may be additionally related to myo/pericarditis incidence.

Evidence Source(s) and Strength of Evidence:

Myocarditis and/or pericarditis have been reported as rare events following vaccination against smallpox, hepatitis B, tetanus, human papillomavirus, and viral influenza and have been documented for COVID-19 vaccines (Mei 2018, Su 2021). A systemic review and meta-analysis revealed higher incidence of myopericarditis following smallpox vaccination but no significant difference after influenza vaccinations compared to COVID-19 vaccination (Ling 2022).

Among COVID-19 vaccines, myocarditis and/or pericarditis has been observed with mRNA vaccines (Husby 2021, Karlstad 2022, Ling 2022, Patone 2022) with an incidence significantly higher in males versus females, in people younger than 30 years, and after a second dose (compared to first or third dose). Additionally, a recombinant adjuvanted protein-based COVID-19 vaccine has been associated with a disproportional myopericarditis induction (Macías Saint-Gerons 2023).

Events of myocarditis and pericarditis have been observed very rarely following vaccination with Ad26.COV2.S both in clinical trials and in the postmarketing setting. Real-world evidence data of US claims data sources showed a high level of certainty of an increased risk of myocarditis and pericarditis for males aged 18 to 39 years within 28 days of vaccination with Ad26.COV2.S.

Myocarditis and pericarditis are adverse drug reactions described in the SmPC.

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Characterization of the Risk:

Clinical Trial Data

A table presenting the data for the 28-day post any dose period of the primary pooling is provided in this section. A table presenting data for the entire study follow-up period and by each post-dose period (including the follow-up period beyond 28 days of vaccination) of the primary pooling is provided in Annex 7.8.1. A table presenting data for the cross-dose level pooling is provided in Annex 7.8.2.

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Frequency, Seriousness, Outcomes, and Severity of Myocarditis and Pericarditis in Primary Pooling; Full Analysis Set

	Double Blind Ad26.COV2.S	Double Blind Placebo
Post Any Dose Period		
Number of participants exposed	38538	37809
PY follow-up	3608	3490
n (%)	2 (<0.1%)	0
95% CI (%)	(0.00%;0.02%)	(0.00%;0.00%)
Incidence per PY follow-up	0.06%	.%
95% CI (%) for Incidence rate	(0.009%;0.171%)	-
Number of Myocarditis and pericarditis AEs	2	-
Seriousness		
Was serious	2 (100.0%)	-
Outcomes		
Resulted in Death	0	-
Recovered with sequelae	0	-
Recovered without sequelae	1 (50.0%)	-
Did not recover (Persisted)	0	-
Recovering/Resolving	1 (50.0%)	-
Unknown	0	-
Severity		
Grade 1	0	-
Grade 2	0	-
Grade 3	0	-
Grade 4	2 (100.0%)	-
Relatedness		
Related	2 (100.0%)	-
Not related	0	-

Adverse events are coded using MedDRA version 24.1
This table includes 5 trials ie COV1001, COV1002, COV2001, COV3001 and COV3009. Only the primary dose ie $5x10^{10}$ vp dose level, regardless volume, is considered.
Person*Years (PY) follow-up for Entire Double-blind Phase is defined as time participant was followed up from first randomized dose datetime till the double-blind end datetime defined as earliest of unblinding datetime, open label vaccination datetime, other COVID-19 vaccination datetime or EoS* datetime (whichever comes first).
*EoS = earliest of End of study date, early discontinuation date, cut-off date.
Post-Dose 1, 2 etc. is the period from the day of the vaccination 1, 2, etc. (Day 1) until Day 29 ie Day 1+28 or earlier because of discontinuation, unblinding, open label vaccination, taking another COVID-19 vaccine or cut-off. Post any dose is combination of all post-doses (post dose 1, 2, etc.).
n (%): number (percentage) of participants with 1 or more events. 95% CI= 95% Confidence Interval.
The 95% CI for the percentage of participants is the Clopper-Pearson 95% CI; the 95% CI for the incidence rate is the exact Poisson 95% CI.
If participants received Ad26.COV2.S before the placebo vaccination (e.g. randomized sequence Ad26.COV2.S-Placebo), then the placebo vaccination is not reported. For these participants, time to onset of adverse events of interests (AEI) is linked to active dose received by the participant.
Note: Data cutoff for COV1001 of 21JUL2021, COV1002 of 02AUG2021, COV2001 of 11MAY2021, COV3001 of 09JUL2021, COV3009 of 25JUN2021

Modified from [TSFAE1P7.RTF] [PROD/VAC31518/Z_RMP/DBR_ADHOC_JAN22/RE_ADHOC_JAN22_BLA/TSFAE1P7.SAS]
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In the primary pooling, within 28 days post any dose, 2 events of myocarditis/pericarditis were reported in 2 (<0.1%) participants following Ad26.COV2.S administration. Both events were events of pericarditis, reported post-dose 1, and considered to be related to the study vaccine. One event was reported in a PP -year-old male and 1 event was reported in a PP -year-old female. No cases of either myocarditis or pericarditis were reported in participants younger than 40 years.

There were no new events observed in the cross-dose level pooling analysis within 28 days post any dose following Ad26.COV2.S administration.

Between the cut-off date of the cross-dose level pooling analysis (24 February 2022) and of the extended cross-dose level pooling analysis (03 July 2023), no additional events of myocarditis or pericarditis were reported within 28 days post any dose in the Ad26.COV2.S group.

No new information to further characterize this safety concern was identified from clinical trials evaluating an Ad26.COV2.S booster dose as compared with the first dose of Ad26.COV2.S.

COV3012 (Sisonke-1) and COV3021 (Sisonke Boost)

Two myocarditis/pericarditis cases have been reported in study COV3012. Of these 2 cases, 1 myocarditis and 1 pericarditis event was reported. Both events were reported as not recovered. There were no fatal events of myocarditis or pericarditis. Of the 2 cases reported, both concerned females and the ages were within the age category of 36 to 50 years.

Up to 24 February 2023, 1 myocarditis/pericarditis case was reported in study COV3021. This case reported 1 non-fatal pericarditis event. The event was resolved. This case concerned a female with the age within the age category of 18 to 35 years.

Postmarketing Experience

Cumulatively, from launch to 24 February 2023, a total of 436 myocarditis/pericarditis primary dose cases have been received from postmarketing experience, of which 197 cases reported myocarditis and 177 cases reported pericarditis (4 of these cases reported both myocarditis and pericarditis [Brighton Collaboration Level 1-3]) within the risk window of 42 days. Excluding solicited cases, this represents a spontaneous reporting rate of 4.32 cases per million primary doses administered for myocarditis and 4.15 cases per million primary doses administered for pericarditis (limited to Brighton Collaboration Level 1-4). Of the 436 cases, 22 had a fatal outcome. In terms of gender distribution, 278 cases were reported as male, 128 were reported as female, and 30 cases did not have gender reported. The age/gender group with the highest number of cases were males aged 18 to 29 years (n=102). In this group, almost half of the patients (n=49) developed myocarditis/pericarditis within 7 days following vaccination.

Cumulatively, from launch to 24 February 2023, a total of 33 myocarditis/pericarditis booster dose cases (20 homologous and 13 heterologous) have been received from postmarketing experience. Of these 33 cases, 8 cases after heterologous administration were excluded from further assessment since the events of interest did not occur after Ad26.COV2.S vaccination. Of the remaining 25 cases, 18 cases reported myocarditis and 9 cases reported pericarditis (2 of these cases reported

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both myocarditis and pericarditis), none had a fatal outcome. Excluding solicited cases, this represents a spontaneous reporting rate of 4.47 cases per million booster doses administered for myocarditis and 2.55 cases per million booster doses administered for pericarditis (limited to Brighton Collaboration Level 1-4). In terms of gender distribution, 17 cases were reported as male, 4 were reported as female, and 4 cases did not have gender reported.

In a real-world evidence rapid cycle analysis of data from 3 US claims datasets (cut-off date: February 2023; including age and gender stratified analysis), there was a high level of certainty of an increased risk of composite myocarditis-pericarditis following the first Ad26.COV2.S dose for males aged 18 to 39 years in 1 to 14 days (meta-analysis relative risk estimates = 2.3-5.4) and 1 to 28 days (meta-analysis relative risk estimates = 1.1-3.3); of myocarditis for males aged 18 to 39 years in 1 to 14 days (meta-analysis relative risk estimates = 2.8-7.0); and of pericarditis for males aged 18 to 39 years in 1 to 14 days (meta-analysis relative risk estimates = 1.7-5.0) and 1 to 28 days (meta-analysis relative risk estimates = 1.3-5.2). There was a lack of evidence of increased risks for other sex-age groups; however, data are insufficient to confidently exclude the possibility of small effects in these groups.

