COVID-19 Vaccine (Ad26.COV2-S [recombinant])

RISK MANAGEMENT PLAN (RMP)

For a summary of the RMP, please refer to PART VI.

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

Data lock point for current RMP	22 Jan 2021	Version number	1.4

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Note: This document contains unblinded clinical trial data

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QPPV Name(s):	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	1.4
Rationale for submitting an updated RMP (if applicable)	Not applicable
Summary of significant changes in this RMP:	Initial submission for Ad26.COV2.S.

Other RMP Versions Under Evaluation:

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Not applicable		

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Version number of last agreed RMP:	Not applicable
Approved within procedure	
Date of approval (Competent authority opinion date)	

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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)	Vaccines, covid-19 vaccines (ATC code: J07BX03)
Marketing Authorisation Applicant	Janssen-Cilag International NV
Medicinal products to which the RMP refers	1
Invented name(s) in the EEA	COVID-19 Vaccine Janssen
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

Indication(s) in the EEA	Current: Ad26.COV2.S is indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. Ad26.COV2.S should be used in accordance with official recommendations.	
	Proposed: Not applicable	
Dosage in the EEA	Current: Ad26.COV2.S is administered as a single dose of 0.5 mL by IM injection only.	
	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**

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:

Ad26.COV2.S 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 01 February 2021, over 102 million cases and over 2.1 million deaths from COVID-19 have been reported worldwide (WHO 2021). Globally, 4.1 million new cases and 95,991 deaths were reported in the week between 18 and 24 January 2021. As of 28 January 2021, approximately 18,849,065 cases and 449,395 deaths have been reported in the European Union/EEA (ECDC 2021a) and, as of 03 February 2021, approximately 3,882,959 cases and 109,547 deaths have been reported in the United Kingdom (Johns Hopkins 2021). Ending 04 February 2021, the 14-day case notification rate for the European Union/EEA was 402 (country range: 11-1,652) per 100,000 cases based on data collected by ECDC from official national sources from 30 countries. The 14-day COVID-19 death rate for the European Union/EEA was 103.9 (country range: 0.0-362.9) per million population (ECDC 2021b).

In several parts of the world, including in the European Union, nonpharmaceutical interventions have been implemented and allowed reducing transmission. However, the vulnerability of the population to infection remains high, as available data from seroprevalence studies suggest that the level of immunity in the population is <15% in most areas within the European Union/EEA and the United Kingdom (ECDC 2020a).

Over the course of the SARS-CoV-2 pandemic, there has been a growing concern over faster-spreading SARS-CoV-2 variants. The reason why these strains seem to spread so quickly, which variants are concerning and why, and whether they might diminish the efficacy of vaccines is currently poorly understood and are currently topics of intensive research (Callaway 2021, Davies 2020, Greaney 2021, Lauring 2021, Plante 2020, Tegally 2020, Xie 2021).

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 getting severe COVID-19. It has been estimated that up to 30% of the population in the European Union/EEA and the United Kingdom is either >60 years or has one of the underlying conditions associated with increased risk of COVID-19 (ECDC 2020b, see risk factors below). Long-term care facilities, which commonly house the elderly and the frail, have been heavily affected by COVID-19. The virus spreads rapidly on introduction, causing high morbidity in residents, commonly with a case fatality rate of >25%. Long-term care facilities were the focus of over half of the fatal COVID-19 cases in several EU/EEA countries and the United Kingdom (ECDC 2020d, ECDC Public Health Emergency Team 2020).

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 2020).

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 being disproportionately affected by COVID-19 (Price-Haywood 2020, Millett 2020, CDC 2020e, ECDC 2020c, Johns Hopkins 2020). 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 2020c, Johns Hopkins 2020).

Risk Factors for the Disease

Lifestyle factors related to an increased risk for more severe disease include smoking, a higher body mass index (obesity), and longer waiting time to hospital admission. Demographic factors

increasing the risk for a severe disease course are older age, male sex, and postmenopausal state. The most common pre-existing comorbidities in COVID-19 patients are hypertension, diabetes mellitus, cardiovascular diseases, chronic obstructive pulmonary disease, malignancy, chronic kidney disease, sickle cell disease, obesity, and weakened immune system (Wolff 2021, Emami 2020, CDC 2020b, ECDC 2020b).

Main Existing Treatment and Prevention Options:

Prophylaxis

As of 01 February 2021, 3 vaccines have received conditional marketing authorisation from EMA (EMA 2021a) and temporary authorisation from the United Kingdom MHRA (RAPS 2021): the mRNA-based BNT162b2 vaccine from Pfizer and BioNTech, the mRNA-1273 vaccine from Moderna Inc, and the ChAdOx1 nCoV-19 (recombinant) vaccine from AstraZeneca.

Therapeutics

As of 01 February 2021, remdesivir (Veklury) and dexamethasone received conditional approval by the EMA for the treatment of COVID-19 (EMA 2021a, EMA 2021b).

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 2020d). 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 Untreated Population, Including Mortality and Morbidity:

SARS-CoV-2 can be transmitted from human to human by respiratory droplets, and possibly by fecal-oral contact (Gouvea dos Santos 2020). 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. It was recently shown that airborne transmission represents the dominant transmission route (Gouvea dos Santos 2020).

Approximately 40% to 45% of infected individuals will remain asymptomatic (Feehan 2020, 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 2020c, Guan 2020, Linton 2020, US San Diego Health 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%) (Grant 2020). Overall, 19% of hospitalized patients required non-invasive ventilation, 17% required intensive care, 9% required invasive ventilation, and 2% required extra-corporeal membrane oxygenation. CDC descriptions of COVID-19 clinical case definitions and interviews with COVID-19-experienced clinicians sponsored by the Applicant 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 2020f). 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).

Available data on the weekly number of new hospital admissions for COVID-19 across European countries for the week ending 24 January 2021 ranged from 2 to 969 per million population depending on the country (Our World in Data 2021). Pooled data from 20 EU/EEA countries showed that there were 1.6 patients per 100,000 population in ICU due to COVID-19 for the week ending 24 January 2021 (ECDC 2021b). Reported case fatality rate, which estimates the proportion of deaths among identified confirmed cases, ranges from <0.1% to >25%. However, this measure is likely to be biased because those who have very mild or atypical disease, or have an asymptomatic infection are frequently left undetected and therefore omitted from fatality-rate calculations. Moreover, diagnostic testing strategies highly vary geographically and over time (WHO 2020e). Alternatively, a recent systematic review and meta-analysis of published research data estimated an overall infection fatality rate (ie, proportion of deaths among all infected individuals) of 0.68% (0.53%-0.82%) (Meyerowitz-Katz 2020).

At present, it appears that individuals aged ≥65 years, especially those with comorbidities such as cancer, cardiovascular disease, type 2 diabetes mellitus, (severe) obesity, hypertension, chronic kidney disease, and underlying pulmonary disease, are subject to the highest incidence of morbidity and mortality (CDC 2020a, Garg 2020, Verity 2020, Luo 2020).

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.

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 (TOX14382), and a combined EF-PPND toxicity study (TOX14389). Biodistribution studies (with 2 other Ad26-based vaccines, ie, CCI [redacted]) 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 intended 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.

To investigate whether there were any indications of VAERD, histopathologic analysis of lung tissues was performed after Ad26.COV2.S vaccination and subsequent respiratory inoculation with SARS-CoV-2 in rhesus monkeys (NHP) and Syrian hamsters. The aim was to monitor for disease-associated histopathologic findings after SARS-CoV-2 infection of vaccinated animals compared with a non-vaccinated infected control group. Rhesus monkey study NHP 20-14 and Syrian hamster study TKO766 included lower dose levels of Ad26.COV2.S, which resulted in a suboptimal humoral immune response. This allowed breakthrough SARS-CoV-2 replication in the lungs, a condition which is hypothesized to contribute to the risk of VAERD. Control groups received either saline (NHP studies) or Ad26 vectors not encoding any SARS-CoV-2 antigens (Syrian hamster studies), and were challenged with SARS-CoV-2 in parallel with vaccine groups. Selected respiratory tract tissues were evaluated (semi-quantitatively graded/scored) for disease-associated pathology findings, such as the severity and extent of alveolar, bronchial, bronchiolar, tracheal, or nasal inflammation and/or inflammatory infiltrates, and evidence of alveolar edema. In addition, viral load was assessed in the lung. Immunogenicity was assessed in different species to show induction of neutralizing antibodies and a Th1-skewed immune response, factors that are thought to minimize the potential risk of VAERD. Also potentially non-respiratory

clinical signs were evaluated in the NHP and Syrian hamster challenge studies, such as body temperature and body weight loss, respectively, as additional parameters to monitor VAED.

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

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 (TOX14382). 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. 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 TOX14382 (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 (TOX14389) 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 (TOX14382) 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 TOX14389 (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.

Key Safety Findings	Relevance to Human Usage
Developmental toxicity	
In the EF-PPND toxicity study (TOX14389) 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 2020b). Upon transduction of a cell, the adenoviral DNA does not integrate into the host genome, but rather resides episomally in the host nucleus. Such episomal transduction reduces 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.

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.	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	
Immunogenicity assessments	The available nonclinical data do not indicate any risk related to possible VAERD in humans.
Ad26.COV2.S induced neutralizing antibody responses in all species tested (mice, rabbits, Syrian hamsters, and NHP). Immunization with Ad26.COV2.S consistently induced the Th1-associated cytokine IFN-γ in mice, rabbits, and NHP, and elicited a Th1-skewed immune response in mice and NHP. The Th1-skewing of cellular immune responses measured in NHP (Solforosi 2021) appears similar to clinical trial results in humans (Sadoff 2021).	
Histopathology assessment study NHP 20-09	
No evidence of VAED and VAERD was observed in the challenge study NHP 20-09 in rhesus monkeys, based on clinical observations (daily observations after virus inoculation), viral load, and the cumulative histopathology score or any individual score in animals dosed with Ad26.COV2.S compared with the non-vaccinated SARS-CoV-2-challenged control group. The following histopathological parameters were assessed: alveolar edema, inflammation, interstitial/septal thickening, mononuclear cell infiltrates in perivascular/peribronchiolar space, macrophage infiltrates in alveolar space, macrophage infiltrates in bronchiolar space, neutrophil infiltrates in alveoli, bronchioloalveolar hyperplasia, and bronchus-associated lymphoid tissue hyperplasia.	
Histopathology assessment study NHP 20-14	
No evidence of VAED and VAERD was observed in the challenge study NHP-20-14 in rhesus monkeys, assessing also lower dose levels of Ad26.COV2.S, based on clinical observations (daily observations after virus inoculation), viral load, and the cumulative histopathology score or any individual score in animals dosed with Ad26.COV2.S compared with the non-vaccinated SARS-CoV-2-challenged control group. Vaccination with Ad26.COV2.S at all dose levels, including the lower dose levels, was not associated with an increase in the severity of lung findings (no increase in lung scores) after SARS-CoV-2 challenge, even in animals with breakthrough infection when	

Key Safety Findings	Relevance to Human Usage
compared to non-vaccinated animals after challenge, indicating there was no histopathologic evidence of VAERD. The following histopathological parameters were assessed: alveolar edema, inflammation, interstitial/septal thickening, mononuclear cell infiltrates in perivascular/peribronchiolar space, macrophage infiltrates in alveolar space, macrophage infiltrates in bronchiolar space, neutrophil infiltrates in alveoli, bronchioloalveolar hyperplasia, and bronchus-associated lymphoid tissue hyperplasia.	
Histopathology assessment Syrian hamster study TKO707	
No evidence of VAED and VAERD was observed in the challenge study TKO707 in hamsters, based on clinical observations, viral load, and histopathology scores. The following histopathology parameters were assessed: alveolitis, alveolar damage, alveolar edema, alveolar hemorrhage, type II pneumocyte hyperplasia, bronchitis, bronchiolitis, peribronchial and perivascular cuffing, tracheitis, and rhinitis.	
Histopathology assessment Syrian hamster study TKO766	
No evidence of VAED and VAERD was observed in the challenge study TKO766 in hamsters, based on clinical observations, viral load, and histopathology scores. This study included lower dose levels of Ad26.COV2.S, which resulted in a suboptimal humoral immune response, allowing breakthrough SARS-CoV-2 replication in the lungs. The following histopathological parameters were assessed: extent of alveolitis/alveolar damage, thickening alveolar septa, alveolar hemorrhage, type II pneumocyte hyperplasia, bronchitis, bronchiolitis, peribronchial and perivascular cuffing, tracheitis, and rhinitis. In addition, no prominent eosinophilic infiltrates were observed in any of the hamster lungs after breakthrough SARS-CoV-2 replication.	

Summary of Nonclinical Safety Concerns

Important identified risks	None
Important potential risks	None
Missing information	None

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 ($1.25x10^{10}$ vp, $2.5x10^{10}$ vp, $5x10^{10}$ vp, and $1x10^{11}$ vp), vaccination schedules (1-dose or 2-dose primary regimens with or without a booster dose), and intervals between doses (1 to 3 months) are being or will be assessed.

The first-in-human Phase 1/2a trial COV1001 performs an initial evaluation of the safety and immunogenicity of Ad26.COV2.S. This trial assesses 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 is being conducted in Japan, in parallel with trial COV1001, to evaluate the safety and immunogenicity of Ad26.COV2.S in Japanese adults aged 20 to 55 years and ≥65 years.

A Phase 2a trial COV2001 in adults aged 18 to 55 years and ≥65 years evaluates 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) primary vaccination regimens, and safety and immunogenicity of 28-, 56-, and 84-day vaccination intervals for the 2-dose regimen ($5x10^{10}$ vp).

Two Phase 3 trials, COV3001 (ENSEMBLE) and COV3009 (ENSEMBLE-2) evaluate 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. Enrollment in trial COV3009 is currently still ongoing.

All clinical trials are randomized, placebo-controlled, and conducted in a double-blind fashion.

