Janssen Vaccines & Prevention B.V.*

Statistical Analysis Plan for the Open-Label Phase

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

ENSEMBLE 2

Protocol VAC31518COV3009; Phase 3
AMENDMENT 1

VAC31518 (JNJ-78436735)

* Janssen Vaccines & Prevention B.V. is a Janssen pharmaceutical company of Johnson & Johnson and is hereafter referred to as the sponsor of the study.

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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VERSION HISTORY

Table 1: SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	19 August 2021	Not Applicable	Initial release
2		• Adding changes based on protocol amendment 6 - A 1-dose booster vaccination with Ad26.COV2.S at the $5x10^{10}$ virus particles (vp) dose level is offered to all ongoing participants who have only received a single vaccination with Ad26.COV2.S in the study • Adding changes based on protocol amendment 7 - Replacing active follow-up of COVID-19 events with passive follow-up - In addition to the changes to the study protocol, the COVID-19 epidemic has evolved, vaccines such as Ad26.COV2.S and many other vaccines are now used in many countries. The COVID-19 clinical development program has evolved towards a life-cycle management and the scope and the extent of analyses have been adapted	Changes to protocol amendments 6 and 7
3		• Adding analysis of the open-label passive phase	

1. INTRODUCTION

Since the initial protocol of COV3009 dated August 22, 2020, several protocol amendments have been implemented. Of importance, after Ad26.COV2.S Emergency Use Authorization (EUA) in the United States (US), a single dose of Ad26.COV2.S vaccine will be offered to enrolled participants who initially received placebo, resulting in de facto unblinding of all participants and investigators. In addition, the study design has been updated to replace the 2-dose placebo arm with a 1-dose active vaccination arm and further updated to offer a single dose booster vaccination with Ad26.COV2.S to all ongoing participants who received only a single vaccination with Ad26.COV2.S in the study. Hence, from Protocol Amendment 4 onwards, the study consists of two separate phases: the Phase A part of the study will assess in a double-blind manner the efficacy of the two-dose schedule versus placebo and the Phase B part concerns the evaluations for different study cohorts (two-dose schedule cohort, one-dose schedule cohort, booster dose schedule cohort) in an open-label setting. The Statistical Analysis Plan (SAP) dated 13 August 2021 outlined the primary analysis of the study related to the double-blind phase.

With Protocol Amendment 6, a single dose booster vaccination with Ad26.COV2.S at the $5x10^{10}$ vp dose level was offered to all ongoing participants who received only a single vaccination with Ad26.COV2.S in the study. Participants who had already received 2 vaccinations with Ad26.COV2.S at the $5x10^{10}$ vp dose level or any COVID-19 vaccinations outside of the study (including the Janssen vaccine) at the time of local approval of Protocol Amendment 6 were not eligible to receive the booster vaccination.

With Protocol Amendment 7, requirements for COVID-19 episode reporting are changed from active to passive follow-up, defined as safety follow-up phone call visits by the site instead of on-site visits to document COVID-19 events as (S)AEs and MAAEs.

On 27 February 2021, the US Food and Drug Administration (FDA) issued an EUA for the Ad26.COV2.S vaccine for the prevention of coronavirus disease 2019 (COVID-19). On 11 March 2021, the European Commission granted conditional marketing authorization for the Ad26.COV2.S vaccine. Additionally the World Health Organization granted Ad26.COV2.S vaccine emergency use listing on 12 March 2021. Other regulatory agencies have subsequently authorized or (conditionally) approved the vaccine. On 20 October 2021, the FDA amended the EUA for Ad26.COV2.S to authorize the vaccine as homologous or heterologous booster. On 16 December 2021, the European Commission authorized (as part of the conditional marketing authorization) Ad26.COV2.S as homologous booster or as heterologous booster following completion of primary vaccination with an approved mRNA COVID-19 vaccine in individuals 18 years of age or older.The European commission approved on January 9th 2023 Ad26.COV2.S fully, ie no longer a conditional approval. The vaccine has received authorization of use in over 100 countries, the clinical development program has moved from ‘Development’ to a ‘Life cycle management’ phase. Hence the scope and the extent of the open-label analysis has been reduced. For the open-label phase, the safety, immunogenicity, and efficacy endpoints following cross-over and/or booster vaccination will be descriptively summarized by study cohort. Relative vaccine efficacy will not be assessed during the open-label phase. Results will be presented as incidence rates per study cohort (eg incidence of moderate to severe molecularly confirmed COVID-19).