Risk Factors and Risk Groups:

Myocarditis and pericarditis have been reported in association with SARS-CoV-2 infection. Historically, myocarditis and/or pericarditis have been reported as a rare event following vaccination against smallpox, hepatitis B and viral influenza (Su 2021). Myocarditis and pericarditis have also been reported with other COVID-19 vaccines (including mRNA-based COVID-19 vaccines and a recombinant adjuvanted protein-based COVID-19 vaccine). Young males appear to be at highest risk, predominantly after receiving the second dose of COVID-19 vaccination. The disease course is self-limiting in a vast majority of cases: 95% of patients show a rapid resolution of symptoms and normalization of cardiac biomarkers, electro- and echocardiographic findings within days (Klamer 2022).

Preventability:

The SmPC Section 4.4 states that healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis and should consult guidance and/or specialists to diagnose and treat these conditions. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis.

Impact on the Risk-Benefit Balance of the Product:

Myocarditis and/or pericarditis has been reported very rarely in clinical trials and the post-marketing setting following vaccination with Ad26.COV2.S. Based on current clinical trial and postmarketing data and the information in the SmPC, the identified risk of myocarditis and pericarditis does not change the existing established risk-benefit balance for Ad26.COV2.S.

Medicinal product no longer authorised

Public Health Impact:

The occurrence of myocarditis and pericarditis is very rare following vaccination with Ad26.COV2.S. Epidemiologic analysis of real-world data sources such as electronic medical records and healthcare claims, showed that the risk of myocarditis and pericarditis following COVID-19 vaccination is lower than following natural SARS-CoV-2 infection (Patone 2022). Therefore, the public health impact is currently considered to be low.

Annex 1 MedDRA Term:

HLT Noninfectious myocarditis and HLT Noninfectious pericarditis

Medicinal product no longer authorised

Important Potential Risk: Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)

Potential Mechanisms:

Potential mechanisms of enhanced disease may include both T cell-mediated immune responses (a Th2-skewed immune response favoring immunopathology) and antibody-mediated immune responses (antibody responses with insufficient neutralizing activity leading to formation of immune complexes and activation of complement or allowing for Fc-mediated increase in viral entry to cells) (Graham 2020).

Evidence Source(s) and Strength of Evidence:

Based on past experiences in the development of vaccines against RSV, Dengue virus, SARS-CoV, and MERS-CoV, there is a theoretical risk for VAED, including VAERD, for SARS-CoV-2 vaccines (Chin 1969, Fulginiti 1969, Kapikian 1969, Kim 1969, Su 2020, Agrawal 2016, Bolles 2011, Deming 2006, Honda-okubo 2015, Houser 2017). As COVID-19 clinical manifestations are not limited to respiratory symptoms, not only VAERD, but also the broader term VAED is being taken into account.

VAED/VAERD has not been described in association with JCOVDEN and has not been confirmed from any other late phase clinical trial of other COVID-19 vaccines.

Studies in Ad26.COV2.S-immunized Syrian hamsters and NHP conducted by the MAH have shown the absence of enhanced lung pathology, absence of increased viral load, and absence of enhanced clinical signs of disease compared with controls after SARS-CoV-2 inoculation, even under conditions of suboptimal immunity allowing breakthrough infection (van der Lubbe 2021, He 2021). Together with induction of neutralizing antibodies and a Th1-skewed immune response after Ad26.COV2.S dosing, these data suggest that the theoretical risk of VAERD and VAED for Ad26.COV2.S is low. These data were corroborated by the findings in clinical trials which have shown no indication of the presence of VAED, including VAERD.

Characterization of the Risk:

Clinical Trial Data

No events of VAED or VAERD were reported in either the primary pooling (Annex 7.8.1), the cross-dose level pooling (Annex 7.8.2), or the extended cross-dose level pooling.

In the primary pooling, case splits for COVID-19 associated SAEs and deaths showed a lower incidence of severe COVID-19 in the Ad26.COV2.S versus the placebo group. Therefore, there was no evidence for VAED/VAERD.

No new information to further characterize this safety concern was identified from clinical trials evaluating an Ad26.COV2.S booster dose as compared with the first dose of Ad26.COV2.S.

Medicinal product no longer authorised

COV3012 (Sisonke-1) and COV3021 (Sisonke Boost)

Up to 24 February 2023, no VAED/VAERD cases were retrieved from studies COV3012 and COV3021.

Postmarketing Experience

Up to 24 February 2023, 1 primary dose case reported by a healthcare professional was reported as VAED following Ad26.COV2.S administration. However, no clinical details were available for this individual, nor information on its SARS-CoV.2 status, and therefore this case is not assessable.

Risk Factors and Risk Groups:

It is postulated that the potential risk may be increased in individuals producing lower neutralizing antibody titers or in those demonstrating waning immunity (Graham 2020, Munoz 2021).

Preventability:

An effective vaccine against COVID-19 that produces strong humoral and cellular immune responses with a clear Th1 bias is expected to mitigate the risk of VAED, including VAERD (Lambert 2020, Graham 2020). Such an immune profile is elicited by Ad26.COV2.S in clinical trials and nonclinical studies.

Impact on the Risk-Benefit Balance of the Product:

A confirmed risk of VAED, including VAERD could significantly impact the risk-benefit balance of Ad26.COV2.S. The risk will be further characterized through follow-up of study participants in Phase 3 trials for the occurrence of severe COVID-19. Within post-authorisation effectiveness studies, the incidence of severe COVID-19 in vaccinated versus non-vaccinated populations will be used as an indirect measure of VAED, including VAERD.

Public Health Impact:

The potential risk of VAED, including VAERD could have a public health impact if large populations of individuals are affected.

Annex 1 MedDRA Term:

PT Vaccine associated enhanced disease

Medicinal product no longer authorised

SVII.3.2. Presentation of the Missing Information

Missing information: Use in pregnancy and while breastfeeding

Evidence source:

There is limited experience with the use of Ad26.COV2.S in pregnant women.

Animal data from the EF-PPND toxicity study with Ad26.COV2.S indicate no adverse effect of Ad26.COV2.S on reproductive performance, fertility, ovarian and uterine examinations, or parturition. In addition, there was no adverse effect of vaccination on fetal body weights, external, visceral and skeletal evaluations, or on postnatal development of the offspring.

Pregnancy at baseline was not an exclusion criterion in trial COV2008, and trial COV2004 is a trial in pregnant women. Up to the cut-off date of 24 February 2022, 23 women who were pregnant at baseline received at least one dose of Ad26.COV2.S (cross-dose level pooling; all dose levels). Of the pregnancies reported in trial COV2004 (n=22), 9 were still ongoing, 11 had a normal outcome, and 2 had an outcome of preterm neonate (1 without complications and 1 with complications). The pregnancy reported in trial COV2008 had an outcome of premature without complications. No safety concerns have been identified in this population.

Any case of study vaccine exposure during pregnancy was included in the Company's Global Safety Database when reported during the course of the trials. As of the cut-off date of 24 February 2023, 131 unique pregnancies were retrieved from Company-sponsored clinical trials post-baseline; 111 involved maternal exposure and 20 were partner pregnancies; all following Ad26.COV2.S administration. Overall, reported outcomes were live birth (n=53), spontaneous abortion (n=14, including 1 case of missed abortion due to Trisomy 21), elective abortion (n=4, 2 due to congenital anomalies: skeletal dysplasia and unspecified anomaly), intrauterine death, live birth with congenital anomaly (congenital tracheomalacia and ventricular septal defect) (n=2 each), ectopic pregnancy (n=1), unknown (n=56). Of note, 1 participant reported a twin pregnancy during the trial (1 with an outcome of spontaneous abortion, 1 with an unknown outcome).

Up to the cut-off date of 24 February 2023, 731 unique cases reporting use in pregnancy were retrieved from postmarketing sources (including spontaneous and solicited primary and booster dose cases); 729 involved maternal exposure and 2 were partner pregnancies. Of these unique pregnancy cases, 233 cases reported 237 outcomes due to 4 twin pregnancies. One twin pregnancy resulted in a spontaneous abortion of one twin and a live birth without congenital anomaly of the other and are included in the following counts. The outcomes included live birth without congenital anomaly (n=146 [including 1 set of twins]), spontaneous abortion (n=64 [including 2 sets of twins]), live birth with congenital anomaly (n=16), ectopic pregnancy (n=5), blighted ovum (n=2), and 1 case each of still birth without congenital anomaly, still birth with congenital anomaly, maternal death, and intrauterine death. Of the 64 spontaneous abortion outcomes, there were 14 outcomes with exposure before conception, 26 outcomes with exposure during the first trimester of pregnancy, and for the remaining 24 outcomes timing of vaccine exposure was not reported.