SIII.2. Clinical Trial Exposure

Data from the following 5 trials were used for characterization of exposure:

- 1 Phase 1/2a trial: COV1001 (group-unblinded data for Cohorts 1a, 1b, and 3; blinded data for Cohort 2)
- 1 Phase 1 trial: COV1002 (blinded data)
- 1 Phase 2a trial: COV2001 (adult cohort, blinded data)
- 2 Phase 3 trials: COV3001 (participant-unblinded data) and COV3009 (blinded data)

The primary adult pooling included exposure to Ad26.COV2.S at the selected dose level ($5x10^{10}$ vp), while the extended adult pooling included exposure to Ad26.COV2.S at any dose level (ie, $1.25x10^{10}$ vp, $2.5x10^{10}$ vp, $5x10^{10}$ vp, and $1x10^{11}$ vp), as detailed below.

For trial COV3001, the following data analysis sets were used for characterization of exposure and/or safety in this EU-RMP:

- Full Analysis Set (FAS): All randomized participants with a documented study vaccine administration, regardless of the occurrence of protocol deviations and serostatus at enrollment. The FAS included 21,895 participants who received Ad26.COV2.S and was used for characterization of exposure and safety.
- Safety Subset: Subset of the FAS for the analysis of solicited AEs (reactogenicity, recorded in e-Diary from the day of vaccination until 7 days after each vaccination) and unsolicited AEs (recorded in e-Diary from the day of vaccination until 28 days after each vaccination). The Safety Subset included 3,356 participants who received Ad26.COV2.S, and was used for characterization of reactogenicity.
- Per-protocol Set: Participants in the FAS who received study vaccine and who were seronegative at the time of vaccination, and who had no other major protocol deviations that were judged to possibly impact the efficacy of the vaccine. The Per-protocol Set was the main analysis population for efficacy analyses and included 19,630 participants who received Ad26.COV2.S.

Exposure in the Primary Adult Pooling

At the cut-off date of this EU-RMP (ie, 22 January 2021), a total of 53,873 participants are included in the primary adult pooling, of which 27,181 participants were enrolled to receive at least one dose of Ad26.COV2.S at the selected dose level ($5x10^{10}$ vp) (ie, 22,218 unblinded and 4,963 blinded participants). This could be either as a single-dose or as a 2-dose vaccination regimen with an interval between doses of at least 56 days. Data for the booster dose are not yet available and therefore not included. The exposure data are presented in separate columns for unblinded data (group-unblinded data from trial COV1001 Cohorts 1a, 1b, and 3, and participant-unblinded data from trial COV3001) and blinded data (trials COV1001 Cohort 2, COV1002, COV2001, and COV3009). For blinded data, exposure to Ad26.COV2.S and placebo is shown in separate columns, with the split based on the randomization ratio of the trial and the number of participants vaccinated.

Exposure to Ad26.COV2.S and matching placebo in the primary adult 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, participants with comorbidities associated with increased risk for severe COVID-19, and participants who are SARS-CoV-2 seropositive at baseline). Of note, no pregnant women were part of the primary adult pooling as they were excluded from all clinical trials at baseline. Any case of study vaccine exposure during pregnancy was however included in the Global Safety Database when reported during the trials.

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

	Ad26.COV2.S*	Placebo*	Blinded Ad26.COV2.S**	Blinded Placebo**	Total Ad26.COV2.S	Total
Number of doses administered, N	22373	22368	5184	4883	27557	54808
Participants receiving						
Dose 1	22218 (99.3%)	22051 (98.6%)	4963 (95.7%)	4641 (95.0%)	27181 (98.6%)	53873 (98.3%)
Dose 2	155 (0.7%)	317 (1.4%)	221 (4.3%)	242 (5.0%)	376 (1.4%)	935 (1.7%)

Ad26.COV2.S refers to the $5x10^{10}$ vp dose.
*Trials included are COV1001 (Cohorts 1a, 1b, and 3) and COV3001.
**For trials that are still blinded, data are shown in the blinded columns. The split is based on the randomization ratio. Trials included are COV1001 (Cohort 2), COV1002, COV2001, and COV3009.

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

	Ad26.COV2.S*	Placebo*	Blinded Ad26.COV2.S**	Blinded Placebo**	Total Ad26.COV2.S	Total
Age, N	22218	22051	4963	4641	27181	53873
Age group I						
18-59 years	14726 (66.3%)	14629 (66.3%)	3585 (72.2%)	3312 (71.4%)	18311 (67.4%)	36252 (67.3%)
≥60 years	7492 (33.7%)	7422 (33.7%)	1377 (27.7%)	1329 (28.6%)	8869 (32.6%)	17620 (32.7%)
Missing	0	0	1 (<0.1%)	0	1 (<0.1%)	1 (<0.1%)
Age group II						
18-64 years	17798 (80.1%)	17668 (80.1%)	4125 (83.1%)	3855 (83.1%)	21923 (80.7%)	43446 (80.6%)
≥65 years	4420 (19.9%)	4383 (19.9%)	837 (16.9%)	786 (16.9%)	5257 (19.3%)	10426 (19.4%)
Missing	0	0	1 (<0.1%)	0	1 (<0.1%)	1 (<0.1%)
Age group III						
18-74 years	21386 (96.3%)	21305 (96.6%)	4842 (97.6%)	4537 (97.8%)	26228 (96.5%)	52070 (96.7%)
≥75 years	832 (3.7%)	746 (3.4%)	120 (2.4%)	104 (2.2%)	952 (3.5%)	1802 (3.3%)
Missing	0	0	1 (<0.1%)	0	1 (<0.1%)	1 (<0.1%)

Ad26.COV2.S refers to the $5x10^{10}$ vp dose.
N= number of participants
*Trials included are COV1001 (Cohorts 1a, 1b, and 3) and COV3001.
**For trials that are still blinded, data are shown in the blinded columns. The split is based on the randomization ratio. Trials included are COV1001 (Cohort 2), COV1002, COV2001, and COV3009.

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

	Ad26.COV2.S*	Placebo*	Blinded Ad26.COV2.S**	Blinded Placebo**	Total Ad26.COV2.S	Total
Sex, N	22218	22051	4963	4641	27181	53873
Female	9980 (44.9%)	9987 (45.3%)	2291 (46.2%)	2140 (46.1%)	12271 (45.1%)	24398 (45.3%)
Male	12234 (55.1%)	12060 (54.7%)	2668 (53.8%)	2500 (53.9%)	14902 (54.8%)	29462 (54.7%)
Undifferentiated	2 (<0.1%)	4 (<0.1%)	3 (0.1%)	1 (<0.1%)	5 (<0.1%)	10 (<0.1%)
Unknown	2 (<0.1%)	0	0	0	2 (<0.1%)	2 (<0.1%)
Missing	0	0	1 (<0.1%)	0	1 (<0.1%)	1 (<0.1%)

Ad26.COV2.S refers to the $5x10^{10}$ vp dose.
N= number of participants
*Trials included are COV1001 (Cohorts 1a, 1b, and 3) and COV3001.
**For trials that are still blinded, data are shown in the blinded columns. The split is based on the randomization ratio. Trials included are COV1001 (Cohort 2), COV1002, COV2001, and COV3009.

[TRMPEX03-PEU.RTF] [VAC31518\Z_RMP\DBR_2021_02\RE_2021_02\PROD\TRMPEXEU.SAS] 04FEB2021, 12:45

Table SIII.4: Exposure to Study Vaccine by Race (Primary Adult Pooling)

	Ad26.COV2.S*	Placebo*	Blinded Ad26.COV2.S**	Blinded Placebo**	Total Ad26.COV2.S	Total
Race, N	22218	22051	4963	4641	27181	53873
American Indian or Alaska Native	2087 (9.4%)	2060 (9.3%)	117 (2.4%)	113 (2.4%)	2204 (8.1%)	4377 (8.1%)
Asian	748 (3.4%)	687 (3.1%)	245 (4.9%)	183 (3.9%)	993 (3.7%)	1863 (3.5%)
Black or African American	4256 (19.2%)	4273 (19.4%)	322 (6.5%)	317 (6.8%)	4578 (16.8%)	9168 (17.0%)
Native Hawaiian or other Pacific Islander	58 (0.3%)	48 (0.2%)	16 (0.3%)	11 (0.2%)	74 (0.3%)	133 (0.2%)
White	13165 (59.3%)	12989 (58.9%)	3907 (78.7%)	3698 (79.7%)	17072 (62.8%)	33759 (62.7%)
Multiple	1204 (5.4%)	1245 (5.6%)	32 (0.6%)	25 (0.5%)	1236 (4.5%)	2506 (4.7%)
Unknown	309 (1.4%)	318 (1.4%)	30 (0.6%)	26 (0.6%)	339 (1.2%)	683 (1.3%)
Not reported	390 (1.8%)	429 (1.9%)	53 (1.1%)	43 (0.9%)	443 (1.6%)	915 (1.7%)
Missing	1 (<0.1%)	2 (<0.1%)	241 (4.9%)	225 (4.8%)	242 (0.9%)	469 (0.9%)

Ad26.COV2.S refers to the $5x10^{10}$ vp dose.
N= number of participants
*Trials included are COV1001 (Cohorts 1a, 1b, and 3) and COV3001.
**For trials that are still blinded, data are shown in the blinded columns. The split is based on the randomization ratio. Trials included are COV1001 (Cohort 2), COV1002, COV2001, and COV3009.

[TRMPEX04-PEU.RTF] [VAC31518\Z_RMP\DBR_2021_02\RE_2021_02\PROD\TRMPEXEU.SAS] 04FEB2021, 12:45

Table SIII.5: Exposure to Study Vaccine by Ethnicity (Primary Adult Pooling)

	Ad26.COV2.S*	Placebo*	Blinded Ad26.COV2.S**	Blinded Placebo**	Total Ad26.COV2.S	Total
Ethnicity, N	22218	22051	4963	4641	27181	53873
Hispanic or Latino	9883 (44.5%)	9970 (45.2%)	488 (9.8%)	444 (9.6%)	10371 (38.2%)	20785 (38.6%)
Not Hispanic or Latino	11783 (53.0%)	11516 (52.2%)	4051 (81.6%)	3821 (82.3%)	15834 (58.3%)	31171 (57.9%)
Unknown	197 (0.9%)	200 (0.9%)	39 (0.8%)	40 (0.9%)	236 (0.9%)	476 (0.9%)
Not reported	354 (1.6%)	364 (1.7%)	144 (2.9%)	111 (2.4%)	498 (1.8%)	973 (1.8%)
Missing	1 (<0.1%)	1 (<0.1%)	241 (4.9%)	225 (4.8%)	242 (0.9%)	468 (0.9%)

Ad26.COV2.S refers to the $5x10^{10}$ vp dose.
N= number of participants
*Trials included are COV1001 (Cohorts 1a, 1b, and 3) and COV3001.
**For trials that are still blinded, data are shown in the blinded columns. The split is based on the randomization ratio. Trials included are COV1001 (Cohort 2), COV1002, COV2001, and COV3009.

[TRMPEX05-PEU.RTF] [VAC31518\Z_RMP\DBR_2021_02\RE_2021_02\PROD\TRMPEXEU.SAS] 04FEB2021, 12:45

Table SIII.6: Exposure to Study Vaccine by Special Populations (Primary Adult Pooling)

	Ad26.COV2.S*	Placebo*	Blinded Ad26.COV2.S**	Blinded Placebo**	Total Ad26.COV2.S	Total
HIV infection, N	22218	22051	4963	4641	27181	53873
Yes	601 (2.7%)	617 (2.8%)	45 (0.9%)	41 (0.9%)	646 (2.4%)	1304 (2.4%)
No	8335 (37.5%)	8305 (37.7%)	1312 (26.4%)	1306 (28.1%)	9647 (35.5%)	19258 (35.7%)
Missing	13282 (59.8%)	13129 (59.5%)	3606 (72.7%)	3294 (71.0%)	16888 (62.1%)	33311 (61.8%)
Breastfeeding women, N	3867	3866	1232	1140	5099	10105
Yes	128 (3.3%)	157 (4.1%)	15 (1.2%)	16 (1.4%)	143 (2.8%)	316 (3.1%)
No	3543 (91.6%)	3532 (91.4%)	855 (69.4%)	873 (76.6%)	4398 (86.3%)	8803 (87.1%)
Missing	196 (5.1%)	177 (4.6%)	362 (29.4%)	251 (22.0%)	558 (10.9%)	986 (9.8%)
Comorbidities with increased risk for severe COVID-19, N	22218	22051	4963	4641	27181	53873
Yes	8936 (40.2%)	8922 (40.5%)	1159 (23.4%)	1156 (24.9%)	10095 (37.1%)	20173 (37.4%)
No	12959 (58.3%)	12966 (58.8%)	3284 (66.2%)	3297 (71.0%)	16243 (59.8%)	32506 (60.3%)
Missing	323 (1.5%)	163 (0.7%)	520 (10.5%)	188 (4.1%)	843 (3.1%)	1194 (2.2%)
SARS-CoV-2 seropositive at baseline, N	22218	22051	4963	4641	27181	53873
Yes	2155 (9.7%)	2069 (9.4%)	186 (3.7%)	171 (3.7%)	2341 (8.6%)	4581 (8.5%)
No	19423 (87.4%)	19351 (87.8%)	2425 (48.9%)	2197 (47.3%)	21848 (80.4%)	43396 (80.6%)
Missing	640 (2.9%)	631 (2.9%)	2352 (47.4%)	2273 (49.0%)	2992 (11.0%)	5896 (10.9%)

Ad26.COV2.S refers to the $5x10^{10}$ vp dose.
N= number of participants
*Trials included are COV1001 (Cohorts 1a, 1b, and 3) and COV3001.
**For trials that are still blinded, data are shown in the blinded columns. The split is based on the randomization ratio. Trials included are COV1001 (Cohort 2), COV1002, COV2001, and COV3009.