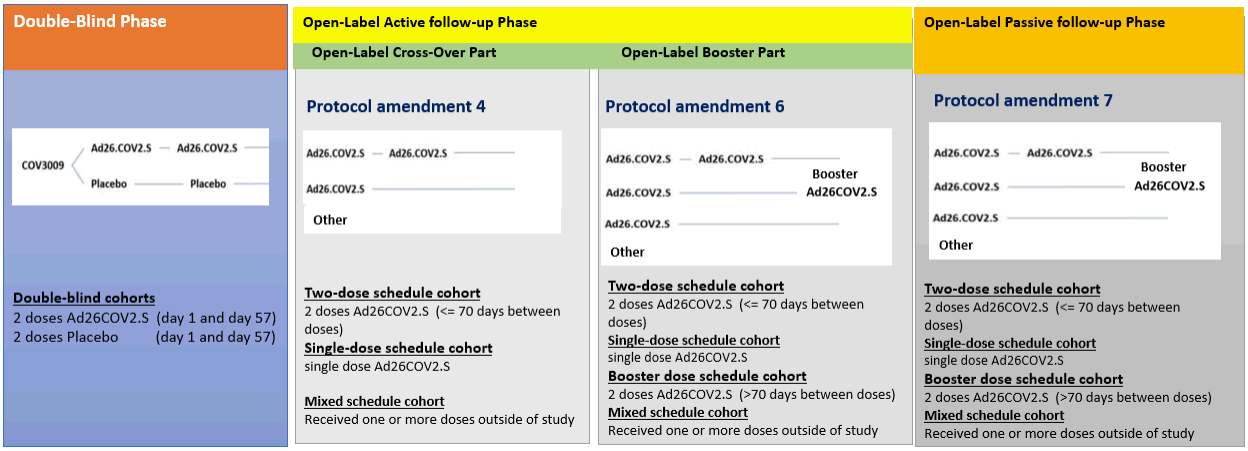
From 8 July 2022, suspected COVID-19 events were no longer sent to the Clinical Severity Adjudication Committee (CSAC) for assessment and sequencing of cases was stopped on 4 July 2022. Since the implementation of Protocol Amendment 7 (PA7) dated 27 April 2022, at sites where the protocol is approved, there is a passive follow-up of COVID-19 episodes.

With PA7 the open-label phase is divided into two parts:

1. Active follow-up of suspected COVID-19 episodes (according to the initial design of the study, from unblinding up to the date the study site approves PA7)

2. After implementation of PA7, the active follow-up of suspected COVID-19 is replaced by a passive follow-up (from study site approval of PA7 up to end of study).

Figure 1: Study Overview



Note: 'Mixed schedule cohort' is used for safety evaluation only.

The SAP for the double-blind phase dated 13 August 2021 provided the details to support the primary analysis of the study (Phase A) comparing efficacy, immunogenicity and safety of the 2-dose vaccine versus placebo.

The data from the open-label phase will be reported in two parts, one related to the active follow-up of events (open-label active follow-up analysis) and one related to the passive follow-up of events (end-of-study analysis).

For the open-label phase, the safety, immunogenicity, and efficacy endpoints will be descriptively summarized by study cohort. This SAP describes how the safety, immunogenicity, and efficacy endpoints will be descriptively summarized by study cohort for evaluation of the objectives of the active follow-up part and the passive follow-up part of the open-label phase of the study.

For a given participant, all data up to implementation of PA7 will be incorporated in the descriptive evaluations of the active follow-up part of the open-label phase of the study. Participants will enter the passive follow-up on the day that their study site has approval to follow PA7. For a given

participant, all data after implementation of PA7 up to the end of the study will be incorporated in the descriptive evaluations of the passive follow-up part of the open-label phase of the study.

The vaccine has been designed for the prevention of SARS-CoV-2 mediated COVID-19 in adults aged 18 years and older.

This SAP will detail the analytical plan for the study objectives of the active follow-up part and for the study objectives of the passive follow-up part of the open-label phase.