Safety data with Ad26.COV2.S when administered within 3 months before pregnancy as well as during pregnancy have shown no safety concerns in the mother or child in over 500 reported pregnancies, with over 100 reported pregnancy outcomes.

Breastfeeding women were excluded from all clinical trials, except from the Phase 2 trial COV2008 and the Phase 3 trials COV3001, COV3003, and COV3009. Up to the cut-off date of 24 February 2022, 718 women who were breastfeeding at baseline have received at least one dose of Ad26.COV2.S (cross-dose level pooling; all dose levels). No safety concerns have been identified for breastfeeding women. However, safety data for their breastfed children is currently not available.

Up to 24 February 2023, there have been 137 unique cases (postmarketing spontaneous or non-interventional cases) of exposure to JCOVDEN via breastfeeding. No safety signals were identified.

Medicinal product no longer authorised

It is not known whether the components of Ad26.COV2.S or the antibodies induced by Ad26.COV2.S are excreted in human milk. Human data are not available to assess the impact of Ad26.COV2.S on milk production or its effects on the breastfed child.

Anticipated risk/consequence of the missing information:

Based on the nonreplicating nature of the vaccine and on nonclinical and limited clinical and postmarketing data available to date, the safety profile of Ad26.COV2.S when used in pregnant women is not expected to differ from that in the general population, with no specific safety concerns for pregnant women or fetuses to date. Therefore, as stated in the SmPC Section 4.6, the administration of JCOVDEN in pregnancy should only be considered when the potential benefits outweigh any potential risks to the mother and fetus.

A Phase 2 trial (COV2004) and a post-authorisation pregnancy exposure registry (COV4005) are ongoing to assess the safety and immunogenicity of Ad26.COV2.S in pregnant women and their offspring. The adequacy of the post-authorisation safety study COV4003 to address pregnancy outcomes is to be assessed.

No effects on the breastfed child are anticipated considering results from animal and human studies with Ad26-based vaccines, showing limited dissemination of this nonreplicating vector following IM injection. In the event that a small quantity of Ad26.COV2.S would be (transiently) excreted via the milk, it would not be considered a risk to the breastfed child, specifically with regard to infections, as Ad26.COV2.S is replication-incompetent and does not encode a complete SARS-CoV-2 virus.

A small subset of participants within trial COV2004 will be followed up during breastfeeding to assess the transfer of antibodies via breast milk. Breastfeeding women were also allowed to participate in trials COV2008, COV3001, COV3003, and COV3009 to characterize the safety profile of Ad26.COV2.S in this subpopulation.

Missing information: Use in immunocompromised patients

Evidence source:

Patients with stable and well-controlled medical condition including comorbidities associated with an increased risk of progression to severe COVID-19 (eg, stable/well-controlled HIV infection), or those receiving chronic low-dose (less than 20 mg of prednisone or equivalent) immunosuppressive therapy were included in trials COV2008, COV3001, and COV3009.

The efficacy of Ad26.COV2.S may be lower in immunosuppressed individuals.

The final analysis results of the double-blind phase in trial COV3001 showed that, overall, the vaccine was efficacious against molecularly confirmed moderate to severe/critical COVID-19 with onset at least 14 days and 28 days after vaccination across demographic and baseline characteristics subgroups. An exception was noted for HIV-positive participants (with a stable/well-controlled HIV infection) in which the VE was lower. Due to few COVID-19 cases in HIV-positive participants, this conclusion should be interpreted with caution. No clinically relevant difference in the reactogenicity profile could be observed in HIV-infected versus HIV-negative participants (COV3001 CSR Dec 2021).

In the FAS of trial COV3001, SAEs were reported in 8 (1.3%) out of 604 HIV-infected participants who received Ad26.COV2.S, of which none were considered to be related to the study vaccine by the investigator. The frequency of reported SAEs was similar in the Ad26.COV2.S and Placebo groups (COV3001 CSR Dec 2021).

Medicinal product no longer authorised

Based on the final analysis results of the double-blind phase in trial COV3009, no conclusion can currently be made about VE in HIV-infected participants due to the limited number of HIV-positive participants. In the FAS of trial COV3009, SAEs were reported in 3 (1.4%) out of 213 HIV-infected participants who received Ad26.COV2.S, of which none were considered to be related to the study vaccine by the investigator. The frequency of reported SAEs was similar in the Ad26.COV2.S and Placebo groups (COV3009 CSR Dec 2021).

Of the 65,490 participants in the cross-dose level pooling who received at least one dose of Ad26.COV2.S (all dose levels), 1,440 (2.2%) participants had a stable/well-controlled HIV infection. Participants with other immunodeficiencies were included at low numbers.

Anticipated risk/consequence of the missing information:

Given the fact that Ad26.COV2.S is a replication-incompetent vaccine, the safety profile of Ad26.COV2.S when used in immunocompromised individuals is not expected to differ from that in the general population. There were no specific safety concerns and no notable differences between HIV-infected and healthy participants with regard to reporting frequency or severity of AEs at any timepoint from the 2 pivotal trials.

Use in immunocompromised patients will be further characterized in the post-authorisation safety studies COV4003 and COV4001 and effectiveness study COV4004.

Missing information: Use in patients with autoimmune or inflammatory disorders

Evidence source:

There is limited information on the safety of Ad26.COV2.S in individuals with autoimmune or inflammatory disorders and a theoretical concern that the vaccine may exacerbate their underlying disease.

Participants with clinical conditions stable under non-immunomodulator treatment (eg, autoimmune thyroiditis, autoimmune inflammatory rheumatic disease such as rheumatoid arthritis) were eligible for enrollment in Phase 3 trials COV3001 and COV3009 at the discretion of the investigator. Of the 21,898 participants in the FAS of trial COV3001 who received Ad26.COV2.S ($5x10^{10}$ vp dose level), 552 participants had a medical history of at least 1 immune-mediated/autoimmune disorder at baseline. Of these 552 participants, 5 (0.9%) reported an exacerbation (flare-up) of their pre-existing autoimmune disorder during the double-blind phase of the trial. Of the 15,708 participants in the FAS of trial COV3009 who received at least 1 dose of Ad26.COV2.S ($5x10^{10}$ vp dose level), 458 participants had a medical history of at least 1 immune-mediated/autoimmune disorder at baseline. Of these 458 participants, 2 (0.4%) reported an exacerbation (flare-up) of their pre-existing autoimmune disorder, during the double-blind phase of the trial.

Population in need of further characterization:

Use in patients with autoimmune or inflammatory disorders will be further characterized in the post-authorisation safety studies COV4003 and COV4001.

Medicinal product no longer authorised

Missing information: Use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)

Evidence source:

Frail individuals, especially those with multiple comorbidities that may compromise their immune response, are at an increased risk for severe COVID-19. In addition, the safety profile in this subpopulation could vary from that seen in healthy adults. Increased age and comorbidities are the 2 major risk factors for frailty.

Of the 65,490 participants in the cross-dose level pooling who received at least one dose of Ad26.COV2.S (all dose levels), 25,737 (39.3%) participants had 1 or more comorbidities associated with an increased risk for severe COVID-19. Of these 25,737 participants, 11,102 (43.1%) were aged ≥60 years, 6,378 (24.8%) were ≥65 years, and 1,216 (4.7%) were aged ≥75 years.

There is limited information on the safety of Ad26.COV2.S in frail patients with comorbidities that may compromise their immune response.

Following a protocol amendment for trial COV3001 on 14 December 2020, calculation of a frailty index has been included to be applied to participants enrolled. Of the 19,577 participants in the Per Protocol set who received Ad26.COV2.S ($5x10^{10}$ vp dose level), 6 (<0.1%) were defined as frail and 2,147 (11.0%) were defined as pre-frail. Of the 6 frail participants, 5 (83.3%) were aged ≥60 years. Of the 2,147 pre-frail participants, 1,338 (62.3%) were aged ≥60 years (COV3001 CSR Dec 2021).

Population in need of further characterization:

Safety data will be further collected in individuals who are frail due to age or debilitating disease in the post-authorisation safety studies COV4003 and COV4001, and through routine pharmacovigilance.

Missing information: Long-term safety

Evidence source:

There are limited data available on the long-term safety of Ad26.COV2.S. Participants in trial COV3001 were followed for at least 2 years. No new safety concerns were identified. Note that due to several study limitations, no conclusions on group comparisons could be drawn.

Based on long-term safety data from other Ad26-based vaccines (at least 6 months up to 5 years post-vaccination in clinical trials), no long-term safety issues have been identified (Adenoviral Vaccine Safety Database V7.0 2022).

Population in need of further characterization:

The long-term safety of Ad26.COV2.S is not fully known, however there are no known risks with a potentially late onset based on the available evidence with other Ad26-based vaccines.