[TRMPEX07-PEU.RTF] [VAC31518\Z_RMP\DBR_2021_02\RE_2021_02\PROD\TRMPEXPOPEU.SAS] 04FEB2021, 12:48

Exposure in the Extended Adult Pooling

At the cut-off date of this EU-RMP (ie, 22 January 2021), a total of 54,586 participants are included in the extended adult pooling, of which 22,537 participants (who are currently unblinded) were enrolled to receive a single-dose or 2-dose vaccination regimen (irrespective of interval between doses) with Ad26.COV2.S at the selected dose level (ie, $5x10^{10}$ vp, 22,218 participants), or at other dose levels (ie, no participants receiving $1.25x10^{10}$ vp or $2.5x10^{10}$ vp, and 319 participants receiving $1x10^{11}$ vp). The exposure data are presented in separate columns for Ad26.COV2.S and placebo for group-unblinded data from trial COV1001 (Cohorts 1a, 1b, and 3) and participant-unblinded data from trial COV3001. For blinded data from trials COV1001 (Cohort 2), COV1002, COV2001, and COV3009, exposure to Ad26.COV2.S and placebo are shown together in a single column. As the 2 lower dose levels were only used in COV2001, which is still blinded, the exposure numbers to these dose levels are included in the "blinded" column and the dose level columns for $1.25x10^{10}$ vp or $2.5x10^{10}$ vp are therefore empty.

Exposure to Ad26.COV2.S and matching placebo in the extended adult pooling is summarized in Tables SIII.7 through SIII.12 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, participants with comorbidities associated with increased risk for severe COVID-19, and participants who are SARS-CoV-2 seropositive at baseline). Of note, no pregnant women were part of the extended adult pooling as they were excluded from all clinical trials at baseline. Any case of study vaccine exposure during pregnancy was however included in the Global Safety Database when reported during the trials.

Table SIII.7: Exposure to Study Vaccine by Dose (Extended Adult Pooling)

	Ad26 1.25e10	Ad26 2.5e10	Ad26 5e10*	Ad26 1e11**	Placebo*	Blinded***	Total
Number of doses administered, N	-	-	22373	478	22518	10813	56182
Participants receiving							
Dose 1	-	-	22218 (99.3%)	319 (66.7%)	22051 (97.9%)	9998 (92.5%)	54586 (97.2%)
Dose 2	-	-	155 (0.7%)	159 (33.3%)	467 (2.1%)	815 (7.5%)	1596 (2.8%)

Ad26 1.25e10: Ad26.COV2.S ($1.25x10^{10}$ vp); Ad26 2.5e10: Ad26.COV2.S ($2.5 x10^{10}$ vp); Ad26 5e10: Ad26.COV2.S ($5x10^{10}$ vp); Ad26 1e11: Ad26.COV2.S ($1x10^{11}$ vp).
*Trials included are COV1001 (Cohorts 1a, 1b, and 3) and COV3001.
**Trial included is COV1001 (Cohorts 1a, 1b, and 3).
***For trials that are still blinded, data are shown in the blinded column (active and placebo combined). Trials included are COV1001 (Cohort 2), COV1002, COV2001, and COV3009.

[TRMPEX01-EEU.RTF] [VAC31518\Z_RMP\DBR_2021_02\RE_2021_02\PROD\TRMPEXEU.SAS] 04FEB2021, 12:45

Table SIII.8: Exposure to Study Vaccine by Age (Extended Adult Pooling)

	Ad26 1.25e10	Ad26 2.5e10	Ad26 5e10*	Ad26 1e11**	Placebo*	Blinded***	Total
Age, N	-	-	22218	319	22051	9998	54586
Age group I							
18-59 years	-	-	14726 (66.3%)	158 (49.5%)	14629 (66.3%)	7132 (71.3%)	36645 (67.1%)
≥60 years	-	-	7492 (33.7%)	161 (50.5%)	7422 (33.7%)	2865 (28.7%)	17940 (32.9%)
Missing	-	-	0	0	0	1 (<0.1%)	1 (<0.1%)
Age group II							
18-64 years	-	-	17798 (80.1%)	158 (49.5%)	17668 (80.1%)	8215 (82.2%)	43839 (80.3%)
≥65 years	-	-	4420 (19.9%)	161 (50.5%)	4383 (19.9%)	1782 (17.8%)	10746 (19.7%)
Missing	-	-	0	0	0	1 (<0.1%)	1 (<0.1%)
Age group III							
18-74 years	-	-	21386 (96.3%)	299 (93.7%)	21305 (96.6%)	9747 (97.5%)	52737 (96.6%)
≥75 years	-	-	832 (3.7%)	20 (6.3%)	746 (3.4%)	250 (2.5%)	1848 (3.4%)
Missing	-	-	0	0	0	1 (<0.1%)	1 (<0.1%)

Ad26 1.25e10: Ad26.COV2.S ($1.25x10^{10}$ vp); Ad26 2.5e10: Ad26.COV2.S ($2.5 x10^{10}$ vp); Ad26 5e10: Ad26.COV2.S ($5x10^{10}$ vp); Ad26 1e11: Ad26.COV2.S ($1x10^{11}$ vp).
N= number of participants
*Trials included are COV1001 (Cohorts 1a, 1b, and 3) and COV3001.
**Trial included is COV1001 (Cohorts 1a, 1b, and 3).
***For trials that are still blinded, data are shown in the blinded column (active and placebo combined). Trials included are COV1001 (Cohort 2), COV1002, COV2001, and COV3009.

[TRMPEX02-EEU.RTF] [VAC31518\Z_RMP\DBR_2021_02\RE_2021_02\PROD\TRMPEXEU.SAS] 04FEB2021, 12:45

Table SIII.9: Exposure to Study Vaccine by Sex (Extended Adult Pooling)

	Ad26 1.25e10	Ad26 2.5e10	Ad26 5e10*	Ad26 1e11**	Placebo*	Blinded***	Total
Sex, N	-	-	22218	319	22051	9998	54586
Female	-	-	9980 (44.9%)	168 (52.7%)	9987 (45.3%)	4586 (45.9%)	24721 (45.3%)
Male	-	-	12234 (55.1%)	151 (47.3%)	12060 (54.7%)	5407 (54.1%)	29852 (54.7%)
Undifferentiated	-	-	2 (<0.1%)	0	4 (<0.1%)	4 (<0.1%)	10 (<0.1%)
Unknown	-	-	2 (<0.1%)	0	0	0	2 (<0.1%)
Missing	-	-	0	0	0	1 (<0.1%)	1 (<0.1%)

Ad26 1.25e10: Ad26.COV2.S ($1.25x10^{10}$ vp); Ad26 2.5e10: Ad26.COV2.S ($2.5 x10^{10}$ vp); Ad26 5e10: Ad26.COV2.S ($5x10^{10}$ vp); Ad26 1e11: Ad26.COV2.S ($1x10^{11}$ vp).
N= number of participants
*Trials included are COV1001 (Cohorts 1a, 1b, and 3) and COV3001.
**Trial included is COV1001 (Cohorts 1a, 1b, and 3).
***For trials that are still blinded, data are shown in the blinded column (active and placebo combined). Trials included are COV1001 (Cohort 2), COV1002, COV2001, and COV3009.

[TRMPEX03-EEU.RTF] [VAC31518\Z_RMP\DBR_2021_02\RE_2021_02\PROD\TRMPEXEU.SAS] 04FEB2021, 12:45

Table SIII.10: Exposure to Study Vaccine by Race (Extended Adult Pooling)

	Ad26 1.25e10	Ad26 2.5e10	Ad26 5e10*	Ad26 1e11**	Placebo*	Blinded***	Total
Race, N	-	-	22218	319	22051	9998	54586
American Indian or Alaska Native	-	-	2087 (9.4%)	0	2060 (9.3%)	230 (2.3%)	4377 (8.0%)
Asian	-	-	748 (3.4%)	5 (1.6%)	687 (3.1%)	531 (5.3%)	1971 (3.6%)
Black or African American	-	-	4256 (19.2%)	9 (2.8%)	4273 (19.4%)	640 (6.4%)	9178 (16.8%)
Native Hawaiian or other Pacific Islander	-	-	58 (0.3%)	0	48 (0.2%)	27 (0.3%)	133 (0.2%)
White	-	-	13165 (59.3%)	303 (95.0%)	12989 (58.9%)	7893 (78.9%)	34350 (62.9%)
Multiple	-	-	1204 (5.4%)	1 (0.3%)	1245 (5.6%)	57 (0.6%)	2507 (4.6%)
Unknown	-	-	309 (1.4%)	0	318 (1.4%)	57 (0.6%)	684 (1.3%)
Not reported	-	-	390 (1.8%)	1 (0.3%)	429 (1.9%)	97 (1.0%)	917 (1.7%)
Missing	-	-	1 (<0.1%)	0	2 (<0.1%)	466 (4.7%)	469 (0.9%)

Ad26 1.25e10: Ad26.COV2.S ($1.25x10^{10}$ vp); Ad26 2.5e10: Ad26.COV2.S ($2.5 x10^{10}$ vp); Ad26 5e10: Ad26.COV2.S ($5x10^{10}$ vp); Ad26 1e11: Ad26.COV2.S ($1x10^{11}$ vp).
N= number of participants
*Trials included are COV1001 (Cohorts 1a, 1b, and 3) and COV3001.
**Trial included is COV1001 (Cohorts 1a, 1b, and 3).
***For trials that are still blinded, data are shown in the blinded column (active and placebo combined). Trials included are COV1001 (Cohort 2), COV1002, COV2001, and COV3009.

[TRMPEX04-EEU.RTF] [VAC31518\Z_RMP\DBR_2021_02\RE_2021_02\PROD\TRMPEXEU.SAS] 04FEB2021, 12:45

Table SIII.11: Exposure to Study Vaccine by Ethnicity (Extended Adult Pooling)

	Ad26 1.25e10	Ad26 2.5e10	Ad26 5e10*	Ad26 1e11**	Placebo*	Blinded***	Total
Ethnicity, N	-	-	22218	319	22051	9998	54586
Hispanic or Latino	-	-	9883 (44.5%)	7 (2.2%)	9970 (45.2%)	1010 (10.1%)	20870 (38.2%)
Not Hispanic or Latino	-	-	11783 (53.0%)	312 (97.8%)	11516 (52.2%)	8173 (81.7%)	31784 (58.2%)
Unknown	-	-	197 (0.9%)	0	200 (0.9%)	79 (0.8%)	476 (0.9%)
Not reported	-	-	354 (1.6%)	0	364 (1.7%)	270 (2.7%)	988 (1.8%)
Missing	-	-	1 (<0.1%)	0	1 (<0.1%)	466 (4.7%)	468 (0.9%)

Ad26 1.25e10: Ad26.COV2.S ($1.25x10^{10}$ vp); Ad26 2.5e10: Ad26.COV2.S ($2.5 x10^{10}$ vp); Ad26 5e10: Ad26.COV2.S ($5x10^{10}$ vp); Ad26 1e11: Ad26.COV2.S ($1x10^{11}$ vp).
N= number of participants
*Trials included are COV1001 (Cohorts 1a, 1b, and 3) and COV3001.
**Trial included is COV1001 (Cohorts 1a, 1b, and 3).
***For trials that are still blinded, data are shown in the blinded column (active and placebo combined). Trials included are COV1001 (Cohort 2), COV1002, COV2001, and COV3009.

[TRMPEX05-EEU.RTF] [VAC31518\Z_RMP\DBR_2021_02\RE_2021_02\PROD\TRMPEXEU.SAS] 04FEB2021, 12:45

Table SIII.12: Exposure to Study Vaccine by Special Populations (Extended Adult Pooling)

	Ad26 1.25e10	Ad26 2.5e10	Ad26 5e10*	Ad26 1e11**	Placebo*	Blinded***	Total
HIV infection, N	-	-	22218	319	22051	9998	54586
Yes	-	-	601 (2.7%)	0	617 (2.8%)	86 (0.9%)	1304 (2.4%)
No	-	-	8335 (37.5%)	0	8305 (37.7%)	2618 (26.2%)	19258 (35.3%)
Missing	-	-	13282 (59.8%)	319 (100.0%)	13129 (59.5%)	7294 (73.0%)	34024 (62.3%)
Breastfeeding women, N	-	-	3867	73	3866	2453	10259
Yes	-	-	128 (3.3%)	0	157 (4.1%)	31 (1.3%)	316 (3.1%)
No	-	-	3543 (91.6%)	0	3532 (91.4%)	1728 (70.4%)	8803 (85.8%)
Missing	-	-	196 (5.1%)	73 (100.0%)	177 (4.6%)	694 (28.3%)	1140 (11.1%)
Comorbidities with increased risk for severe COVID-19, N	-	-	22218	319	22051	9998	54586
Yes	-	-	8936 (40.2%)	0	8922 (40.5%)	2315 (23.2%)	20173 (37.0%)
No	-	-	12959 (58.3%)	0	12966 (58.8%)	6581 (65.8%)	32506 (59.6%)
Missing	-	-	323 (1.5%)	319 (100.0%)	163 (0.7%)	1102 (11.0%)	1907 (3.5%)
SARS-CoV-2 seropositive at baseline, N	-	-	22218	319	22051	9998	54586
Yes	-	-	2155 (9.7%)	4 (1.3%)	2069 (9.4%)	357 (3.6%)	4585 (8.4%)
No	-	-	19423 (87.4%)	315 (98.7%)	19351 (87.8%)	4622 (46.2%)	43711 (80.1%)
Missing	-	-	640 (2.9%)	0	631 (2.9%)	5019 (50.2%)	6290 (11.5%)

Ad26 1.25e10: Ad26.COV2.S ($1.25x10^{10}$ vp); Ad26 2.5e10: Ad26.COV2.S ($2.5 x10^{10}$ vp); Ad26 5e10: Ad26.COV2.S ($5x10^{10}$ vp); Ad26 1e11: Ad26.COV2.S ($1x10^{11}$ vp).
N= number of participants
*Trials included are COV1001 (Cohorts 1a, 1b, and 3) and COV3001.
**Trial included is COV1001 (Cohorts 1a, 1b, and 3).
***For trials that are still blinded, data are shown in the blinded column (active and placebo combined). Trials included are COV1001 (Cohort 2), COV1002, COV2001, and COV3009.