The objective of the open-label active phase of the study is to evaluate descriptively the effect of two doses of Ad26.COV2.S and of one dose of Ad26.COV2.S on the rate of molecularly confirmed COVID-19, in adults at high risk for infection and/or disease. The objective of the open-label passive phase of the study is to evaluate descriptively the effect of two doses of Ad26.COV2.S and of one dose of Ad26.COV2.S on the rate of COVID-19 episodes recorded as serious adverse events (SAEs), adverse events (AEs), or medically-attended adverse events (MAAEs).

For the open-label active phase of the study period until completion of Visit 8 (Visit 4 (Day 57) + 1 year), each participant will be asked at least twice a week, through the electronic clinical outcome assessment (eCOA), if they have experienced any new symptoms or health concerns that could be related to infection with SARS-CoV-2. As of completion of Visit 8, until the end of the 2-year follow-up period, the frequency of this (suspected) COVID-19 surveillance (symptom check) through eCOA will decrease to once every 2 weeks. At the time of PA7 eCOA was stopped for all participants.

For the open-label passive phase of the study, the active follow-up of suspected COVID-19 episodes using eCOA is replaced by a passive follow-up. Passive follow-up of COVID-19 consists of recording of new COVID-19 episodes as SAEs, AEs, or MAAEs. The information of these AEs is collected during the scheduled phone calls with the participants.

1.1. Objectives, Endpoints

The list of objectives and endpoints for the open-label active surveillance phase and for the open-label passive follow-up phase can be found in PA7. Note that no efficacy evaluations or group comparisons will be performed. All objectives will be evaluated using descriptive statistics.

As of protocol amendment 2, subjects were allowed to receive vaccination outside of the study while still following the same protocol scheduled procedures as those subjects that remained in the study with the Ad26.COV2.S vaccine. The safety for subjects that received other vaccines outside of the study will also be described. No tabulations of efficacy data following vaccines received outside of the study will be provided.

The exploratory endpoints associated with the correlate of risk/efficacy objective will not be evaluated in this study. Correlate of risk/efficacy objectives will be evaluated in the context of study COV3001.

The exploratory endpoints associated with immunogenicity objectives will not be evaluated in the open-label active surveillance phase.

Estimands for the open-label active surveillance analysis:

Objectives	Endpoints/Variable	Population	Intervention	Intercurrent events	Summary measure
Safety	SAEs, AEIs and AESIs from study start until PA7 site approval	Adults>= 18 years old	Ad26.COV2.S, placebo, one or more doses of mRNA + Ad26.COV2.S OR one or more doses of non-mRNA + Ad26.COV2.S, mixed schedule	LTFU	Number of subjects with events and incidence rates per 100 person years per reporting period
Molecularly confirmed[a], symptomatic COVID-19[b]	Symptomatic COVID-19 according to mild, moderate or severe programmed algorithmic definition, with onset at least 28 days after last vaccination.	Adults>= 18 years old	Single dose Ad26.COV2.S Two doses Ad26.COV2.S (maximum of 70 days between doses) Booster dose Ad26.COV2.S (minimum of 71 days between doses)	LTFU-Outside vaccinations	Number of subjects with events and incidence rates per 100 person-years
Molecularly confirmed[a], severe/critical COVID-19[b]	Severe/critical COVID-19 according to programmed algorithmic definition, with onset at least 28 days after last vaccination	Adults>= 18 years old	Single dose Ad26.COV2.S Two doses Ad26.COV2.S (maximum of 70 days between doses) Booster dose Ad26.COV2.S (minimum of 71 days between doses)	LTFU- Outside vaccinations	Number of subjects with events and incidence rates per 100 person-years