Long-term safety data are being collected for at least 2 years in trial COV3009 following administration of Ad26.COV2.S, and for up to 1 year in the post-authorization safety studies COV4003 and COV4001.

Participants of trial COV3009 who initially received placebo were unblinded and offered a single dose of Ad26.COV2.S (crossover vaccination), since the vaccine has received an EUA in the United States and conditional Marketing Authorisation in the European Union/EEA. All participants have been encouraged to remain in the trial and will be followed for safety as originally planned up to 2 years from time of enrollment into study.

Medicinal product no longer authorised

PART II: SAFETY SPECIFICATION

Module SVIII: Summary of the Safety Concerns

Table SVIII.1: Summary of Safety Concerns

Important identified risks	Thrombosis with thrombocytopenia syndrome
	Guillain-Barré syndrome
	Thrombocytopenia, including immune thrombocytopenia
	Venous thromboembolism
	Myocarditis and pericarditis
Important potential risks	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)
Missing information	Use in pregnancy and while breastfeeding
	Use in immunocompromised patients
	Use in patients with autoimmune or inflammatory disorders
	Use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)
	Long-term safety

Medicinal product no longer authorised

PART III: PHARMACOVIGILANCE PLAN (Including Post-authorisation Safety Studies)

Routine Pharmacovigilance Activities

The MAH follows standard pharmacovigilance processes with regard to Ad26.COV2.S, along with the additional actions referenced in the EU-RMP. Due to the special circumstances of the pandemic, enhancement of these routine activities has been undertaken. The MAH has a Global Safety Database in place to manage the receipt, processing, and reporting of individual and aggregate safety data to regulatory authorities, and to support pharmacovigilance activities including safety signal detection and ongoing evaluation of the benefit-risk profile of the vaccine. The MAH conducts both passive and active surveillance activities for continued vaccine safety monitoring, as further specified below.

ICSR reporting

The MAH submits ICSRs in accordance to GVP Module VI, GVP Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases, and the detailed guidance on ICSRs in the context of COVID-19 (EMA 2022a).

Follow-up for spontaneous and solicited ICSRs

ICSRs are followed up promptly to obtain additional information relevant to the report as necessary to provide a complete description of the safety event. Two follow-up attempts are performed for all ICSRs regardless of validity (non-valid/valid case), seriousness, expectedness, or causal relationship. For all ICSRs with product exposure during pregnancy (regardless of source, including literature reports), 2 additional follow-up attempts are performed to obtain information regarding pregnancy outcome in addition to the standard 2 follow-up attempts.

The MAH has created an AESI list including events recommended by Brighton Collaboration (SPEAC), the ACCESS protocol, the US CDC, and the MHRA (see Annex 7.4). For the AESIs, questions are added to the standard vaccine AE follow-up questionnaire on a case-by-case basis.

Furthermore, the ICSR Medical reviewer retains the ability to request follow-up with phone call on any case, regardless of seriousness.

Literature review

Monitoring of the medical and scientific literature includes a weekly scheduled search of 2 commercial databases (Ovid MEDLINE and EMBASE).

Medicinal product no longer authorised

Signal investigation

All available safety information across clinical investigations, postmarketing data, and all other sources of information is reviewed on a regular basis. Other sources of pertinent data may include nonclinical studies, manufacturing and product quality reports, relevant publications, epidemiology data, data from external safety databases, safety-related health authority and healthcare provider queries, and safety-related health authority communications and assessment reports.

Routine aggregate signal detection includes regular surveillance of AE reports received in the Company's Global Safety Database, irrespective of country of origin, seriousness, medical confirmation, or validity. Additional reviews are performed in external databases listed below.

Key routine aggregate surveillance activities for Ad26.COV2.S are summarized in the table below:

Data source	Type of analysis and frequency of monitoring
Company's Global Safety Database	Monthly for PTs: • Disproportionality analyses: spontaneous, non-interventional, age group • Temporal analysis • Fatal outcome • Positive rechallenge • Custom groupings: cerebral venous sinus thrombosis, lack of efficacy/effectiveness Quarterly time to onset analysis as a proof of concept Quarterly vaccine lot analysis pilot
FDA VAERS	Ad hoc data mining
EudraVigilance	Quarterly data mining
WHO VigiBase	Ad hoc data mining

1) Database Review by the MAH: an assessment of all AEs reported in the Company's Global Safety Database for Ad26.COV2.S is performed. Analyses are at the PT level and clustered using custom grouping of select PTs. Methods for signal detection activities include:
   a) Monthly disproportionality analysis
   b) Quarterly time-to-onset analysis
   c) Temporal analyses are done using monthly TFA which signals changes in reporting patterns for drug-event(s) pairs over time. This includes review of reporting percentages by AE and AE groupings through trend analysis. TFA may be useful to detect batch issues or spurious reports. A baseline must be established before this method is maximally effective.

Medicinal product no longer authorised

d) Vaccine lot disproportionality analysis: A Qlik-based application for data visualization of Company safety data is being implemented as a proof-of-concept methodology for signal detection of vaccine lot analysis every 3 months (quarterly). The dashboard may be validated, and the methodology formalized following demonstrated success of the pilot(s) process and tool.

e) O/E analysis: Background rates to support the O/E analyses are extracted from the literature. Peer-review papers are used as best evidence. In case such papers are not available, data generated by ACCESS (EMA-funded project) or OHDSI (FDA-funded collaboration) are used.

2) Data Mining Review: a review of cumulative data in external databases is performed to identify AEs reported disproportionately for Ad26.COV2.S relative to all other products in the database including:

a) EudraVigilance: quarterly data mining

b) WHO VigiBase: ad hoc data mining

c) FDA VAERS: ad hoc data mining.

3) Real World Data Analytics: The MAH has access to large US real world databases to monitor the exposure to Ad26.COV2.S and to conduct sequential analyses to support and complement ongoing routine pharmacovigilance activities to further contextualize potential safety signals in a rapid manner.

This signal detection strategy is based on the current risk profile of Ad26.COV2.S and is anticipated to evolve over time as greater understanding of the safety profile is acquired.

Traceability

The SmPC includes instructions for healthcare professionals to:

- clearly record the name and batch number of the administered vaccine to improve traceability (Section 4.4);
- report any suspected adverse reactions including batch/lot number if available (Section 4.8).

Traceability is available for every shipping container of JCOVDEN, which is fitted with a unique device that provides real-time monitoring of geographic location 24 hours per day, 7 days per week. Each device will also trace the batch/lot of the associated shipment. The device is activated prior to shipment and information is transmitted wirelessly to the MAH at a predefined cadence until delivery to each country's government distribution center. Each shipment will be accompanied by a passive temperature datalogger. Alarms for excursions (per predefined specifications) are programmed into the device. If the display on the device doesn't show an alarmed status, the vaccine can be received. If the display shows an alarmed status, the product needs to be stored in the appropriate temperature conditions upon arrival and the receiver needs to follow the MAH's instructions for reporting an alarmed shipment. These data may be used for the assessment of a safety signal.

The vaccine carton box includes a 2D matrix barcode (encoding lot number, GTIN product code, and expiry date) for utilization as an information source.

Medicinal product no longer authorised

Further, the MAH is making available vaccination cards that may be completed at the time of vaccination. The vaccination cards contain the following elements:

- Preprinted vaccine brand name (without reference to pharmaceutical form and active substance) and manufacturer name.
- Placeholder space for name of vaccinee.
- Placeholder space for date of vaccination and associated lot number.
- For EEA countries, reference to the National Reporting System for AE reporting.
- QR code and URL for additional product information.

Vaccination card use will depend on national requirements and/or national competent authority guidance. Printed vaccination cards available in a country may include additional, nationally-required details.

For EEA countries, in addition to the vaccination cards, 2 stickers per dose containing preprinted vaccine brand name (without reference to pharmaceutical form and active substance), lot number, and a 2D matrix barcode (encoding vaccine brand name and lot number) are made available to support documentation of the lot number on both the vaccination cards for vaccinees and in the vaccinee medical records in vaccination centers. It is acknowledged that some countries may require utilization of nationally-mandated vaccination cards or electronic systems to document the lot number; therefore, the available vaccination cards and stickers with printed lot number may not be utilized in all countries.