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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

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)	Anaphylaxis is an important identified risk. 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 Ad26.COV2.S 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.

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[1]), 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:	Yes
Rationale (if not included as missing information)	Not applicable

[1] 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.

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.

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.

At the time of the primary analysis of trial COV3001, the median follow-up after vaccination was 58 days and 21,491 participants in the Per-protocol Set had at least 2 months (8 weeks) of follow-up (of which 10,715 received Ad26.COV2.S).

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

Table SIV.1: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Pregnant women were not eligible for enrollment in the clinical development program, and therefore not part of the clinical database. However, up to the cut-off date of 31 December 2020, 8 pregnancies **(4 in the Ad26.COV2.S group and 4 in the Placebo group)** were reported in the Global Safety Database for trial COV3001. No additional pregnancies were reported between 31 December 2020 and 22 January 2021 (COV3001 CSR Feb 2021).
Breastfeeding women	To date, 128 breastfeeding women have received Ad26.COV2.S in trial COV3001.
Pediatric population	Individuals aged <18 years were excluded from Phase 1 trials and currently ongoing Phase 3 trials. The use in pediatrics is not in scope of the indication.
Elderly	Of the 27,181 participants in the primary adult pooling who received at least one dose of Ad26.COV2.S (blinded and unblinded data), 8,869 (32.6%) participants were aged ≥60 years, 5,257 (19.3%) participants were aged ≥65 years, and 952 (3.5%) participants were aged ≥75 years. Of the 21,895 participants in the FAS of trial COV3001 who received Ad26.COV2.S, 5,224 (23.9%) participants were aged 60 to 69 years, 1,893 (8.6%) were aged 70 to 79 years, and 214 (1.0%) were aged ≥80 years (COV3001 CSR Feb 2021). Refer to Module SIII.2 for more detailed exposure data.
Individuals with a disease severity different from inclusion criteria in clinical trials	Not applicable
Population with relevant different ethnic origin	Of the 27,181 participants in the primary adult pooling who received at least one dose of Ad26.COV2.S (blinded and unblinded data), 17,072 (62.8%) participants were white, 4,578 (16.8%) were black or African American, 2,204 (8.1%) were American Indian or Alaska Native (who were mainly enrolled in Latin America), 1,236 (4.5%) were of multiple race, 993 (3.7%) were Asian, and 74 (0.3%) were Native Hawaiian or other Pacific Islander. Overall, 10,371 (38.2%) participants were Hispanic or Latino. Refer to Module SIII.2 for more detailed exposure data.

Type of Special Population	Exposure
Subpopulations carrying relevant genetic polymorphisms	Not applicable
Patients with relevant comorbidities:	
• Immunocompromised individuals	Of the 21,895 participants in the FAS of trial COV3001 who received Ad26.COV2.S, 601 (2.7%) participants had a stable/well-controlled HIV infection. Participants with other immunodeficiencies were included at very low numbers, precluding the provision of meaningful data (COV3001 CSR Feb 2021). In trial COV3009 (blinded data), 45 (0.9%) participants who received at least one dose of Ad26.COV2.S had a stable/well-controlled HIV infection.
• Individuals with comorbidities associated with increased risk for severe COVID-19	Of the 21,895 participants in the FAS of trial COV3001 who received Ad26.COV2.S, 8,936 (40.8%) participants had one or more comorbidities associated with increased risk for severe COVID-19, 6,339 (29.0%) had 1 comorbidity, 1,910 (8.7%) had 2 comorbidities, and 687 (3.1%) had 3 or more comorbidities (COV3001 CSR Feb 2021). In trial COV3009 (blinded data), 1,159 (23.4%) participants who received at least one dose of Ad26.COV2.S had a comorbidity associated with 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) could be enrolled in Phase 3 trials COV3001 (Stages 1b and 2b) and COV3009 (Stage 2) at the discretion of the investigator. However, these participants were included at very low numbers, precluding the provision of meaningful data.
• 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, but these data are not available as part of the primary analysis of this trial.
• Individuals who are SARS-CoV-2 seropositive at baseline	Of the 21,895 participants in the FAS of trial COV3001 who received Ad26.COV2.S, 2,151 (9.8%) participants were SARS-CoV-2 seropositive at baseline (COV3001 CSR Feb 2021). In trial COV3009 (blinded data), 186 (3.7%) participants who received at least one dose of Ad26.COV2.S were SARS-CoV-2 seropositive at baseline.

Rationale for not considering special populations as safety concerns

Use in pediatrics

Although children appear to be at lower risk of developing severe COVID-19 and death is rare, children can develop serious complications such as multisystem inflammatory syndrome. Children with underlying conditions and those with immune deficiency or who are immunocompromised

are at higher risk for severe disease. Also, studies suggest that children are likely to be important vectors of community spread and have higher levels of viral shedding than adults. The availability of a SARS-CoV-2 vaccine for the pediatric population is therefore warranted.

Children and adolescents aged <18 years were excluded from Phase 1 and currently ongoing Phase 3 trials. The safety and efficacy of Ad26.COV2.S in children and adolescents (<18 years of age) have not yet been established.

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 adult pooling included 8,869 (32.6%) participants aged ≥60 years, 5,257 (19.3%) participants aged ≥65 years, and 952 (3.5%) participants aged ≥75 years who received Ad26.COV2.S.

Of the 3,356 participants in the Safety Subset of trial COV3001 who received Ad26.COV2.S, 1,320 (39.3%) were aged ≥60 years, 763 (22.7%) were aged ≥65 years, and 150 (4.5%) were aged ≥75 years. In addition, 923 (27.5%) participants were aged 60 to 69 years, 357 (10.6%) were aged 70 to 79 years, and 40 (1.2%) were aged ≥80 years (COV3001 CSR Feb 2021).

In trial COV3001, no overall differences in safety or efficacy were observed between older adults aged ≥65 years and ≥75 years, and younger adults (aged ≥18 to <65 years).

Based on the Safety Subset of trial COV3001, the overall frequency of solicited local and systemic AEs in the Ad26.COV2.S group was lower in participants aged ≥65 years (49.9%) and ≥75 years (45.3%) compared to participants aged ≥18 to <65 years (70.8%). In general, this lower frequency in participants aged ≥65 years and ≥75 years was reported for all selected solicited local and systemic AEs (COV3001 CSR Feb 2021).

Of the 4,259 participants in the FAS of trial COV3001 aged ≥65 years who received Ad26.COV2.S, SAEs were reported in 30 (0.7%) participants, of which 1 was considered related to the study vaccine by the investigator. Of the 809 participants aged ≥75 years who received Ad26.COV2.S, SAEs were reported in 4 (0.5%) participants, of which none were considered related to the study vaccine by the investigator. The frequency of reported SAEs was similar in the Ad26.COV2.S and placebo groups.

The potential benefit of receiving Ad26.COV2.S in elderly populations outweighs the risks. This age group is one of the primary targets for the early stages of vaccination worldwide. Based on the number of elderly participants and the primary analysis results of trial COV3001, 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 not excluded from trials 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.

In trial COV3009 (blinded data), 1,159 (23.4%) participants who received at least one dose of Ad26.COV2.S had one or more comorbidities associated with increased risk for severe COVID-19.

In trial COV3001, 8,936 (40.8%) participants in the FAS and 1,135 (33.8%) participants in the Safety Subset who received Ad26.COV2.S had one or more comorbidities associated with increased risk for severe COVID-19. Of the 21,895 participants in the FAS receiving Ad26.COV2.S, 6,339 (29.0%) had 1 comorbidity, 1,910 (8.7%) had 2 comorbidities, and 687 (3.1%) had 3 or more comorbidities (COV3001 CSR Feb 2021).

In trial COV3001, the vaccine was efficacious against moderate to severe/critical COVID-19 in participants with and without comorbidities (see Annex 7.5 for case definition). Note that since the number of participants was lower in the subgroup with comorbidities, there was a reduced person-years of follow-up time for case accrual (COV3001 CSR Feb 2021).

In the Safety Subset of trial COV3001, in general, no clinically relevant differences in the frequency of solicited local and systemic 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 with a lower frequency in participants with one or more comorbidities (40.9%) compared to participants without comorbidities (52.7%). In general, a similar frequency for all other selected solicited local AEs was reported in participants with and without comorbidities (COV3001 CSR Feb 2021).

In the FAS of trial COV3001, SAEs were reported in 40 (0.4%) out of 8,936 participants who received Ad26.COV2.S and had one or more comorbidities, of which 4 participants reported a total of 4 SAEs which 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.

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.

In trial COV3009 (blinded data), 186 (3.7%) participants who received at least one dose of Ad26.COV2.S were SARS-CoV-2 seropositive at baseline.

In trial COV3001, 2,151 (9.8%) participants in the FAS and 154 (4.6%) participants in the Safety Subset who received Ad26.COV2.S were SARS-CoV-2 seropositive at baseline (COV3001 CSR Feb 2021).

In the Safety Subset of trial COV3001, 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 seronegative at baseline compared to participants who were SARS-CoV-2 seropositive at baseline.

In the FAS of trial COV3001, SAEs were reported in 8 (0.4%) out of 2,151 participants who received Ad26.COV2.S and were SARS-CoV-2 seropositive at baseline, of which 1 participant reported 1 SAE of Type IV hypersensitivity which was 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.

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)
Interaction with other vaccines
Long-term safety

PART II: SAFETY SPECIFICATION

Module SV: Post-authorisation Experience

SV.1. Post-authorisation Exposure

Up to the data lock point of this EU-RMP, Ad26.COV2.S had not been marketed in any country in the European Union/EEA. No participants had been dosed with the vaccine outside of a clinical trial setting, so no post-authorisation experience is available. Of note, FDA issued an emergency use authorisation in the United States on 27 February 2021, after the data lock point of this EU-RMP.

SV.1.1. Method used to Calculate Exposure

Not applicable.

SV.1.2. Exposure

Not applicable.

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.

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

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)

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. 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).

Adverse Reactions Reported Following Vaccination with Ad26.COV2.S

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.

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 7.7. 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).

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 postvaccination 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.

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 and RSV, have been associated with exacerbations of both asthma and COPD (Duffy 2017, Lotz 2013). 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.

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.

Currently, the Applicant considers 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.

List of AESIs

There were no pre-specified AESIs for Ad26.COV2.S clinical development. The Applicant 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.

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 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.

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. To date, 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.
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.

Safety Concerns for Inclusion in the RMP	Risk-Benefit Impact
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, for 1 year in study COV4003, and for 2 years in study 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

Not applicable.

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

Important identified risks

1. Anaphylaxis

Important potential risks

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

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. Interaction with other vaccines
6. Long-term safety

MedDRA version 23.1 was used to classify the clinical trials AE information that is summarized in this Section.

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

Important Identified Risk: Anaphylaxis

Potential Mechanisms:

Anaphylaxis is an acute hypersensitivity reaction with multi-organ-system involvement that can present as, or rapidly progress to, a severe life-threatening reaction. Anaphylaxis is triggered by the binding of allergens to specific IgE. It implies previous exposure and sensitization to the triggering substance or a cross-reactive allergen. When an allergen binds to the IgE receptors on the surface of mast cells and basophils, this results in cellular activation and degranulation. These cells release preformed mediators such as histamine and tryptase that elicit the signs and symptoms of anaphylaxis. This mechanism is also known as the Type 1 immediate hypersensitivity reaction in the Gel and Coombs classification (Rüggeberg 2007).

"Anaphylactoid" reactions are clinically indistinguishable, but differ from anaphylaxis by their immune mechanism, being characterized by mast cell activation due to a range of chemical or physical triggers independently of IgE. This mechanism is less well understood (Rüggeberg 2007).

Evidence Source(s) and Strength of Evidence:

Allergic reactions, including possibly severe reactions (eg, hypersensitivity reactions and anaphylaxis), are known to occur with any injectable vaccine. Ad26.COV2.S contains ingredients with known potential to cause allergic reactions, including polysorbate 80. The structure of polysorbate 80 presents similarities with polyethylene glycol, recently suspected to be involved in anaphylactic reactions with mRNA vaccines. The potential for polysorbate 80 to trigger hypersensitivity and the possibility of cross-reactivity between polyethylene glycol and polysorbate 80 have been discussed in the literature (Stone 2019, Worm 2021). Cases of polysorbate 80-induced hypersensitivity have been reported and have involved different drugs, including a human papillomavirus vaccine (Badiu 2012), and different routes of administration, including the IM route.

After the data lock point of this EU-RMP, severe allergic reactions and one case of anaphylaxis have been identified following vaccination with Ad26.COV2.S. All of these events occurred in the

context of an open-label study COV3012[2] in South Africa. Anaphylaxis is an adverse drug reaction described in the SmPC.

Characterization of the Risk:

In general, hypersensitivity reactions are a rare occurrence with Ad26-based vaccines. Only one case of anaphylaxis (ie, meeting the Brighton Collaboration criteria) has been reported to date.

In trial COV3001, the most frequently reported AEs within the broad SMQ 'non-anaphylactic allergic reactions' (≥6 participants in the Ad26.COV2.S group) were rash (24 Ad26.COV2.S, 16 placebo), urticaria (8 Ad26.COV2.S, 3 placebo), and hypersensitivity (6 Ad26.COV2.S, 4 placebo). Events of urticaria and rash were considered as likely related to the vaccine. Further assessment of the events under the PT 'hypersensitivity' showed most of these events to be either seasonal allergies or allergy to a medication other than the vaccine. The AEs within the broad SMQ 'anaphylactic reaction' were infrequent (≤0.1%) in both the Ad26.COV2.S group and placebo group. A total of 15 participants in the Ad26.COV2.S group and 8 participants in the placebo group developed an AE within the aforementioned SMQ. However, upon further evaluation, all reported events correspond to the broad definition, with none of the events meeting the Brighton Collaboration criteria for anaphylaxis. There were no severe allergic reactions with close temporal relation to the vaccine. One SAE of Type IV hypersensitivity with onset 2 days after vaccination with Ad26.COV2.S was reported, not meeting the Brighton Collaboration criteria for anaphylaxis. The event was considered likely related to the study vaccine by the investigator and Janssen due to close temporal association.