Objectives	Endpoints/Variable	Population	Intervention	Intercurrent events	Summary measure
Molecularly confirmed[a], COVID-19[b] cases requiring medical intervention	COVID-19 cases according to programmed algorithmic definition requiring medical intervention, with onset at least 28 days after last vaccination	Adults>= 18 years old	Single dose Ad26.COV2.S Two doses Ad26.COV2.S (maximum of 70 days between doses) Booster dose Ad26.COV2.S (minimum of 71 days between doses)	LTFU- Outside vaccinations censoring	Number of subjects with events and incidence rates per 100 person-years
COVID-19 related death	COVID-19 related deaths with onset at least 28 days after last vaccination	Adults>= 18 years old	Single dose Ad26.COV2.S Two doses Ad26.COV2.S (maximum of 70 days between doses) Booster dose Ad26.COV2.S (minimum of 71 days between doses)	LTFU- Outside vaccinations	Number of subjects with events and incidence rates per 100 person-years
Severity of breakthrough infections	The severity of COVID-19 cases may be evaluated by the severity and number of symptoms (severity) of COVID-19 cases, ratio of severe/critical COVID-19 cases (number of severe/critical COVID-19/ total number of moderate and severe/critical COVID-19) and ratio of long COVID-19 cases (duration of more than 28 days) (the number of long moderate/severe COVID-19/ total number of moderate/ severe COVID-19)	Adults>= 18 years old	Single dose Ad26.COV2.S Two doses Ad26.COV2.S (maximum of 70 days between doses) Booster dose Ad26.COV2.S (minimum of 71 days between doses)	LTFU – Outside vaccinations	Percentage of cases that are severe/critical; Percentage of cases that have a long duration (duration of more than 28 days)
Immunogenicity of Ad26.COV2.S at available timepoints	Analysis of antibodies binding to the SARS-CoV-2 S protein by ELISA	Adults>= 18 years old	Two doses Ad26.COV2.S	LTFU- Outside vaccinations	GMR, responder rate

Objectives	Endpoints/Variable	Population	Intervention	Intercurrent events	Summary measure
	• Immune response to Ad26.COV2.S as compared to Functional and molecular antibody placebo characterization including, but not limited to avidity, Fc-mediated viral clearance, Fc characteristics, Ig subclass, IgG isotype, antibody glycosylation, and assessment of antibody repertoire	Adults>= 18 years old	Two doses Ad26.COV2.S	LTFU- Outside vaccinations	This endpoint will not be evaluated.
	• Original and/or emerging SARS-CoV-2 lineage neutralization as measured by virus neutralization assay (VNA; wt virus and/or pseudovirion expressing SARS-CoV-2 S protein)				This endpoint will not be evaluated
	• Adenovirus neutralization as measured by VNA				This endpoint will not be evaluated
	• Analysis of antibodies binding to the receptor-binding domain (RBD) of the SARS-CoV-2 S protein				This endpoint will not be evaluated

Objectives	Endpoints/Variable	Population	Intervention	Intercurrent events	Summary measure
Potential correlate of risk/efficacy	• Analysis of binding antibody titer measured by S-ELISA and/or MSD assay, as available for participants having COVID-19 compared to non-infected participants • Analysis of SARS-CoV-2 neutralizing antibody titers measured by psVNA or wild-type VNA, as available for participants having COVID-19 compared to non-infected participants	Adults>= 18 years old	Two doses Ad26.COV2.S	LTFU- Outside vaccinations	Not evaluated in this study.
Duration of protection following booster vaccination with Ad26.COV2.S	Symptomatic COVID-19 cases, severe COVID-19, COVID-19 cases requiring medical intervention, and COVID-19 related deaths with onset at least 28 days after vaccination, over time	Adults>= 18 years old	Single dose Ad26.COV2.S Two doses Ad26.COV2.S (maximum of 70 days between doses) Booster dose Ad26.COV2.S (minimum of 71 days between doses)	LTFU- Outside vaccinations	Number of subjects with events and incidence per 100 person-years by month

[a] Molecularly confirmed COVID-19 is defined as a positive SARS-CoV-2 viral RNA result by a central laboratory using a reverse-transcriptase polymerase chain reaction (RT-PCR)-based or other molecular diagnostic test.
[b] Per case definition for mild, moderate or severe/critical COVID-19 according to programmed algorithmic definition.