III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection

Specific Follow-up Questionnaires for Safety Concerns	
Safety Concern	Purpose/Description
Not applicable	

III.2. Additional Pharmacovigilance Activities

Additional Pharmacovigilance Activities	
Trial VAC31518COV3009	
Study name and title	VAC31518COV3009 – A randomized, double-blind, placebo-controlled Phase 3 study to assess the efficacy and safety of Ad26.COV2.S for the prevention of SARS-CoV-2-mediated COVID-19 in adults aged 18 years and older.
Rationale and study objectives:	To evaluate the efficacy, safety, reactogenicity, and immunogenicity of 2 doses of Ad26.COV2.S for the prevention of SARS-CoV-2-mediated COVID-19.
Safety concern(s) addressed	Thrombosis with thrombocytopenia syndrome Guillain-Barré syndrome Thrombocytopenia, including immune thrombocytopenia

Medicinal product no longer authorised

Additional Pharmacovigilance Activities	
	Venous thromboembolism Myocarditis and pericarditis Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Use in pregnancy and while breastfeeding (This trial will only address use while breastfeeding) Long-term safety
Study design	Randomized, double-blind, placebo-controlled trial. After unblinding, participants who initially received placebo were offered a single dose of Ad26.COV2.S. All participants who received a single dose of Ad26.COV2.S are offered an Ad26.COV2.S booster. Long-term safety follow-up post-booster will continue for at least 6 months.
Study population	Adults aged ≥18 years with and without comorbidities that are associated with increased risk of progression to severe COVID-19.
Milestones	Final study report: 30 June 2024
Trial VAC31518COV2004	
Study name and title	VAC31518COV2004 – An open-label, Phase 2 study to evaluate the safety, reactogenicity, and immunogenicity of Ad26.COV2.S in healthy pregnant participants.
Rationale and study objectives:	Rationale: In view of the increased risk of severe COVID-19 during pregnancy, and the increased rates of complications, cesarean sections, preterm delivery, and of stillbirth that have been observed during pregnancy with SARS-CoV-2 infection so far, access to vaccination against COVID-19 is warranted during pregnancy. Study objectives: To assess the safety, reactogenicity, and immunogenicity of Ad26.COV2.S in adult participants during the 2nd and/or 3rd trimester of pregnancy, to assess the safety and reactogenicity of Ad26.COV2.S (potentially) post-partum, and to assess pregnancy outcomes. To assess the presence of immunoglobulins against SARS-CoV-2 in colostrum and breast milk.
Safety concern(s) addressed	Use in pregnancy and while breastfeeding
Study design	Open-label trial.
Study population	Healthy pregnant participants (2nd or 3rd trimester of pregnancy) aged ≥18 to ≤45 years. A small subset of participants will be followed up during breastfeeding.
Milestones	Protocol submission: 06 March 2021 Final study report: 31 December 2024

Medicinal product no longer authorised

Additional Pharmacovigilance Activities	
Study VAC31518COV4005	
Study name and title	VAC31518COV4005 – COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER).
Rationale and study objectives:	To assess the occurrence of obstetric, neonatal, and infant outcomes among women administered with Ad26.COV2.S during pregnancy.
Safety concern(s) addressed	Use in pregnancy and while breastfeeding (This study will only address use in pregnancy)
Study design	Multi-country, observational, prospective cohort study of pregnant women administered with Ad26.COV2.S and including follow-up of liveborn infants to one year of age.
Study population	Women administered with Ad26.COV2.S during pregnancy to prevent COVID-19.
Milestones	Protocol submission: 15 February 2021 Final study report: 30 June 2027
Study VAC31518COV4003	
Study name and title	VAC31518COV4003 – An observational post-authorization safety study to assess the safety of Ad26.COV2.S using European healthcare data through VAC4EU.
Rationale and study objectives:	To assess the occurrence of pre-specified AESIs within specific risk periods following administration of Ad26.COV2.S.
Safety concern(s) addressed	Thrombosis with thrombocytopenia syndrome Guillain-Barré syndrome Thrombocytopenia, including immune thrombocytopenia (this study will only address immune thrombocytopenia) Venous thromboembolism Myocarditis and pericarditis Use in immunocompromised patients Use in patients with autoimmune or inflammatory disorders Use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) Long-term safety Use in pregnancy and while breastfeeding (The adequacy of the study to address pregnancy outcomes is to be assessed. The safety of Ad26.COV2.S in breastfeeding women will not be studied.)
Study design	Multi-country, observational study using European healthcare data.
Study population	General population in Europe.
Milestones	Protocol submission: 31 May 2021 1st feasibility report: 31 December 2022 Final study report: 31 March 2025

Medicinal product no longer authorised

Additional Pharmacovigilance Activities	
Study VAC31518COV4004	
Study name and title	VAC31518COV4004 – Brand-specific COVID-19 vaccine effectiveness of COVID-19 Vaccine Janssen against severe COVID-19 disease in Europe.
Rationale and study objectives:	To estimate the effectiveness of Ad26.COV2.S in preventing laboratory-confirmed SARS-CoV-2 hospitalizations.
Safety concern(s) addressed	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Use in immunocompromised patients
Study design	Multi-country, observational, prospective hospital-based study, following a test-negative and/or a case-control design.
Study population	General population in Europe.
Milestones	Protocol submission: 31 March 2021 Interim analysis report: 30 December 2022 Final study report: 30 June 2024
Study VAC31518COV4001	
Study name and title	VAC31518COV4001 – An observational post-authorization safety study to assess the safety of Ad26.COV2.S using health insurance databases in the United States.
Rationale and study objectives:	To assess the occurrence of pre-specified AESIs within specific risk periods following administration of Ad26.COV2.S.
Safety concern(s) addressed	Thrombosis with thrombocytopenia syndrome Guillain-Barré syndrome Thrombocytopenia, including immune thrombocytopenia (this study will only address immune thrombocytopenia) Venous thromboembolism Myocarditis and pericarditis Use in immunocompromised patients Use in patients with autoimmune or inflammatory disorders Use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) Long-term safety
Study design	Observational study using US health insurance databases.
Study population	General population in the United States.
Milestones	Protocol submission: 30 July 2021 Final study report: 31 December 2025

Medicinal product no longer authorised

Additional Pharmacovigilance Activities	
Trial VAC31518COV3003	
Study name and title	VAC31518COV3003 – A randomized, double-blind Phase 3 study to evaluate 6 dose levels of Ad26.COV2.S administered as a two-dose schedule in healthy adults.
Rationale and study objectives:	To evaluate the safety, reactogenicity, and immunogenicity of Ad26.COV2.S at different dose levels and after 1 or 2 doses and to characterize the innate, pro-inflammatory and other relevant (eg, prothrombotic) responses to the Ad26.COV2.S vector to better understand a possible risk for thrombotic events.
Safety concern(s) addressed	Thrombosis with thrombocytopenia syndrome Thrombocytopenia, including immune thrombocytopenia Venous thromboembolism
Study design	Randomized, double-blind trial.
Study population	Healthy adults aged 18 to ≥55 years
Milestones	Final study report: 30 June 2024
RNA transcriptome analyses post-vaccination using clinical samples from Ad26.COV2.S and other Ad26-based Company vaccine studies (Trial VAC18193RSV2008)	
Study name and title	VAC18193RSV2008 – A randomized, observer-blind, Phase 1 study to evaluate innate and pro-inflammatory responses of an Ad26.RSV.preF-based vaccine, Ad26.COV2.S vaccine and Ad26.ZEBOV vaccine in adults aged 18 to 59 years.
Rationale and study objectives:	To examine gene expression in whole blood, that may inform on the inflammation signals triggered by Ad26.COV2.S and other Ad26-based Company vaccines.
Safety concern(s) addressed	Thrombosis with thrombocytopenia syndrome Thrombocytopenia, including immune thrombocytopenia Venous thromboembolism
Study design	Gene expression analysis
Study population	Clinical samples (blood) from participants after Ad26.COV2.S vaccination or after vaccination with an Ad26-based vaccine.
Milestones	Final study report: 30 September 2024

Medicinal product no longer authorised

III.3. Summary Table of Additional Pharmacovigilance Activities

Table Part III.1: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				
Category 3 – Required additional pharmacovigilance activities				
A randomized, double-blind, placebo-controlled Phase 3 study to assess the efficacy and safety of Ad26.COV2.S for the prevention of SARS-CoV-2-mediated COVID-19 in adults aged 18 years and older (VAC31518COV3009) Ongoing	To evaluate the efficacy, safety, reactogenicity, and immunogenicity of 2 doses of Ad26.COV2.S for the prevention of SARS-CoV-2-mediated COVID-19.	• Thrombosis with thrombocytopenia syndrome • Guillain-Barré syndrome • Thrombocytopenia, including immune thrombocytopenia • Venous thromboembolism • Myocarditis and pericarditis • Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) • Use in pregnancy and while breastfeeding (This trial will only address use while breastfeeding) • Long-term safety	Final study report	30 June 2024
An open-label, Phase 2 study to evaluate the safety, reactogenicity, and immunogenicity of Ad26.COV2.S in healthy pregnant participants (VAC31518COV2004) Ongoing	To assess the safety, reactogenicity, and immunogenicity of Ad26.COV2.S in adult participants during the 2nd and/or 3rd trimester of pregnancy, to assess the safety and reactogenicity of Ad26.COV2.S (potentially) post-partum, and to assess pregnancy outcomes. To assess the presence of immunoglobulins against SARS-CoV-2	• Use in pregnancy and while breastfeeding	Protocol submission Final study report	06 March 2021 31 December 2024