After the data lock point of this EU-RMP, the Applicant received reports of severe allergic reactions, including one non-fatal case of anaphylaxis (Brighton Collaboration criteria level 2 of diagnostic certainty), following administration of Ad26.COV2.S in over 75,000 participants in study COV3012. The case was considered related to the study vaccine by the investigator and Janssen given biological and temporal plausibility.

Severe allergic reactions (anaphylaxis) have not been identified as a safety issue in the broader safety dataset for other Ad26-based vaccines developed by Janssen. In the over 193,000 participants who have been administered other Ad26-based vaccines, one SAE of anaphylaxis and one SAE of hypersensitivity have been reported (vaccination with Ad26.ZEBOV and Ad26.Mos.HIV, respectively). However, the 'anaphylaxis' case does not meet Brighton Collaboration criteria for anaphylaxis, and due to the symptoms and time to onset, is considered to be a case of vasovagal reaction (syncope) due to vaccination. The event of hypersensitivity was not witnessed by the principal investigator and contained multiple confounders that precluded an objective assessment of the report.

[2] Open-label Phase 3b implementation study to monitor the effectiveness of Ad26.COV2.S among healthcare workers in South Africa, which is sponsored by the South African Medical Research Council and conducted in collaboration with the Applicant.

Risk Factors and Risk Groups:

Participants with a known history of hypersensitivity to any component of the vaccine may be at risk for hypersensitivity reactions.

Preventability:

The SmPC Section 4.3 states that Ad26.COV2.S is contraindicated in individuals with hypersensitivity to the active substance or to any of the excipients. Section 4.4 states that 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.

Impact on the Risk-Benefit Balance of the Product:

Anaphylactic reaction is a potentially life-threatening event requiring medical intervention.

Public Health Impact:

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

Hypersensitivity reactions (serious and non-serious) were found to be rare during Ad26.COV2.S clinical development. Only one case of anaphylaxis (ie, meeting the Brighton Collaboration criteria) has been reported to date. It is unknown how many cases of anaphylaxis will be observed in the postmarketing setting but it is anticipated to be very rare.

Annex 1 MedDRA Term:

SMQ (narrow) Anaphylactic reaction

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. 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.

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 (Chin 1969, Fulginiti 1969, Kapikian 1969, Kim 1969). Subsequently, reports of VAED were reported in individuals without prior exposure to Dengue who received tetravalent Dengue vaccines (Su 2020). Nonclinical experience with SARS-CoV- and MERS-CoV-based vaccines (Agrawal 2016, Bolles 2011, Deming 2006, Honda-okubo 2015, Houser 2017) also indicated a risk for VAERD, however, this risk could not be confirmed in humans due to the lack of efficacy studies. To date there is no published evidence of VAED in nonclinical studies with IM SARS-CoV-2 vaccines. Furthermore, clinical trials with SARS-CoV-2 vaccines based on technologies other than the Ad26-vector platform, including the large-scale Phase 3 trials that are currently ongoing, have so far not reported any VAED either (Baden 2021, Polack 2020, Voysey 2021).

The observed VAERD in nonclinical studies with SARS-CoV- and MERS-CoV-based vaccines were attributed to induction of a Th2-skewed immune response. A Th1-skewed immune response as well as the induction of high levels of neutralizing antibodies is considered desirable to prevent predisposition to enhanced respiratory disease as observed for RSV vaccines. It has been demonstrated in clinical trials that Ad26-based vaccines do induce humoral and strong cellular responses with a clear Th1 skewing (Anywaine 2019, Barouch 2018, Colby 2020, Milligan 2016, Mutua 2019, Stephenson 2020, Williams 2020). This type 1 skewing of the immune response is considered to minimize the risk of enhanced disease after SARS-CoV-2 infection.

Studies in Ad26.COV2.S-immunized Syrian hamsters and NHP conducted by the Applicant 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:

The interim immunogenicity analysis of trial COV1001 clearly indicates that Ad26.COV2.S is able to elicit a cellular response with Th1-skewed CD4 response as well as to induce a high level of neutralizing antibodies, indicative of a low risk for VAED, including VAERD.

In trial COV3001, continuous monitoring for VAED, including VAERD was performed through an external Statistical Support Group to look at each of the diagnosed FAS COVID-19 events. Vaccine harm monitoring was performed for severe/critical COVID-19/death endpoints, and more specifically, a higher rate of severe/critical disease or death in the vaccine group compared to placebo. Events were monitored in real-time starting at the 5th event and at each additional event, until the efficacy analysis was triggered, to assess if a pre-specified stopping boundary was reached. The stopping boundary has not been met at any time from study onset through the primary analysis. In addition, VE of Ad26.COV2.S against confirmed severe/critical COVID-19 was established (VE [adjusted CI]: 85.4% [54.15; 96.90]) with >5 severe/critical COVID-19 cases in the placebo group and a favorable split of 5 cases in the Ad26.COV2.S group with onset at least 28 days after vaccination and 34 cases in the placebo group. VE against severe/critical COVID-19 with onset at least 14 days after vaccination was 76.7% (54.56; 89.09), with a favorable split of 14 cases in the Ad26.COV2.S group and 60 cases in the placebo group. Therefore, as indicated in FDA's guidance for EUA (FDA 2020a), it can be assumed that the risk of VAED, including VAERD, is low. Finally, throughout the trials, SAEs were monitored in all participants and it was observed that the number of SAEs was higher in the placebo group versus the Ad26.COV2.S group in trial COV3001, and balanced out after removal of the COVID-19-associated SAEs. For both moderate and severe/critical COVID-19 cases, symptoms in the Ad26.COV2.S group were on average milder than in the placebo group.

The duration of efficacy of Ad26.COV2.S has not yet been established. Longer and more follow-up data is being collected to determine duration of protection beyond 2 months after vaccination. Although there was no indication of waning of immunity up to Day 85, it is unknown whether waning of immunity occurs in Ad26.COV2.S and what would be the clinical implications.

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 2020).

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:

SMQ (broad) COVID-19

Important Potential Risk: Venous thromboembolism

Potential Mechanisms:

A potential mechanism for the occurrence of VTE includes a hypercoagulable state due to an excessive 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). Vaccination with other viral vaccines such as those against influenza (Christian 2011, Tsai 2005) and human papillomavirus (Scheller 2014) have shown to cause a transient increase in pro-inflammatory cytokine production that may lead to the onset of VTE. This may also translate to other vaccines (Cruz-Tapias 2012, Mendoza-Pinto 2018).

Evidence Source(s) and Strength of Evidence:

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 (Gerotziafas 2020). The hypercoagulable state observed in patients with severe COVID-19 is thought to be related to the high-grade systemic inflammatory response (Ribes 2020), 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 (Bikdeli 2020).

It is unknown whether these proposed mechanisms linking COVID-19 and thromboembolic events could also be applicable for vaccines against COVID-19.

Characterization of the Risk:

Thrombotic and Thromboembolic Events in Trial COV3001 (Primary Analysis)

Full Analysis Set	Ad26.COV2.S N=21,895 n	Placebo N=21,888 n
Total participants with any event	14	10
Venous thromboembolic events		
Deep vein thrombosis	6*	2
Pulmonary embolism	4	1
Transverse sinus thrombosis	1	0
Thrombosed hemorrhoid	0	1
Total participants with venous events	11	4
Arterial thromboembolic events		
Cerebrovascular events	3**	3
Cardiovascular events	1	3
Total participants with arterial events	3	6

*Includes one event reported as venous thrombosis limb and one event reported as embolism venous.
**Two events occurred in 1 participant.

Adapted from [TSFAE08.RTF] [VAC31518\VAC31518COV3001\DBR_IA_PRIMARY\RE_IA_PRIMARY\PROD\TSFAE08.SAS] 23JAN2021, 18:19

In trial COV3001 (primary analysis), the overall incidence of thrombotic and thromboembolic events (arterial and venous) was similar across the Ad26.COV2.S (n=14, 0.1%) and placebo (n=10, <0.1%) groups. A numerical imbalance was observed for VTE, with a total of 11 events in the Ad26.COV2.S group (6 events were serious and 8 occurred within 28 days following vaccination) and 4 events in the placebo group (2 serious, all within 28 days of vaccination). Two of the VTE cases were considered to be related to the study vaccine by the investigator: 1 nonserious AE of DVT reported with onset 27 days after vaccination with Ad26.COV2.S in a participant with a medical history of obesity, and 1 SAE of DVT reported in the placebo group. In addition, an SAE of TST reported in the Ad26.COV2.S group was initially considered related to the study vaccine by the investigator, which was subsequently downgraded to not related based on additional clinical findings. Finally, 1 participant in the placebo group developed thrombosed hemorrhoids. Most of these participants with VTE had underlying medical conditions (such as obesity, hypothyroidism, and diabetes) that may have contributed to the onset of these events.

Of the participants in the Ad26.COV2.S group with either DVT or PE, 6 were reported as recovered/recovering and the remaining 4 were reported as not recovered. In the placebo group, out of the 3 DVT/PE events, 1 participant was assessed as recovering and the remaining 2 were reported as not recovered. No fatalities were recorded among these participants.

The observed incidence rates of DVT and PE by age group in the Ad26.COV2.S group were similar to those reported in the literature for the general population (Huang 2014), acknowledging interpretation limitation due to an overall small number of observed cases per age group and potential uncontrolled bias. Rates of TST and thrombosed hemorrhoids were not considered due to only 1 case for each event being reported in the study.

Risk Factors and Risk Groups:

In the general population, important intrinsic factors for the onset of DVT and PE include a prior medical or family history of DVT or PE, venous insufficiency, heart disease, obesity, long periods of standing position, and multiparity. Important triggering factors for a DVT/PE event include pregnancy, trauma or a violent effort, deterioration of the general condition, immobilization, long distance travel, and infection (Samama 2000). On the other hand, TST is a disease more commonly observed in children and young adults. Important risks factors for TST include thrombophilia, trauma, puerperium, and chronic inflammatory diseases (Stam 2005). In addition, patients with transverse sinus stenosis have a strong risk for thrombosis, usually misdiagnosed as idiopathic intracranial hypertension (Aldossary 2018).

In trial COV3001, the following risk factors have been identified in participants with VTE: male gender, old age (>65 years), long-haul travel, thrombophilia, obesity, hypertension, and COPD. SARS-COV-2 infection is also considered an important risk factor, with 2 participants (1 per study group) having a positive PCR test. Anatomical malformations were also found to be risk factors for cranial venous thrombotic events.

Preventability:

Further characterization of this risk is required before risk minimization measures can be identified.

Impact on the Risk-Benefit Balance of the Product:

VTE is a potentially life-threatening event.

Public Health Impact:

Although a numerical imbalance of VTE events was observed between the Ad26.COV2.S and placebo groups, it is important to note that the incidence rates fall within those expected among the general population. Natural infection and disease due to SARS-COV-2 carries an important risk of thrombotic and thromboembolic events associated with a poor outcome (Gerotziafas 2020; Bikdeli 2020). It is worth noting the role COVID-19 may have had in the number of DVT/PE events observed, with at least 2 cases being PCR-confirmed for SARS-COV-2. Participants who received Ad26.COV2.S and subsequently developed a DVT/PE event were mostly reported as recovered or recovering with no fatal outcomes.

Over 27,000 participants were exposed to Ad26.COV2.S at the selected dose level in clinical trials and the occurrence of VTE was found to be rare and occurring mostly in participants with comorbidities associated with DVT/PE. No imbalance was observed for arterial thrombotic events in the vaccine group compared to placebo. It is unknown how many thrombotic and thromboembolic events will be observed in the post-authorisation setting; however, it is anticipated to be rare, within the expected rates for the general population, and lower than the number expected among patients with COVID-19.

Annex 1 MedDRA Term:

SMQ (narrow) Thrombotic and thromboembolic events

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 (TOX14389) 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.

To date, active vaccination of pregnant women has not been evaluated, as being pregnant or planning to become pregnant is an exclusion criterion in all clinical trials being conducted to date, with the requirement for use of adequate birth control methods for female participants of childbearing potential. A pregnancy test is systematically being performed in these women before each study vaccine administration.

Up to the cut-off date of 31 December 2020, 8 pregnancies (4 in the Ad26.COV2.S group and 4 in the Placebo group) were reported in the Global Safety Database for trial COV3001. In 3 cases, vaccine exposure (Ad26.COV2.S or placebo) occurred within 3 months preceding the date of conception, with pregnancy outcomes reported as continuing/ongoing (n=2) or unknown/not reported (n=1). In 5 cases, vaccine exposure (Ad26.COV2.S or placebo) occurred during the first trimester of pregnancy, with pregnancy outcomes reported as continuing/ongoing (n=3), elective abortion (n=1), or spontaneous abortion (n=1, assessed as not related to blinded vaccine/placebo). No additional pregnancies were reported between 31 December 2020 and 22 January 2021 (COV3001 CSR Feb 2021).

Safety data with other Janssen Ad26-based vaccines when administered within 3 months before pregnancy as well as during pregnancy have shown no evidence of an increased risk of adverse outcomes in the mother or child in over 1,600 reported pregnancies, with over 900 reported pregnancy outcomes.

Breastfeeding women were excluded from all clinical trials, except from the Phase 3 trials COV3001 and COV3009. To date, 128 breastfeeding women have received Ad26.COV2.S in trial COV3001, but no data to assess the safety profile are currently available in this subpopulation and the risk in this population has not yet been defined. Approximately 1,042 breastfeeding women have received Janssen's Ad26-based Ebola vaccine in a clinical trial in Democratic Republic of the Congo.

Currently, there is no evidence of SARS-CoV-2 transmission through breast milk. Limited data on breastfeeding women with active SARS-CoV-2 infection showed limited excretion of viral particles but no live virus in breastmilk (Centeno-Tablante 2021). In addition, several reports suggest the presence of secretory IgA against SARS-CoV-2 S protein in breast milk from donors with prior COVID-19 (Fox 2020, Dong 2020, Demers-Mathieu 2020).