LTFU: Lost to follow-up

Estimands for the open-label passive follow-up analysis:

Objectives	Endpoints/Variable	Population	Intervention	Intercurrent events	Summary measure
Safety	SAEs, AEIs and AESIs from PA7 site approval until end of the study	Adults>= 18 years old	Ad26.COV2.S, placebo, one or more doses of mRNA + Ad26.COV2.S OR one or more doses of non-mRNA + Ad26.COV2.S, mixed schedule	LTFU	Number of subjects with events and incidence rates per 100 person years per reporting period
COVID-19 in terms of (S)AEs, MAAEs, hospitalizations and fatal AEs linked to COVID-19	• SAEs and AEs linked to COVID-19 • MAAEs linked to COVID-19 • SAEs linked to COVID-19 that require hospitalization • Fatal AEs linked to COVID-19	Adults>= 18 years old	Single dose Ad26.COV2.S Two doses Ad26.COV2.S (maximum of 70 days between doses) Booster dose Ad26.COV2.S (minimum of 71 days between doses)	LTFU-Outside vaccinations	Number of subjects with events and incidence rates per 100 person-years
Immunogenicity of Ad26.COV2.S at available timepoints	• Analysis of antibodies binding to the SARS-CoV-2 S protein by ELISA • Analysis of SARS-CoV-2 neutralizing antibody titers as measured by psVNA and/or wtVNA	Adults>= 18 years old	Two doses Ad26.COV2.S	LTFU- Outside vaccinations	GMR, responder rate GMR, responder rate
Correlate of immunity	• Analysis of binding antibody titer measured by S-ELISA and/or MSD assay, as available for participants having COVID-19 compared to non-infected participants • Analysis of SARS-CoV-2 neutralizing antibody titers measured by psVNA or wtVNA,	Adults>= 18 years old	Two doses Ad26.COV2.S	LTFU- Outside vaccinations	Not evaluated in this study.

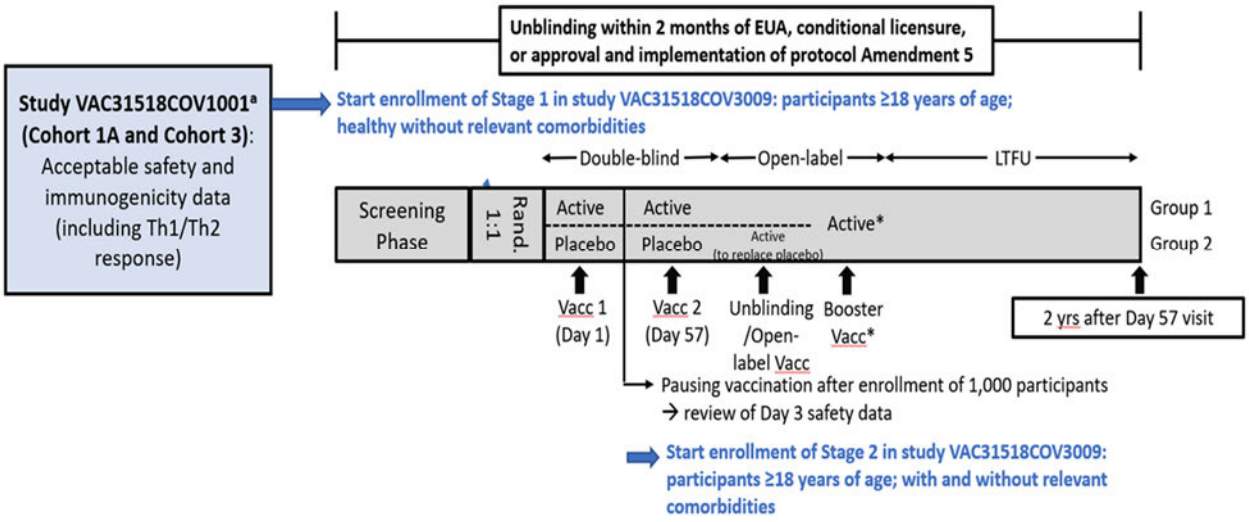
Objectives	Endpoints/Variable	Population	Intervention	Intercurrent events	Summary measure
	as available for participants having COVID-19 compared to non-infected participants				

LTFU: Lost to follow-up

1.2. Study Design

This is a multicenter, randomized, double-blind, placebo-controlled phase 3 study to assess the efficacy, safety, and immunogenicity of Ad26.COV2.S for the prevention of SARS-CoV-2-mediated COVID-19 in adults aged 18 years and older. An overview of the study design is provided in Figure 2.