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Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	in colostrum and breast milk.			
COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER) (VAC31518COV4005) Ongoing	To assess the occurrence of obstetric, neonatal, and infant outcomes among women administered with Ad26.COV2.S during pregnancy.	• Use in pregnancy and while breastfeeding (This study will only address use in pregnancy)	Protocol submission Final study report	15 February 2021 30 June 2027
An observational post-authorization study to assess the safety of Ad26.COV2.S using European healthcare data through VAC4EU (VAC31518COV4003) Ongoing	To assess the occurrence of pre-specified AESIs within specific risk periods following administration of Ad26.COV2.S.	• Thrombosis with thrombocytopenia syndrome • Guillain-Barré syndrome • Thrombocytopenia, including immune thrombocytopenia (this study will only address immune thrombocytopenia) • Venous thromboembolism • Myocarditis and pericarditis • Use in immunocompromised patients • Use in patients with autoimmune or inflammatory disorders • Use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) • Long-term safety • Use in pregnancy and while breastfeeding (The adequacy of the study to address pregnancy outcomes is to be assessed. The safety of Ad26.COV2.S in breastfeeding women will not be studied.)	Protocol submission 1st feasibility report Final study report	31 May 2021 31 December 2022 31 March 2025

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Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Brand-specific COVID-19 vaccine effectiveness of COVID-19 Vaccine Janssen against severe COVID-19 disease in Europe (VAC31518COV4004) Ongoing	To estimate the effectiveness of Ad26.COV2.S in preventing laboratory-confirmed SARS-CoV-2 hospitalizations.	• Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) • Use in immunocompromised patients	Protocol submission Interim analysis report Final study report	31 March 2021 30 December 2022 30 June 2024
An observational post-authorization safety study to assess the safety of Ad26.COV2.S using health insurance databases in the United States (VAC31518COV4001) Ongoing	To assess the occurrence of pre-specified AESIs within specific risk periods following administration of Ad26.COV2.S.	• Thrombosis with thrombocytopenia syndrome • Guillain-Barré syndrome • Thrombocytopenia, including immune thrombocytopenia (this study will only address immune thrombocytopenia) • Venous thromboembolism • Myocarditis and pericarditis • Use in immunocompromised patients • Use in patients with autoimmune or inflammatory disorders • Use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) • Long-term safety	Protocol submission Final study report	30 July 2021 31 December 2025

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Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
A randomized, double-blind Phase 3 study to evaluate 6 dose levels of Ad26.COV2.S administered as a two-dose schedule in healthy adults (VAC31518COV3003) Ongoing	To evaluate safety, reactogenicity, and immunogenicity of Ad26.COV2.S at different dose levels and after 1 or 2 doses and to characterize the innate, pro-inflammatory and other relevant (eg, prothrombotic) responses to the Ad26.COV2.S vector to better understand a possible risk for thrombotic events.	• Thrombosis with thrombocytopenia syndrome • Thrombocytopenia, including immune thrombocytopenia • Venous thromboembolism	Final study report	30 June 2024
RNA transcriptome analyses post-vaccination using clinical samples from Ad26.COV2.S and other Ad26-based Company vaccine studies (Trial VAC18193RSV2008, a randomized, observer-blind, Phase 1 study to evaluate innate and pro-inflammatory responses of an Ad26.RSV.preF-based vaccine, Ad26.COV2.S vaccine and Ad26.ZEBOV vaccine in adults aged 18 to 59 years) Ongoing	To examine gene expression in whole blood, that may inform on the inflammation signals triggered by Ad26.COV2.S and other Ad26-based Company vaccines.	• Thrombosis with thrombocytopenia syndrome • Thrombocytopenia, including immune thrombocytopenia • Venous thromboembolism	Final study report	30 September 2024

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PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Table Part IV.1: Planned and Ongoing Post-Authorisation Efficacy Studies That Are Conditions of the Marketing Authorisation or That Are Specific Obligations

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates
Efficacy Studies which are conditions of the marketing authorisations				
None				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				

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PART V: RISK MINIMIZATION MEASURES (Including Evaluation of the Effectiveness of Risk Minimization Activities)

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks	
Thrombosis with thrombocytopenia syndrome	**Routine risk communication:** • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • SmPC Section 4.4, and PL Section 2 provide recommendations to address the risk of thrombosis with thrombocytopenia syndrome. **Other routine risk minimization measures beyond the Product Information:** • None
Guillain-Barré syndrome	**Routine risk communication:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • SmPC Section 4.4, and PL Section 2 provide recommendations to address the risk of Guillain-Barré syndrome. **Other routine risk minimization measures beyond the Product Information:** • None

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Safety Concern	Routine Risk Minimization Activities
Thrombocytopenia, including immune thrombocytopenia	**Routine risk communication:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • SmPC Section 4.4, and PL Section 2 provide recommendations to address the risk of thrombocytopenia, including immune thrombocytopenia. **Other routine risk minimization measures beyond the Product Information:** • None
Venous thromboembolism	**Routine risk communication:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • SmPC Section 4.4, and PL Section 2 provide recommendations to address the risk of VTE. **Other routine risk minimization measures beyond the Product Information:** • None
Myocarditis and pericarditis	**Routine risk communication:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • SmPC Section 4.4, and PL Section 2 provide recommendations to address the risk of myocarditis and pericarditis. **Other routine risk minimization measures beyond the Product Information:** • None

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Safety Concern	Routine Risk Minimization Activities
Important Potential Risks	
Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)	**Routine risk communication:** • None **Routine risk minimization activities recommending specific clinical measures to address the risk:** • None **Other routine risk minimization measures beyond the Product Information:** • None
Missing Information	
Use in pregnancy and while breastfeeding	**Routine risk communication:** • SmPC Section 4.6 (only for use in pregnancy) • PL Section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • None **Other routine risk minimization measures beyond the Product Information:** • None
Use in immunocompromised patients	**Routine risk communication:** • SmPC Section 4.4 • PL Section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • None **Other routine risk minimization measures beyond the Product Information:** • None
Use in patients with autoimmune or inflammatory disorders	**Routine risk communication:** • None **Routine risk minimization activities recommending specific clinical measures to address the risk:** • None **Other routine risk minimization measures beyond the Product Information:** • None

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Safety Concern	Routine Risk Minimization Activities
Use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)	**Routine risk communication:** • None **Routine risk minimization activities recommending specific clinical measures to address the risk:** • None **Other routine risk minimization measures beyond the Product Information:** • None
Long-term safety	**Routine risk communication:** • None **Routine risk minimization activities recommending specific clinical measures to address the risk:** • None **Other routine risk minimization measures beyond the Product Information:** • None

V.2. Additional Risk Minimization Measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.2.1. Removal of Additional Risk Minimization Activities

Additional Risk Minimization Activity	Safety Concern(s) Addressed/Rationale for the Removal of Additional Risk Minimization Activity
Not applicable	

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V.3. Summary of Risk Minimization Measures and Pharmacovigilance Activities

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
Thrombosis with thrombocytopenia syndrome	**Routine risk minimization measures:** • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • SmPC Section 4.4 and PL Section 2 provide recommendations to address the risk of thrombosis with thrombocytopenia syndrome. **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • Trial VAC31518COV3009 Final study report: 30 June 2024 • Study VAC31518COV4003 Final study report: 31 March 2025 • Study VAC31518COV4001 Final study report: 31 December 2025 • Trial VAC31518COV3003 Final study report: 30 June 2024 • RNA transcriptome analyses post-vaccination using clinical samples from Ad26.COV2.S and other Ad26-based Company vaccine studies (Trial VAC18193RSV2008) Final study report: 30 September 2024

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Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Guillain-Barré syndrome	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • SmPC Section 4.4, and PL Section 2 provide recommendations to address the risk of Guillain-Barré syndrome. **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • Trial VAC31518COV3009 Final study report: 30 June 2024 • Study VAC31518COV4003 Final study report: 31 March 2025 • Study VAC31518COV4001 Final study report: 31 December 2025
Thrombocytopenia, including immune thrombocytopenia	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • SmPC Section 4.4 and PL Section 2 provide recommendations to address the risk of thrombocytopenia, including immune thrombocytopenia. **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • Trial VAC31518COV3009 Final study report: 30 June 2024 • Study VAC31518COV4003 (this study will only address immune thrombocytopenia) Final study report: 31 March 2025 • Study VAC31518COV4001 (this study will only address immune thrombocytopenia) Final study report: 31 December 2025 • Trial VAC31518COV3003 Final study report: 30 June 2024 • RNA transcriptome analyses post-vaccination using clinical samples from Ad26.COV2.S and other Ad26-based Company vaccine studies (Trial VAC18193RSV2008) Final study report: 30 September 2024