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 very limited clinical data available to date, including data on the use of other Ad26-based vaccines during pregnancy, 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 Ad26.COV2.S 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 planned 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.

Breastfeeding women are being included in trials COV3001 and COV3009 to characterize the safety profile of Ad26.COV2.S in this subpopulation. A small subset of participants within trial COV2004 will be followed up during breastfeeding to assess the transfer of antibodies via breast milk.

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 not excluded from trials COV3001 and COV3009.

In trial COV3009 (blinded data), 45 (0.9%) participants who received at least one dose of Ad26.COV2.S had a stable/well-controlled HIV infection.

In trial COV3001, 601 (2.7%) participants in the FAS and 34 (1.0%) participants in the Safety Subset who received Ad26.COV2.S had a stable/well-controlled HIV infection. Participants with other immunodeficiencies were included at very low numbers, not allowing to provide meaningful data (COV3001 CSR Feb 2021).

The efficacy, safety, and immunogenicity of Ad26.COV2.S have not been assessed in immunocompromised individuals including those receiving immunosuppressant therapy. The efficacy of Ad26.COV2.S may be lower in immunosuppressed individuals.

Based on the primary analysis results from trial COV3001, no conclusion could currently be made about VE in HIV-infected participants. In this subpopulation, the number of moderate to severe/critical COVID-19 cases was too small to draw efficacy conclusions but the results did not suggest a negative impact of the vaccine. Additional and longer follow-up time for case accrual data will be gathered as the trial continues to better understand observed data. No clinically relevant difference in the reactogenicity profile could be observed in HIV-infected versus HIV-negative participants.

In the FAS of trial COV3001, SAEs were reported in 4 (0.7%) out of 601 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.

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, with no specific safety concerns. This was confirmed by clinical trial data with Ad26.ZEBOV, for which the safety and immunogenicity was assessed in HIV-infected adults with infection controlled through antiretroviral therapy. In these trials, 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. The limited safety data available from trial COV3001 are comparable to the findings with Ad26.ZEBOV.

Use in immunocompromised patients will be further characterized in an interventional trial and in the post-authorisation safety (COV4003, COV4001) and effectiveness (COV4004, COV4002) studies with Ad26.COV2.S.

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) could be enrolled in Phase 3 trials COV3001 and COV3009 at the discretion of the investigator.

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 with Ad26.COV2.S.

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 8,936 participants in the FAS of trial COV3001 who received Ad26.COV2.S and had one or more comorbidities, 3,704 (41.5%) were aged ≥60 years, 2,271 (25.4%) were aged ≥65 years, and 495 (5.5%) were aged ≥75 years. The proportion of these participants that have been determined to be frail is currently unknown (COV3001 CSR Feb 2021).

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, but these data are not available as part of the primary analysis of this trial.

Population in need of further characterization:

Safety data will be collected in individuals who are frail due to age or debilitating disease in trial COV3001, in the post-authorisation safety studies with Ad26.COV2.S (COV4003, COV4001), and through routine pharmacovigilance.

Missing information: Interaction with other vaccines
Evidence source: As no interaction studies have been performed, there are no data to assess if concomitant administration of Ad26.COV2.S with other vaccines may affect the efficacy or safety of either vaccine. This also applies to mixed schedules with other COVID-19 vaccines.
Population in need of further characterization: All reports describing interactions of Ad26.COV2.S with other vaccines per national recommendations will be collected and analyzed as per routine pharmacovigilance activities. A coadministration study of Ad26.COV2.S with seasonal influenza vaccine is planned.

Missing information: Long-term safety
Evidence source: There are no available data on the long-term safety of Ad26.COV2.S. 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).
Population in need of further characterization: At the time of vaccine availability, the long-term safety of Ad26.COV2.S will not be 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 ongoing trials COV3001 and COV3009 following administration of Ad26.COV2.S, for 1 year in study COV4003, and for 2 years in study COV4001. Participants of trials COV3001 and COV3009 who initially received placebo, will be offered a single dose of Ad26.COV2.S (crossover vaccination) in case Ad26.COV2.S is granted approval by a regulatory authority, resulting in unblinding. All participants will be encouraged to remain in the trial and will be followed for safety as originally planned up to 2 years after vaccination.

PART II: SAFETY SPECIFICATION

Module SVIII: Summary of the Safety Concerns

Table SVIII.1: 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

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

Routine Pharmacovigilance Activities

The Applicant will follow 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 will be undertaken. The Applicant 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. 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. The Applicant will conduct both passive and active surveillance activities for continued vaccine safety monitoring, as further specified below.

ICSR reporting

The Applicant will submit 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 2020c).

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 Applicant 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 will be added to the standard vaccine AE follow-up questionnaire on a case-by-case basis. In addition, TFUQs will be used to collect follow-up information on reports of anaphylaxis, and vaccination failure/lack of effect, including events of VAED and VAERD (see Annex 4).

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

Periodic aggregate review of safety data

Following EMA's 'Consideration on core requirements for RMPs of COVID-19 vaccines' guidance (EMA 2020b), in addition to routine 6-monthly PSURs, the Applicant will submit monthly safety reports containing a review of safety information received during the reporting interval, as well as cumulative data.

Topics covered by the monthly safety reports will include:

- Interval and cumulative number of reports, stratified by report type (medically confirmed/not) and by seriousness (including fatal separately).
- Interval and cumulative number of reports, overall and by age groups, and in special populations (eg, pregnant women).
- Interval and cumulative number of reports per High Level Term and SOC.
- Summary of the designated medical events.
- Reports per EU country.
- Exposure data (including per EU country).
- Changes to reference safety information in the interval.
- Ongoing and closed signals in the interval.
- AESI and RMP safety concerns reports – numbers and relevant cases, including O/E analysis, where appropriate.
- Fatal reports – numbers and relevant cases, including O/E analysis, where appropriate.
- Risk/benefit considerations.

Pregnancy outcomes and sudden death are AEs of interest that will each be discussed in separate sections of the periodic reports.

The submission of monthly reports complements the submission of 6-monthly PSURs. The need and frequency of submission of the monthly summary reports will be re-evaluated based on the available evidence from postmarketing after 6 months (6 submissions).

Literature review

Literature monitoring for Ad26.COV2.S includes both an automated daily[3] search for published and pre-publication/online first references in 2 commercial database products (Embase and Ovid Medline), as well as a daily manual review of one or more literature aggregator services. Search criteria include any COVID-19 vaccine product, irrespective of manufacturer or vaccine technology, and a report of AE(s) without restriction by seriousness or severity. Patient demographics are unrestricted by age group, ethnicity, and pregnancy status. Level of evidence (eg, clinical trials, longitudinal observational data, case reports/case series) is likewise unrestricted.

References retrieved by the above search strategies are reviewed by a healthcare professional and are escalated based on reporting of either new safety observations or new aspects of known risks that require further assessment.

[3] Timing of reference receipt is contingent upon external factors including reference indexing and upload date by the commercial service provider.

As knowledge of the SARS-CoV-2 virus, COVID-19, and vaccines evolves, it is expected that the above search strategies will likewise evolve.

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 will include regular surveillance of AE reports received in the Applicant's Global Safety Database, irrespective of country of origin, seriousness, medical confirmation, or validity. Additional reviews will be performed in external databases listed below. Key routine aggregate surveillance activities for Ad26.COV2.S are summarized in the table below:

Data source	Frequency of monitoring
Applicant's database	Weekly for temporal and disproportionality analyses
	Time to onset analysis as proof of concept every 2 weeks
FDA VAERS	Weekly data review and monthly data mining
EudraVigilance	Weekly data mining
WHO VigiBase	Data mining every 3 months

1) Database Review by the Applicant: an assessment of all AEs reported in the Applicant's safety database for Ad26.COV2.S will be performed at weekly intervals. Analyses will be at the PT level and clustered using custom grouping of select PTs. Methods for signal detection activities will include:
    a) Disproportionality analysis
    b) Time-to-onset analysis
    c) Temporal analyses will be done using weekly TFA which signals changes in reporting patterns for drug-event(s) pairs over time. This includes review of reporting percentages by AEs 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.
    d) O/E analysis, when applicable: Background rates to support the O/E analyses will be extracted from the literature. Peer-review papers will be used as best evidence. In case such papers are not available, data generated by ACCESS (EMA-funded project) or OHDSI (FDA-funded collaboration) will be used.

2) Data Mining Review: a review of cumulative data in external databases will be performed to identify AEs reported disproportionately for Ad26.COV2.S relative to all other products in the database including:
    a) EudraVigilance: weekly data mining
    b) WHO VigiBase: data mining every 3 months
    c) FDA VAERS: weekly data review and monthly data mining. A data analytic platform will be piloted for visualization and exploration of data downloads from VAERS.

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 (SmPC 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 Ad26.COV2.S, 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 Applicant 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 Applicant's instructions for reporting an alarmed shipment. These data may be used for the assessment of a safety signal.

The vaccine carton box also includes a 2D matrix barcode which has the batch/lot number, GTIN product code, and expiry date, should there be capability at a vaccination site to utilize this as an information source.

Further, the Applicant will make available vaccination cards (see Annex 7.6) to vaccinees that may be completed at the time of vaccination. The vaccination cards contain the following elements:

- Preprinted vaccine brand name 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 (www.covid19vaccinejanssen.com) for additional product information.

In addition to the vaccination cards, 2 stickers per dose, containing preprinted vaccine brand name, lot information, and a 2D matrix barcode will be made available to support documentation of the lot information on both the vaccination cards for vaccinees and in the vaccinee medical records in mass 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 information may not be utilized in all countries. The use will depend on national requirements and/or national competent authority guidance. Printed vaccination cards available in a Member State may include additional, nationally-required details.

The following milestones apply for the availability of the stickers with printed lot information:

- For EEA countries: sticker sheets with printed lot information will be provided at the same time and alongside the vial cartons from initial launch.
- Projected 2022: Upon development and approval of single-dose vials, stickers with printed lot information will be available inside the vial box or carton around it.

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

Specific Follow-up Questionnaires for Safety Concerns

Safety Concern	Purpose/Description
Anaphylaxis	TFUQ for the characterization of anaphylactic/anaphylactoid reactions
Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)	TFUQ to collect information on vaccination failure/lack of effect, including events of VAED and VAERD

III.2. Additional Pharmacovigilance Activities

Additional Pharmacovigilance Activities	
Trial VAC31518COV3001	
Study name and title	VAC31518COV3001 – 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 Ad26.COV2.S for the prevention of SARS-CoV-2-mediated COVID-19.
Safety concern(s) addressed	Anaphylaxis Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Venous thromboembolism Use in pregnancy and while breastfeeding (This trial will only address use while breastfeeding) Use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) Long-term safety
Study design	Randomized, double-blind, placebo-controlled trial.
Study population	Adults aged ≥18 to <60 years and ≥60 years with and without comorbidities that are associated with increased risk of progression to severe COVID-19.
Milestones	Final study report: 31 December 2023
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	Anaphylaxis Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Venous thromboembolism 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.

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: 30 September 2023
Interventional trial in immunocompromised patients	
Study name and title	Interventional trial to evaluate the safety and immunogenicity of Ad26.COV2.S in immunocompromised patients.
Rationale and study objectives:	To assess the safety and immunogenicity of Ad26.COV2.S in immunocompromised patients.
Safety concern(s) addressed	Use in immunocompromised patients
Study design	Not available at this time.
Study population	Immunocompromised patients (groups to be defined based on medical need, including patients receiving immunosuppressive therapy).
Milestones	Final study report: 30 June 2023
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 - Post-authorization, observational study to assess the safety of Ad26.COV2.S using electronic health record (EHR) database(s) in Europe.
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	Anaphylaxis Venous thromboembolism 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 EHR database(s).
Study population	General population in Europe.
Milestones	Protocol submission: 15 May 2021. Final study report: 30 June 2024

Study VAC31518COV4004	
Study name and title	VAC31518COV4004 **-** Post-authorization, observational, prospective study to assess the effectiveness of Ad26.COV2.S in Europe.
Rationale and study objectives:	To estimate the effectiveness of Ad26.COV2.S in preventing laboratory-confirmed SARS-CoV-2 hospitalizations up to 2 years post-vaccination.
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. Final study report: 30 June 2024
Study VAC31518COV4001	
Study name and title	VAC31518COV4001 - Post-authorization, observational study to assess the safety of Ad26.COV2.S using health insurance claims and/or electronic health record (EHR) database(s) 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	Anaphylaxis Venous thromboembolism 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 claims and/or EHR database(s).
Study population	General population in the United States.
Milestones	Protocol submission: 30 June 2021. Final study report: 31 December 2024
Study VAC31518COV4002	
Study name and title	VAC31518COV4002 **-** Post-authorization, observational study to assess the effectiveness of Ad26.COV2.S using health insurance claims and/or electronic health record (EHR) database(s) in the United States.
Rationale and study objectives:	To estimate the effectiveness of Ad26.COV2.S in preventing medically-attended COVID-19 up to 2 years post-vaccination.
Safety concern(s) addressed	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Use in immunocompromised patients
Study design	Observational study using US health insurance claims and/or EHR database(s).
Study population	General population in the United States.
Milestones	Protocol submission: 30 June 2021 Final study report: 31 December 2024
Coadministration study of Ad26.COV2.S with seasonal influenza vaccine	
Study name and title	Coadministration study of Ad26.COV2.S with seasonal influenza vaccine.
Rationale and study objectives:	To assess the safety and immunogenicity of Ad26.COV2.S and seasonal influenza vaccine when administered separately or concomitantly.