Figure 2: Schematic Overview of the Study



Active = Ad26.COV2.S; LTFU = long-term follow-up; rand. = randomization; Th = T-helper cell type 1/2.
[a] Available safety data from all ongoing studies with Ad26.COV2.S will be taken into account.
A screening phase of up to 28 days is included, however, screening may also be performed prior to randomization on the day of vaccination.
The enrollment for Stage 1 and Stage 2 will be staggered. In both stages, participants will be enrolled in 1 of the 2 age-dependent subgroups (≥18 years to <60 years of age or ≥60 years of age). Once Stage 2 is initiated, participants with and without relevant comorbidities can be recruited. It is intended that a minimum of approximately 30% of recruited participants will be ≥60 years of age and approximately 20% of recruited participants will be ≥18 to <40 years of age. The analysis of the data will not be staggered: the primary analysis will be based on pooled data from both stages of the study.
Refer to Section 2.1 in the CTP for details on initiation of study VAC31518COV3009 based on data from study VAC31518COV1001.
Refer to the Investigator's Brochure (IB) for details about the VAC31518COV1001 study.[33, 34]
Refer to Section 5.2 in the CTP for details on the relevant comorbidities.
Note: Upon implementation of Amendment 4, all participants from double-blind phase will be unblinded and the study will continue as an open-label study. Participants who received either one dose or two doses of placebo at that time will be offered to receive a single dose of Ad26.COV2.S, under the conditions delineated in Section 6.4 in the CTP. Participants from the Ad26.COV2.S arm enrolled during the double-blinded phase, will continue in the same arm to receive their second dose, if applicable (refer to Section 6.4 in the CTP).
*Upon implementation of Protocol Amendment 6, all ongoing participants in the study who received only a single vaccination with Ad26.COV2.S in the study will be offered a single booster dose of Ad26.COV2.S vaccine under the conditions delineated in Section 6.5 in the CTP. Participants who already received 2 vaccinations with Ad26.COV2.S at the $5x10^{10}$ vp dose level or any COVID-19 vaccination outside of the study (including the Janssen vaccine) at the time of local approval of Protocol Amendment 6 are not eligible to receive a booster vaccination with Ad26.COV2.S.

During the double-blind phase of the study, participants will be vaccinated with two vaccinations according to a 1:1 randomization:

- Ad26.COV2.S supplied at a concentration of 1×10^{11} vp/mL in single-use vials, with an extractable volume of 0.5 mL, and dosed at 5×10^{10} vp
- Placebo: 0.9% sodium chloride (NaCl) solution

For blinding purposes, all participants will receive Ad26.COV2.S or placebo at Day 1 and Day 57, using the same volume (ie 0.5 mL).

Following Ad26.COV2.S EUA in the US for the single dose schedule, all participants from countries where Protocol Amendment 4 is approved by the local Health Authority and the Independent Ethics Committee/Institutional Review Board (IEC/IRB) will be unblinded at the on-site or remote unblinding visit and the study will continue as an open-label study.

Participants from the placebo arm enrolled during the double-blind phase will be offered to receive a single dose of Ad26.COV2.S vaccine, unless they met certain vaccination discontinuation rules during the double-blind phase of the study (refer to Section 6.4 in the CTP).

Participants from the Ad26.COV2.S arm enrolled during the double-blind phase will continue in the same arm to receive their second dose, if applicable (refer to Section 6.4 in the CTP).

Newly enrolled participants in the open-label phase under Amendment 4 will be randomized in a 1:1 ratio to receive either 1 dose or 2 doses of Ad26.COV2.S vaccine.

With implementation of Protocol Amendment 6, all ongoing eligible participants who received only a single vaccination with Ad26.COV2.S in the study will be offered a single booster dose of Ad26.COV2.S vaccine ($5x10^{10}$ vp) (see Table 2) under the conditions delineated in Section 6.5 in the CTP. Participants who already received 2 vaccinations with Ad26.COV2.S at the $5x10^{10}$ vp dose level or any COVID-19 vaccinations outside of the study (including the Janssen vaccine) at the time of local approval of Protocol Amendment 6 (PA6) are not eligible to receive a booster vaccination with Ad26.COV2.S. The booster vaccination will be administered in the open-label phase of the study, preferably within 6 to 12 months after the participant's first Ad26.COV2.S vaccination in the study. If this is not possible, the booster vaccination should not occur earlier than 3 months after the participant's first Ad26.COV2.S vaccination.