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Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Venous thromboembolism	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • SmPC Section 4.4, and PL Section 2 provide recommendations to address the risk of VTE. **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • Trial VAC31518COV3009 Final study report: 30 June 2024 • Study VAC31518COV4003 Final study report: 31 March 2025 • Study VAC31518COV4001 Final study report: 31 December 2025 • Trial VAC31518COV3003 Final study report: 30 June 2024 • RNA transcriptome analyses post-vaccination using clinical samples from Ad26.COV2.S and other Ad26-based Company vaccine studies (Trial VAC18193RSV2008) Final study report: 30 September 2024
Myocarditis and pericarditis	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • SmPC Section 4.4, and PL Section 2 provide recommendations to address the risk of myocarditis and pericarditis. **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • Trial VAC31518COV3009 Final study report: 30 June 2024 • Study VAC31518COV4003 Final study report: 31 March 2025 • Study VAC31518COV4001 Final study report: 31 December 2025

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Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Potential Risks		
Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)	**Routine risk minimization measures:** • None **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • Trial VAC31518COV3009 Final study report: 30 June 2024 • Study VAC31518COV4004 Final study report: 30 June 2024
Missing Information		
Use in pregnancy and while breastfeeding	**Routine risk minimization measures:** • SmPC Section 4.6 (only for use in pregnancy) • PL Section 2 **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • Trial VAC31518COV3009 (This trial will only address use while breastfeeding) Final study report: 30 June 2024 • Trial VAC31518COV2004 Final study report: 31 December 2024 • Study VAC31518COV4005 (This study will only address use in pregnancy) Final study report: 30 June 2027 • Study VAC31518COV4003 (The adequacy of the study to address pregnancy outcomes is to be assessed. The safety of Ad26.COV2.S in breastfeeding women will not be studied.) Final study report: 31 March 2025

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Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Use in immunocompromised patients	**Routine risk minimization measures:** • SmPC Section 4.4 • PL Section 2 **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • Study VAC31518COV4003 Final study report: 31 March 2025 • Study VAC31518COV4004 Final study report: 30 June 2024 • Study VAC31518COV4001 Final study report: 31 December 2025
Use in patients with autoimmune or inflammatory disorders	**Routine risk minimization measures:** • None **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • Study VAC31518COV4003 Final study report: 31 March 2025 • Study VAC31518COV4001 Final study report: 31 December 2025
Use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)	**Routine risk minimization measures:** • None **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • Study VAC31518COV4003 Final study report: 31 March 2025 • Study VAC31518COV4001 Final study report: 31 December 2025

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Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Long-term safety	**Routine risk minimization measures:** • None **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • Trial VAC31518COV3009 Final study report: 30 June 2024 • Study VAC31518COV4003 Final study report: 31 March 2025 • Study VAC31518COV4001 Final study report: 31 December 2025

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PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for JCOVDEN

This is a summary of the risk management plan (RMP) for JCOVDEN. The RMP details important risks of JCOVDEN, how these risks can be minimized, and how more information will be obtained about JCOVDEN's risks and uncertainties (missing information).

JCOVDEN's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how JCOVDEN should be used.

This summary of the RMP for JCOVDEN should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of JCOVDEN's RMP.

I. The Vaccine and What it is Used For

JCOVDEN is authorised for active immunization to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in individuals 18 years of age and older (see SmPC for the full indication). It contains Ad26.COV2.S as the active substance and it is given by intramuscular injection.

Further information about the evaluation of JCOVDEN's benefits can be found in JCOVDEN's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the vaccine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/jcovden-previously-covid-19-vaccine-janssen.

II. Risks Associated With the Vaccine and Activities to Minimize or Further Characterize the Risks

Important risks of JCOVDEN, together with measures to minimize such risks and the proposed studies for learning more about JCOVDEN's risks, are outlined below.

Measures to minimize the risks identified for vaccines can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to individuals and healthcare professionals;
- Important advice on the vaccine's packaging;
- The authorised pack size — the amount of vaccine in a pack is chosen so to ensure that the vaccine is used correctly;
- The vaccine's legal status — the way a vaccine is supplied to the individual (eg, with or without prescription) can help to minimize its risks.

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Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including Periodic Benefit-Risk Evaluation Report/Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of JCOVDEN is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of JCOVDEN are risks that need special risk management activities to further investigate or minimize the risk, so that the vaccine can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of JCOVDEN. Potential risks are concerns for which an association with the use of this vaccine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the vaccine that is currently missing and needs to be collected (eg, on the long-term use of the vaccine).

List of Important Risks and Missing Information	
Important identified risks	Thrombosis with thrombocytopenia syndrome Guillain-Barré syndrome Thrombocytopenia, including immune thrombocytopenia Venous thromboembolism Myocarditis and pericarditis
Important potential risks	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)
Missing information	Use in pregnancy and while breastfeeding Use in immunocompromised patients Use in patients with autoimmune or inflammatory disorders Use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) Long-term safety

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II.B. Summary of Important Risks

Important Identified Risk: Thrombosis with thrombocytopenia syndrome	
Evidence for linking the risk to the medicine	Thrombosis in combination with thrombocytopenia (TTS), in some cases accompanied by bleeding, has been observed very rarely following vaccination with JCOVDEN and is an adverse drug reaction described in the SmPC.
Risk factors and risk groups	Although no clear risk factors have been identified, the cases of thrombosis in combination with thrombocytopenia reported in the postmarketing setting more commonly occurred in individuals aged <60 years.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • SmPC Section 4.4, and PL Section 2 provide recommendations to address the risk of thrombosis with thrombocytopenia syndrome. Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial VAC31518COV3009 • Study VAC31518COV4003 • Study VAC31518COV4001 • Trial VAC31518COV3003 • RNA transcriptome analyses post-vaccination using clinical samples from Ad26.COV2.S and other Ad26-based Company vaccine studies (Trial VAC18193RSV2008) See section II.C of this summary for an overview of the post-authorisation development plan.

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Important Identified Risk: Guillain-Barré syndrome	
Evidence for linking the risk to the medicine	Guillain-Barré syndrome (GBS) has been observed very rarely following vaccination with JCOVDEN both in clinical trials and in the postmarketing setting. Similar adverse events have also been described following administration of other COVID-19 vaccines. Despite no clear biological mechanism being identified, the MAH considers the increase in observed versus expected ratios since authorisation to be sufficient evidence for a plausible association between JCOVDEN and GBS. Guillain-Barré syndrome is an adverse drug reaction described in the SmPC.
Risk factors and risk groups	There are no known risk factors for the development of GBS following JCOVDEN vaccination. Based mainly on data from North America and Europe, it has been shown in literature that the GBS incidence increased by 20% for every 10-year increase in age; GBS is usually more frequent in males, with the highest incidence between 50 to 70 years of age.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • SmPC Section 4.4, and PL Section 2 provide recommendations to address the risk of Guillain-Barré syndrome. Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial VAC3158COV3009 • Study VAC31518COV4003 • Study VAC31518COV4001 See section II.C of this summary for an overview of the post-authorisation development plan.

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Important Identified Risk: Thrombocytopenia, including immune thrombocytopenia	
Evidence for linking the risk to the medicine	Cases of immune thrombocytopenia (ITP) with very low platelet levels (<20,000 per µL) have been reported very rarely after vaccination with JCOVDEN, usually within the first 4 weeks after receiving JCOVDEN. This included cases with bleeding and cases with fatal outcome. Some of these cases occurred in individuals with a history of ITP. Based on the observed imbalance in postmarketing events, ITP is an adverse drug reaction described in the SmPC.
Risk factors and risk groups	Limited data from postmarketing experience with JCOVDEN, including literature, suggest that individuals with chronic or recurrent ITP may be at increased risk of developing ITP following vaccination with JCOVDEN.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • SmPC Section 4.4 and PL Section 2 provide recommendations to address the risk of thrombocytopenia, including immune thrombocytopenia. Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial VAC31518COV3009 • Study VAC31518COV4003 (this study will only address immune thrombocytopenia) • Study VAC31518COV4001 (this study will only address immune thrombocytopenia) • Trial VAC31518COV3003 • RNA transcriptome analyses post-vaccination using clinical samples from Ad26.COV2.S and other Ad26-based Company vaccine studies (Trial VAC18193RSV2008) See section II.C of this summary for an overview of the post-authorisation development plan.