Safety concern(s) addressed	Interaction with other vaccines
Study design	Not available at this time.
Study population	General population.
Milestones	Interim analysis report: 31 December 2022 Final study report: 31 December 2023

Trial VAC31518COV2001	
Study name and title	VAC31518COV2001 – A randomized, double-blind, placebo-controlled Phase 2a study to evaluate a range of dose levels and vaccination intervals of Ad26.COV2.S in healthy adults aged 18 to 55 years inclusive and adults aged 65 years and older and to evaluate 2 dose levels of Ad26.COV2.S in healthy adolescents aged 12 to 17 years inclusive.
Rationale and study objectives:	Rationale: Generate data to assess potential vaccine-induced anti-phospholipid syndrome and potential vaccine-induced activation of coagulation. Study objectives: To evaluate the efficacy, safety, reactogenicity, and immunogenicity of Ad26.COV2.S at different dose levels and as a 2-dose or a 1-dose schedule.
Safety concern(s) addressed	Venous thromboembolism
Study design	Randomized, double-blind, placebo-controlled trial
Study population	Healthy adults aged 18 to ≥55 years and adults aged ≥65 years.
Milestones	Final study report: 31 December 2023

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				
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 (VAC31518COV3001) Ongoing	To evaluate the efficacy, safety, reactogenicity, and immunogenicity of Ad26.COV2.S for the prevention of SARS-CoV-2-mediated COVID-19.	• Anaphylaxis • Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) • Venous thromboembolism • Use in pregnancy and while breastfeeding (This trial will only address use while breastfeeding) • Use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) • Long-term safety	Final study report	31 December 2023
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.	• Anaphylaxis • Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) • Venous thromboembolism • Use in pregnancy and while breastfeeding (This trial will only address use while breastfeeding) • Long-term safety	Final study report	30 June 2024

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
An open-label, Phase 2 study to evaluate the safety, reactogenicity, and immunogenicity of Ad26.COV2.S in healthy pregnant participants (VAC31518COV2004) Planned	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.	• Use in pregnancy and while breastfeeding	Protocol submission Final study report	06 March 2021 30 September 2023
Interventional trial to evaluate the safety and immunogenicity of Ad26.COV2.S in immunocompromised patients Planned	To assess the safety and immunogenicity of Ad26.COV2.S in immuno-compromised patients.	• Use in immuno-compromised patients	Final study report	30 June 2023
COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER) (VAC31518COV4005) Planned	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

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Post-authorization, observational study to assess the safety of Ad26.COV2.S using electronic health record (EHR) database(s) in Europe (VAC31518COV4003) Planned	To assess the occurrence of pre-specified AESIs within specific risk periods following administration of Ad26.COV2.S.	• Anaphylaxis • Venous thromboembolism • 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 Final study report	15 May2021 30 June 2024
Post-authorization, observational, prospective study to assess the effectiveness of Ad26.COV2.S in Europe (VAC31518COV4004) Planned	To estimate the effectiveness of Ad26.COV2.S in preventing laboratory-confirmed SARS-CoV-2 hospitalizations up to 2 years post-vaccination.	• Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) • Use in immunocompromised patients	Protocol submission Final study report	31 March 2021 30 June 2024

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Post-authorization, observational study to assess the safety of Ad26.COV2.S using health insurance claims and/or electronic health record (EHR) database(s) in the United States (VAC31518COV4001) Planned	To assess the occurrence of pre-specified AESIs within specific risk periods following administration of Ad26.COV2.S.	• Anaphylaxis • Venous thromboembolism • 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 June 2021 31 December 2024
Post-authorization, observational study to assess the effectiveness of Ad26.COV2.S using health insurance claims and/or electronic health record (EHR) database(s) in the United States (VAC31518COV4002) Planned	To estimate the effectiveness of Ad26.COV2.S in preventing medically-attended COVID-19 up to 2 years post-vaccination.	• Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) • Use in immunocompromised patients	Protocol submission Final study report	30 June 2021 31 December 2024
Coadministration study of Ad26.COV2.S with seasonal influenza vaccine Planned	To assess the safety and immunogenicity of Ad26.COV2.S and seasonal influenza vaccine when administered separately or concomitantly.	• Interaction with other vaccines	Interim analysis report Final study report	31 December 2022 31 December 2023
A randomized, double-blind, placebo-controlled Phase 2a study to evaluate a range of dose levels and vaccination intervals of Ad26.COV2.S in healthy adults aged 18 to 55 years inclusive and adults aged 65 years and older and to evaluate 2 dose levels of Ad26.COV2.S in healthy adolescents aged 12 to 17 years inclusive (VAC31518COV2001) Ongoing	To evaluate the efficacy, safety, reactogenicity, and immunogenicity of Ad26.COV2.S at different dose levels and as a 2-dose or a 1-dose schedule.	• Venous thromboembolism	Final study report	31 December 2023

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				

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	
Anaphylaxis	**Routine risk communication:** • SmPC Section 4.3 • 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 3 provide recommendations to address the risk of anaphylaxis. **Other routine risk minimization measures beyond the Product Information:** • None
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
Venous thromboembolism	**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

Safety Concern	Routine Risk Minimization Activities
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
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

Safety Concern	Routine Risk Minimization Activities
Interaction with other vaccines	**Routine risk communication:** • SmPC Section 4.5 • 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
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

Not applicable.

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		
Anaphylaxis	**Routine risk minimization measures:** • SmPC Section 4.3 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • SmPC Section 4.4 and PL Section 3 provide recommendations to address the risk of anaphylaxis. **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • TFUQ for the characterization of anaphylactic/anaphylactoid reactions **Additional pharmacovigilance activities:** • Trial VAC31518COV3001 Final study report: 31 December 2023 • Trial VAC31518COV3009 Final study report: 30 June 2024 • Study VAC31518COV4003 Final study report: 30 June 2024 • Study VAC31518COV4001 Final study report: 31 December 2024
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:** • TFUQ to collect information on vaccination failure/lack of effect, including events of VAED and VAERD **Additional pharmacovigilance activities:** • Trial VAC31518COV3001 Final study report: 31 December 2023 • Trial VAC31518COV3009 Final study report: 30 June 2024 • Study VAC31518COV4004 Final study report: 30 June 2024

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
		• Study VAC31518COV4002 Final study report: 31 December 2024
Venous thromboembolism	**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 VAC31518COV3001 Final study report: 31 December 2023 • Trial VAC31518COV3009 Final study report: 30 June 2024 • Study VAC31518COV4003 Final study report: 30 June 2024 • Study VAC31518COV4001 Final study report: 31 December 2024 • Trial VAC31518COV2001 Final study report: 31 December 2023
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 VAC31518COV3001 (This trial will only address use while breastfeeding) Final study report: 31 December 2023 • Trial VAC31518COV3009 (This trial will only address use while breastfeeding) Final study report: 30 June 2024 • Trial VAC31518COV2004 Final study report: 30 September 2023

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
		• 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: 30 June 2024
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:** • Interventional trial to evaluate the safety and immunogenicity of Ad26.COV2.S in immunocompromised patients Final study report: 30 June 2023 • Study VAC31518COV4003 Final study report: 30 June 2024 • Study VAC31518COV4004 Final study report: 30 June 2024 • Study VAC31518COV4001 Final study report: 31 December 2024 • Study VAC31518COV4002 Final study report: 31 December 2024
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: 30 June 2024 • Study VAC31518COV4001 Final study report: 31 December 2024

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
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:** • Trial VAC31518COV3001 Final study report: 31 December 2023 • Study VAC31518COV4003 Final study report: 30 June 2024 • Study VAC31518COV4001 Final study report: 31 December 2024
Interaction with other vaccines	**Routine risk minimization measures:** • SmPC Section 4.5 • PL Section 2 **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • Coadministration study of Ad26.COV2.S with seasonal influenza vaccine Final study report: 31 December 2023
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 VAC31518COV3001 Final study report: 31 December 2023 • Trial VAC31518COV3009 Final study report: 30 June 2024 • Study VAC31518COV4003 Final study report: 30 June 2024 • Study VAC31518COV4001 Final study report: 31 December 2024

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for COVID-19 Vaccine Janssen

This is a summary of the risk management plan (RMP) for COVID-19 Vaccine Janssen. The RMP details important risks of COVID-19 Vaccine Janssen, how these risks can be minimized, and how more information will be obtained about COVID-19 Vaccine Janssen's risks and uncertainties (missing information).

COVID-19 Vaccine Janssen's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how COVID-19 Vaccine Janssen should be used.

This summary of the RMP for COVID-19 Vaccine Janssen 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 COVID-19 Vaccine Janssen's RMP.

I. The Vaccine and What it is Used For

COVID-19 Vaccine Janssen is authorised for active immunization to prevent COVID-19 caused by 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 COVID-19 Vaccine Janssen's benefits can be found in COVID-19 Vaccine Janssen'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/covid-19-vaccine-janssen.

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

Important risks of COVID-19 Vaccine Janssen, together with measures to minimize such risks and the proposed studies for learning more about COVID-19 Vaccine Janssen'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.

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 COVID-19 Vaccine Janssen is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of COVID-19 Vaccine Janssen 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 COVID-19 Vaccine Janssen. 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	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

II.B. Summary of Important Risks

Important Identified Risk: Anaphylaxis	
Evidence for linking the risk to the medicine	Allergic reactions, including possibly severe reactions (eg, hypersensitivity reactions and anaphylaxis), are known to occur with any injectable vaccine. COVID-19 Vaccine Janssen contains ingredients with known potential to cause allergic reactions, including polysorbate 80. The structure of polysorbate 80 presents similarities with polyethylene glycol, recently suspected to be involved in anaphylactic reactions with mRNA vaccines. The potential for polysorbate 80 to trigger hypersensitivity and the possibility of cross-reactivity between polyethylene glycol and polysorbate 80 have been discussed in the literature. Cases of polysorbate 80-induced hypersensitivity have been reported and have involved different drugs, including a human papillomavirus vaccine, and different routes of administration, including the intramuscular route. After the data lock point of this EU-RMP, severe allergic reactions and one case of anaphylaxis have been identified following vaccination with COVID-19 Vaccine Janssen. All of these events occurred in the context of an open-label study in South Africa. Anaphylaxis is an adverse drug reaction described in the SmPC.
Risk factors and risk groups	Participants with a known history of hypersensitivity to any component of the vaccine may be at risk for hypersensitivity reactions.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.3 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • SmPC Section 4.4 and PL Section 3 provide recommendations to address the risk of anaphylaxis. Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial VAC31518COV3001 • 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	VAERD was first seen in the 1960s in infants with respiratory syncytial virus (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 severe acute respiratory syndrome coronavirus (SARS-CoV)- and Middle East respiratory syndrome coronavirus-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 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 VAC31518COV3001 • Trial VAC31518COV3009 • Study VAC31518COV4004 • Study VAC31518COV4002 See section II.C of this summary for an overview of the post-authorisation development plan.
Important Potential Risk: Venous thromboembolism	
Evidence for linking the risk to the medicine	Natural infection with SARS-COV-2 has shown to be associated with hypercoagulability, pulmonary intravascular coagulation, microangiopathy, and venous thromboembolism (VTE) or arterial thrombosis. The occurrence of thrombotic and thromboembolic events in context of coronavirus disease-2019 (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.
Risk factors and risk groups	In the general population, important intrinsic factors for the onset of deep vein thrombosis (DVT) and pulmonary embolism (PE) include a prior medical or family history of DVT or PE, venous insufficiency, heart disease, obesity, long periods of standing position, and multiparity. Important triggering factors for a DVT/PE event include pregnancy, trauma or a violent effort, deterioration of the general condition, immobilization, long distance travel, and infection. On the other hand, transverse sinus thrombosis is a disease more commonly observed in children and young adults. Important risks factors for transverse sinus thrombosis include thrombophilia, trauma, puerperium, and chronic inflammatory diseases. In addition, patients with transverse sinus stenosis have a strong risk for thrombosis, usually misdiagnosed as idiopathic intracranial hypertension. In trial COV3001, the following risk factors have been identified in participants with VTE: male gender, old age (>65 years), long-haul travel, thrombophilia, obesity, hypertension, and COPD. SARS-COV-2 infection is also considered an important risk factor, with 2 participants (1 per study group) having a positive polymerase chain reaction test. Anatomical malformations were also found to be risk factors for cranial venous thrombotic events.
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial VAC31518COV3001 • Trial VAC31518COV3009 • Study VAC31518COV4003 • Study VAC31518COV4001 • Trial VAC31518COV2001 See section II.C of this summary for an overview of the post-authorisation development plan.

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 VAC31518COV3001 (This trial will only address use while breastfeeding) • 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: • Interventional trial to evaluate the safety and immunogenicity of Ad26.COV2.S in immunocompromised patients • Study VAC31518COV4003 • Study VAC31518COV4004 • Study VAC31518COV4001 • Study VAC31518COV4002 See section II.C of this summary for an overview of the post-authorisation development plan.

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: • Trial VAC31518COV3001 • Study VAC31518COV4003 • Study VAC31518COV4001 See section II.C of this summary for an overview of the post-authorisation development plan.
Missing Information: Interaction with other vaccines	
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.5 • PL Section 2 Additional risk minimization measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Coadministration study of Ad26.COV2.S with seasonal influenza vaccine 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 VAC31518COV3001 • Trial VAC31518COV3009 • Study VAC31518COV4003 • Study VAC31518COV4001 See section II.C of this summary for an overview of the post-authorisation development plan.

II.C. Post-authorisation Development Plan

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

VAC31518COV3001: 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 Ad26.COV2.S for the prevention of SARS-CoV-2-mediated COVID-19.

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.

Interventional trial to evaluate the safety and immunogenicity of Ad26.COV2.S in immunocompromised patients.

Purpose of the study: To assess the safety and immunogenicity of Ad26.COV2.S in immunocompromised patients.

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: Post-authorization, observational study to assess the safety of Ad26.COV2.S using electronic health record (EHR) database(s) in Europe.

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: Post-authorization, observational, prospective study to assess the effectiveness of Ad26.COV2.S in Europe.

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

VAC31518COV4001: Post-authorization, observational study to assess the safety of Ad26.COV2.S using health insurance claims and/or electronic health record (EHR) database(s) 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.

VAC31518COV4002: Post-authorization, observational study to assess the effectiveness of Ad26.COV2.S using health insurance claims and/or electronic health record (EHR) database(s) in the United States.