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Important Identified Risk: Venous thromboembolism	
Evidence for linking the risk to the medicine	Venous thromboembolism (VTE) has been observed rarely following vaccination with JCOVDEN in clinical trials and in the postmarketing setting. While a higher proportion of cases of VTE was observed within the JCOVDEN group versus the Placebo group in trial COV3001, there was no increase in VTE events among individuals who received JCOVDEN in trial COV3009. VTE is an adverse drug reaction described in the SmPC.
Risk factors and risk groups	In trials COV3001 and COV3009, underlying risk factors have been identified in participants with VTE such as COVID-19, male gender, old age (>65 years), long-haul travel, thrombophilia, obesity, active malignancy, trauma, previous venous thrombosis, hypertension, and COPD.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • SmPC Section 4.4, and PL Section 2 provide recommendations to address the risk of VTE. Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial VAC31518COV3009 • Study VAC31518COV4003 • Study VAC31518COV4001 • Trial VAC31518COV3003 • RNA transcriptome analyses post-vaccination using clinical samples from Ad26.COV2.S and other Ad26-based Company vaccine studies (Trial VAC18193RSV2008) See section II.C of this summary for an overview of the post-authorisation development plan.

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Important Identified Risk: Myocarditis and pericarditis	
Evidence for linking the risk to the medicine	Myocarditis and/or pericarditis have been reported as rare events following vaccination against smallpox, hepatitis B, tetanus, human papillomavirus, and viral influenza and have been documented for COVID-19 vaccines. A systemic review and meta-analysis revealed higher incidence of myopericarditis following smallpox vaccination but no significant difference after influenza vaccinations compared to COVID-19 vaccination. Among COVID-19 vaccines, myocarditis and/or pericarditis has been observed with mRNA vaccines with an incidence significantly higher in males versus females, in people younger than 30 years, and after a second dose (compared to first or third dose). Additionally, a recombinant adjuvanted protein-based COVID-19 vaccine has been associated with a disproportional myopericarditis induction. Events of myocarditis and pericarditis have been observed very rarely following vaccination with Ad26.COV2.S both in clinical trials and in the postmarketing setting. Real-world evidence data of US claims data sources showed a high level of certainty of an increased risk of myocarditis and pericarditis for males aged 18 to 39 years within 28 days of vaccination with Ad26.COV2.S. Myocarditis and pericarditis are adverse drug reactions described in the SmPC.
Risk factors and risk groups	Myocarditis and pericarditis have been reported in association with SARS-CoV-2 infection. Historically, myocarditis and/or pericarditis have been reported as a rare event following vaccination against smallpox, hepatitis B and viral influenza. Myocarditis and pericarditis have also been reported with other COVID-19 vaccines (including mRNA-based COVID-19 vaccines and a recombinant adjuvanted protein-based COVID-19 vaccine). Young males appear to be at highest risk, predominantly after receiving the second dose of COVID-19 vaccination. The disease course is self-limiting in a vast majority of cases: 95% of patients show a rapid resolution of symptoms and normalization of cardiac biomarkers, electro- and echocardiographic findings within days.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • SmPC Section 4.4, and PL Section 2 provide recommendations to address the risk of myocarditis and pericarditis. Additional risk minimization measures: • None

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Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial VAC31518COV3009 • Study VAC31518COV4003 • Study VAC31518COV4001 See section II.C of this summary for an overview of the post-authorisation development plan.
Important Potential Risk: Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)	
Evidence for linking the risk to the medicine	VAED/VAERD has not been described in association with JCOVDEN and has not been confirmed from any other late phase clinical trial of other COVID-19 vaccines. For candidate SARS-CoV-2 vaccines, no evidence of VAED or VAERD after intramuscular immunization has been reported to date in nonclinical studies or clinical trials. Nevertheless, in the absence of long-term safety and efficacy data, the evidence is not yet sufficient to fully dismiss VAED, including VAERD as a safety concern, and it remains an important potential risk.
Risk factors and risk groups	It is postulated that the potential risk may be increased in individuals producing lower neutralizing antibody titers or in those demonstrating waning immunity.
Risk minimization measures	Routine risk minimization measures • None Additional risk minimization measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial VAC31518COV3009 • Study VAC31518COV4004 See section II.C of this summary for an overview of the post-authorisation development plan.

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Missing Information: Use in pregnancy and while breastfeeding	
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.6 (only for use in pregnancy) • PL Section 2 Additional risk minimization measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial VAC31518COV3009 (This trial will only address use while breastfeeding) • Trial VAC31518COV2004 • Study VAC31518COV4005 (This study will only address use in pregnancy) • Study VAC31518COV4003 (The adequacy of the study to address pregnancy outcomes is to be assessed. The safety of Ad26.COV2.S in breastfeeding women will not be studied.) See section II.C of this summary for an overview of the post-authorisation development plan.
Missing Information: Use in immunocompromised patients	
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.4 • PL Section 2 Additional risk minimization measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study VAC31518COV4003 • Study VAC31518COV4004 • Study VAC31518COV4001 See section II.C of this summary for an overview of the post-authorisation development plan.

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Missing Information: Use in patients with autoimmune or inflammatory disorders	
Risk minimization measures	Routine risk minimization measures • None Additional risk minimization measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study VAC31518COV4003 • Study VAC31518COV4001 See section II.C of this summary for an overview of the post-authorisation development plan.
Missing Information: Use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)	
Risk minimization measures	Routine risk minimization measures • None Additional risk minimization measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study VAC31518COV4003 • Study VAC31518COV4001 See section II.C of this summary for an overview of the post-authorisation development plan.
Missing Information: Long-term safety	
Risk minimization measures	Routine risk minimization measures • None Additional risk minimization measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial VAC31518COV3009 • Study VAC31518COV4003 • Study VAC31518COV4001 See section II.C of this summary for an overview of the post-authorisation development plan.

Medicinal product no longer authorised

II.C. Post-authorisation Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorisation

Not applicable.

II.C.2. Other Studies in Post-authorisation Development Plan

VAC31518COV3009: A randomized, double-blind, placebo-controlled Phase 3 study to assess the efficacy and safety of Ad26.COV2.S for the prevention of SARS-CoV-2-mediated COVID-19 in adults aged 18 years and older.

Purpose of the study: To evaluate the efficacy, safety, reactogenicity, and immunogenicity of 2 doses of Ad26.COV2.S for the prevention of SARS-CoV-2-mediated COVID-19.

VAC31518COV2004: An open-label, Phase 2 study to evaluate the safety, reactogenicity, and immunogenicity of Ad26.COV2.S in healthy pregnant participants.

Purpose of the study: To assess the safety, reactogenicity, and immunogenicity of Ad26.COV2.S in adult participants during the 2nd and/or 3rd trimester of pregnancy, to assess the safety and reactogenicity of Ad26.COV2.S (potentially) post-partum, and to assess pregnancy outcomes. To assess the presence of immunoglobulins against SARS-CoV-2 in colostrum and breast milk.

VAC31518COV4005: COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER).

Purpose of the study: To assess the occurrence of obstetric, neonatal, and infant outcomes among women administered with Ad26.COV2.S during pregnancy.

VAC31518COV4003: An observational post-authorization safety study to assess the safety of Ad26.COV2.S using European healthcare data through VAC4EU.

Purpose of the study: To assess the occurrence of pre-specified adverse events of special interest (AESIs) within specific risk periods following administration of Ad26.COV2.S.

VAC31518COV4004: Brand-specific COVID-19 vaccine effectiveness of COVID-19 Vaccine Janssen against severe COVID-19 disease in Europe.

Purpose of the study: To estimate the effectiveness of Ad26.COV2.S in preventing laboratory-confirmed SARS-CoV-2 hospitalizations.

VAC31518COV4001: An observational post-authorization safety study to assess the safety of Ad26.COV2.S using health insurance databases in the United States.

Purpose of the study: To assess the occurrence of pre-specified AESIs within specific risk periods following administration of Ad26.COV2.S.

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VAC31518COV3003: A randomized, double-blind Phase 3 study to evaluate 6 dose levels of Ad26.COV2.S administered as a two-dose schedule in healthy adults.

Purpose of the study: To evaluate the safety, reactogenicity, and immunogenicity of Ad26.COV2.S at different dose levels and after 1 or 2 doses and to characterize the innate, pro-inflammatory and other relevant (eg, prothrombotic) responses to the Ad26.COV2.S vector to better understand a possible risk for thrombotic events.

RNA transcriptome analyses post-vaccination using clinical samples from Ad26.COV2.S and other Ad26-based Company vaccine studies (Trial VAC18193RSV2008)

Purpose of the study: To examine gene expression in whole blood, that may inform on the inflammation signals triggered by Ad26.COV2.S and other Ad26-based Company vaccines.

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PART VII: ANNEXES

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Annex 4: Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

Annex 6: Details of Proposed Additional Risk Minimization Activities (if applicable)

Not applicable.

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