Purpose of the study: To estimate the effectiveness of Ad26.COV2.S in preventing medically-attended COVID-19 up to 2 years post-vaccination.

Coadministration study of Ad26.COV2.S with seasonal influenza vaccine

Purpose of the study: To assess the safety and immunogenicity of Ad26.COV2.S and seasonal influenza vaccine when administered separately or concomitantly.

VAC31518COV2001: A randomized, double-blind, placebo-controlled Phase 2a study to evaluate a range of dose levels and vaccination intervals of Ad26.COV2.S in healthy adults aged 18 to 55 years inclusive and adults aged 65 years and older and to evaluate 2 dose levels of Ad26.COV2.S in healthy adolescents aged 12 to 17 years inclusive.

Purpose of the study: To evaluate the efficacy, safety, reactogenicity, and immunogenicity of Ad26.COV2.S at different dose levels and as a 2-dose or a 1-dose schedule.

PART VII: ANNEXES

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Annex 4: Specific Adverse Drug Reaction Follow-up Forms

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- TFUQ for the characterization of anaphylactic/anaphylactoid reactions
- TFUQ to collect information on vaccination failure/lack of effect, including events of VAED and VAERD

Of note, these TFUQs are internally referred to as TOIQs.

Follow-up Forms

TFUQ for the characterization of anaphylactic/anaphylactoid reactions

Topic of Interest Questionnaire (TOIQ) for Hypersensitivity and Anaphylactic Reaction

To the Health Care Provider: Complete this form as a supplement to the Health Care Professional Adverse Event Follow-Up Form provided.

Manufacturer Control Number: Date of Report: [dd-MMM-yyyy]

1. Product Details

Did the patient have a prior hypersensitivity reaction to any vaccine, drug, or food?

Product	Drug	Vaccine	Food
Name of the product:			
Date [dd-MMM-yyyy]:			
Time:	☐ AM ☐ PM	☐ AM ☐ PM	☐ AM ☐ PM

How many doses of the product the subject received prior to the hypersensitivity event?

Product	Drug	Vaccine	Food
Number of doses			

When was the patient last time exposed to product causing hypersensitivity reaction?

Product	Drug	Vaccine	Food
Date [dd-MMM-yyyy]			

Was the patient pre-medicated prior to receiving the product?
List the pre-medication regimen:

☐ Did the patient take any new product (prescribed or OTC) or food prior to the hypersensitivity reactions? List additional details including product name, date/time of exposure:

☐ Has the patient been exposed to any toxic materials, fumes, pollution? Provide details including product name, date/time of exposure:

☐ Has the patient been treated with immunomodulating or immunosuppressing medications or received any other vaccine around the time of the COVID-19 vaccination?

2. Relevant Medical History Details

Does the patient have any of the following? (check if applicable)

☐ Drug intolerance/Allergic reactions/Hypersensitivity reactions
To which product/vaccine/substance/food/cosmetics/aeroallergens/insect venom:

☐ Anaphylaxis
To which product/vaccine/substance/food/cosmetics/aeroallergens/insect venom:

☐ Asthma Duration/severity:

☐ Allergic rhinitis (Hay fever) Duration:

☐ Atopic dermatitis Duration/severity:

☐ Urticaria (Hives) Duration/severity:

☐ Inherited/acquired complement abnormalities (Specify):

☐ Other pertinent medical history or concurrent conditions (Specify):

3. Event Details:

Time from the dosing of the product/vaccine to onset of symptoms (TTO):
☐ minutes ☐ hours ☐ days (Check one)

Duration of the event:

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TOIQ for Hypersensitivity and Anaphylactic Reaction

MCN:

Clinical Signs and Symptoms:

- ☐ Red and itchy eyes
- ☐ Generalized prickle sensation
- ☐ Localized injection site urticaria
- ☐ Tachycardia
- ☐ Capillary refill time >3 s (without hypotension)
- ☐ Decreased level of consciousness
- ☐ Persistent dry cough
- ☐ Hoarse voice
- ☐ Difficulty breathing without wheeze or stridor
- ☐ Sensation of throat closure
- ☐ Sneezing, rhinorrhea
- ☐ Diarrhea
- ☐ Abdominal pain
- ☐ Nausea
- ☐ Vomiting
- ☐ Feeling hot
- ☐ Other Specify:
- ☐ Generalized urticaria (hives) or generalized erythema
- ☐ Angioedema, localized or generalized
- ☐ Generalized pruritus with skin rash
- ☐ Measured hypotension
- ☐ Capillary refill time >3 s (with hypotension)
- ☐ Reduced central pulse volume
- ☐ Loss of consciousness
- ☐ Bilateral wheeze (bronchospasm)
- ☐ Stridor
- ☐ Upper airway swelling (lip, tongue, throat, uvula or larynx)
- ☐ Respiratory distress
- ☐ Tachypnea
- ☐ Increased use of accessory muscles
- ☐ Cyanosis
- ☐ Recession
- ☐ Flushing
- ☐ Grunting

Skin manifestation:

Describe in detail and provide a photo, if available (*Erythema, macular, papular, morbilliform, urticaria/angioedema, exfoliative dermatitis/erythroderma, bullous dermatitis, blistering, photoallergic reaction*):

Generalized ☐ No ☐ Yes (Describe):

Localized ☐ No ☐ Yes (Describe):

Grade ☐ 1 ☐ 2 ☐ 3 ☐ 4

Approximate % of Body Surface Area Involvement < 10 % ☐ 10-30 % ☐ >30 % ☐

Mucus membranes: ☐ No ☐ Yes (Specify):

Skin necrosis: ☐ No ☐ Yes (Specify):

Was the patient seen by a dermatologist? ☐ No ☐ Yes (Specify and provide the report, if available):

Was a skin biopsy performed? ☐ No ☐ Yes (Provide report, if available)

Other:

MCN:

4. Diagnosis of the reported event:

- ☐ Hypersensitivity reaction
- ☐ Anaphylactic reaction
- ☐ Anaphylactoid reaction
- ☐ Anaphylactic shock
- ☐ Other (Specify):

5. Laboratory findings *(Please provide and attach results of any relevant laboratory and diagnostic procedures performed, if available.)*

Laboratory test or Diagnostic Studies	**Date Performed** (dd-Mmm-yyyy)	**Results with units, if applicable**	**Reference Ranges, if applicable** (or please state if abnormal or elevated/reduced)
☐ Mast cell tryptase elevation			
☐ IgE			
☐ Complement			
☐ Pathology findings			
☐ Other relevant tests (Please specify):			

6. Treatment *(Specify medications, response, and need for ER evaluation/hospitalization)*

Was the patient treated? (if Yes, specify below)

- ☐ Adrenalin
- ☐ Steroids (Oral)
- ☐ Antihistamines (Oral)
- ☐ IV fluids (Specify):
- ☐ Oxygen
- ☐ Steroids (IV)
- ☐ Antihistamines (IV)
- ☐ Bronchodilators (Specify):
- ☐ CPR
- ☐ Other (Specify):

Thank you for completing this form.

TFUQ to collect information on vaccination failure/lack of effect, including events of VAED and VAERD

Topic of Interest Questionnaire (TOIQ) for Vaccination Failure/Lack of Effect (LOE)

Manufacturer Control Number: **Date of Report:** **[dd-MMM-yyyy]**

To the Health Care Provider: Complete this form as a supplement to the Health Care Professional Adverse Event Follow-Up Form provided.

1. **Did the patient have any of the following prior to vaccination:**
   a. **Exposure to SARS-COV-2 virus?** ☐ Unknown ☐ No ☐ Yes
   If Yes, provide details (date, time):
   b. **Positive SARS-COV-2 test or antibodies?** ☐ Unknown ☐ No ☐ Yes
   If Yes, specify test date
   and type of test:
   ☐ nasal swab reverse transcription–polymerase chain reaction [RT-PCR] test
   ☐ nucleic acid amplification–based test [NAAT]
   ☐ antigen test
   ☐ serology test ELISA
   ☐ X-ray
   ☐ MRI
   ☐ Other:
   c. **Positive symptoms of COVID-19 disease?** ☐ No ☐ Yes, please specify

2. **Does the patient have positive COVID-19 test at diagnosis?** ☐ Unknown ☐ No ☐ Yes
   If Yes, specify test date of test
   and type of test:
   ☐ nasal swab reverse transcription–polymerase chain reaction [RT-PCR] test
   ☐ nucleic acid amplification–based test [NAAT]
   ☐ antigen test
   ☐ serology test ELISA
   ☐ X-ray
   ☐ MRI
   ☐ Other:

3. **Please provide information on any new or worsening symptoms/signs during the COVID-19 illness:**

Respiratory	Cardiovascular	Hematopoietic and Immune system	Inflammatory markers
☐ *Dyspnea* ☐ *Tachypnea* ☐ *Hypoxemia* ☐ *Cough* ☐ *Cyanosis* ☐ *COVID-19 pneumonia* ☐ *Acute respiratory distress syndrome (ARDS)* ☐ *Lower respiratory tract infection* ☐ *Respiratory failure* ☐ *Pulmonary hemorrhage* ☐ *Radiographic abnormalities* ☐ *Other:*	☐ *Heart failure* ☐ *Acute cardiac injury* ☐ *Acute myocardial infarction* ☐ *Arrhythmia* ☐ *Pericarditis* ☐ *Myocarditis* ☐ *Cardiogenic shock* ☐ *Other:*	☐ *Coagulopathy* ☐ *Thrombocytopenia* ☐ *Deep vein thrombosis* ☐ *Disseminated intravascular coagulation (DIC)* ☐ *Vasculitis* ☐ *Limb ischemia* ☐ *Pulmonary embolism* ☐ *Other:*	☐ *Elevated cytokines* ☐ *Other:*

MCN:

Renal System	*Gastrointestinal and Hepatic System*	*Central Nervous System*	*Other Systems*
☐ *Renal disfunction* ☐ *Acute kidney injury* ☐ *Other:*	☐ *Vomiting* ☐ *Diarrhea* ☐ *Jaundice* ☐ *Abdominal pain* ☐ *Acute liver injury* ☐ *Other:*	☐ *Altered mental status* ☐ *Convulsions/seizures* ☐ *Cranial nerve involvement* ☐ *Encephalopathy* ☐ *Meningitis* ☐ *Cerebrovascular accident* ☐ *Other:*	☐ *Acute arthritis* ☐ *Dermatological* ☐ *Chilblains* ☐ *Erythema multiforme* ☐ *Multisystem inflammatory syndrome (MIS)* ☐ *Multiorgan failure* *Specify:* ☐ *Death*

4. Does the patient have medical history of any of the following conditions?

(check applicable and specify details)

☐ Hypertension (specify):
☐ Diabetes (specify):
☐ Heart disease (specify):
☐ Lung disease (specify):
☐ Liver disease (specify):
☐ Kidney disease (specify):
☐ Cancer (specify):
☐ Immunosuppressive disorder (specify):
☐ Obesity (specify):
☐ Infection, respiratory or gastrointestinal (specify):
☐ Lymphoma
☐ HIV positive
☐ Systemic lupus erythematosus
☐ Vasculitis
☐ Other autoimmune disorder (specify):
☐ Other (specify):

Is the patient a smoker/former smoker?

☐ No
☐ Current smoker
☐ Former smoker
Details:

5. Was the patient admitted to Intensive Care Unit?

☐ Unknown ☐ No ☐ Yes

6. Please provide results of any of the following laboratory tests or diagnostic studies if they were performed:

Laboratory Test or Diagnostic Studies	Date Performed (dd-MMM-yyyy)	Results	Reference ranges
☐ Test for SARS-CoV-2 by PCR, or other commercial or public health assay			
☐ Imaging for COVID-Pneumonia (e.g. CXR, CT) Other radiological			
☐ Other radiological investigations (e.g. MRI, angiogram, V/Q scan)			
☐ Imaging for thrombo-embolic events (e.g. doppler or CT)			

MCN:

☐ Hematology (e.g. leucocyte count [including neutrophil and lymphocyte counts], hemoglobin, platelet count, coagulation parameters [PT, PTT, D-Dimer, INR], fibrinogen, B and T cell function assays)			
☐ Clinical chemistry (e.g. serum creatinine, glomerular filtration rate [GFR], liver enzymes, bilirubin, albumin, B-type natriuretic peptide [BNP], troponin)			
☐ Inflammatory markers (e.g. CRP, ESR, procalcitonin, ferritin, LDH, cytokines [including IL-6])			
☐ Urinalysis			
☐ Evidence of hypoxemia (e.g. PaO2/FiO2 [P/F ratio], SpO2/FiO2 [S/F ratio]), hypercapnia (PaCO2) or acidosis (pH)			
☐ Other (specify):			

7. **Did the patient require supplemental oxygen (including high flow or ECMO) or receive mechanical ventilation?**
☐ Unknown ☐ No ☐ Yes, please specify

8. **How was the patient treated?**

Therapy	Start date (DD/MMM/YYYY)	Stop date (DD/MMM/YYYY)	Dose/Additional information
☐ Remdesivir ☐ Hydroxychloroquine/chloroquine ☐ Azithromycin ☐ Corticosteroids ☐ Plasmapheresis ☐ Other (Please Specify)			

9. **Did the patient have SARS-CoV2 antibodies at diagnosis or discharge from the hospital?**
☐ Unknown ☐ No ☐ Yes

10. **Is the patient being treated with immunomodulating or immunosuppressive medication or received other vaccines within past 30 days?** ☐ Unknown ☐ No ☐ Yes
If Yes, provide details (name of the medication/vaccine, dose, and date):

11. **Was there an issue during administration of vaccine (e.g. syringe leak, needle disconnect)?**
☐ Unknown ☐ No ☐ Yes
If Yes, provide details:

12. **Was there an issue with the vaccine temperature/storage/transportation?**
☐ Unknown ☐ No ☐ Yes
If Yes, provide details:

13. **Other comments:**

Please attach additional pages as needed

Thank you for completing this form.