Table 2: Vaccination Schedule VAC31518COV3009 - Open-label Phase

Group	N*	Day 1	Day 57	Unscheduled Unblinding Visit**/ Day 1 for newly enrolled participants***	Booster Vaccination Preferably Vac 1 + 6-12 months Minimally Vac 1 + 3 months*****
1	Approx. 15,000	Ad26.COV2.S (5×10^{10} vp)	Ad26.COV2.S (5×10^{10} vp)		Ad26.COV2.S (5×10^{10} vp)
2	Approx. 15,000	Placebo***	Placebo****	Ad26.COV2.S (5×10^{10} vp)	

N = number of participants; vp = virus particles.

Note: It is intended that a minimum of approximately 30% of recruited participants will be ≥60 years of age and approximately 20% of recruited participants will be ≥18 to <40 years of age.

* It is possible that there might be over enrollment of participants in this study.

** All participants will be unblinded (informed whether they received placebo or Ad26.COV2.S) at the on-site or remote unblinding visit following EUA in the US and approval of Protocol Amendment 4 by the local Health Authority and the IEC/IRB, and the study will continue as an open-label study. Participants who were in the placebo arm will be offered to receive a single dose of Ad26.COV2.S 5×10^{10} vp. After the study pause, the unblinding visit should be scheduled as soon as reasonably practicable and preferably no later than 2 months following local approvals of Protocol Amendment 5 have been received. The unblinding visit may be combined with the next planned study visit, if appropriate.

*** The newly enrolled participants will be randomized to Group 1 (to receive two doses of Ad26.COV2.S) or to Group 2 (to receive one dose of Ad26.COV2.S on Day 1 instead of 2 doses of placebo. (There will be no administration of placebo on Day 57).

**** Vaccination at Day 57 is not applicable for participants who were unblinded after the placebo vaccination at Day 1 and prior to receiving the second placebo vaccination.

*****Following implementation of Protocol Amendment 6, all ongoing eligible participants who received only 1 Ad26.COV2.S vaccination in the study will be offered 1 Ad26.COV2.S booster vaccination. Participants who already received 2 vaccinations with Ad26.COV2.S at the $5x10^{10}$ vp dose level or any COVID-19 vaccinations outside of the study (including the Janssen vaccine) at the time of local approval of Protocol Amendment 6 are not eligible to receive a booster vaccination with Ad26.COV2.S.

For safety, the data of the double-blind phase and the open-label active follow-up phase are combined. Safety data for the following vaccination groups will be presented:

1. Placebo: Participants who were randomized and first vaccinated with Placebo until they received any other active COVID-19 vaccine.
2. Ad26.COV2.S: Participants whose first active vaccination is Ad26.COV2.S. Participants remain in this group (also when receiving a second dose of Ad26.COV2.S) until they receive an outside active COVID-19 vaccination.
3. Any schedule non-mRNA + Ad26.COV2.S OR any schedule mRNA + Ad26.COV2.S: Participants who first received one or more active non-mRNA COVID-19 vaccinations or one or more active mRNA COVID-19 vaccinations and who were boosted with one or more Ad26.COV2.S vaccinations
4. Mixed achedule: all other safety data and safety follow-up, including safety data following only an outside vaccine regimen, or safety data following a mixed schedule of Ad26.COV2.S and mRNA/non-mRNA vaccines.

For efficacy, the open-label phase will include 3 main study cohorts, based on the vaccination schedules received:

– Two-dose schedule cohort: participants who received the 2 doses of the Ad26.COV2.S vaccine according to initial design of the study on Day 1 and Day 57 (Visit 1 and Visit 4), regardless whether this was before or after unblinding. The number of days between

first Ad26.COV2.S vaccination and second Ad26.COV2.S vaccination must be a maximum of 70 days to qualify for the two-dose cohort.

- One-dose schedule cohort: participants who received a single dose of the Ad26.COV2.S vaccine in the context of the open-label vaccination (eg, placebo participants receiving Ad26.COV2.S vaccine during cross-over vaccination) or participants who only received one dose of Ad26.COV2.S vaccine during the double-blind phase of the study. These participants remain in this cohort until they receive the booster vaccination in the context of PA6 or an outside vaccination. Participants who will not receive a booster dose will continue in this cohort until they receive an outside vaccination.
- Booster dose schedule cohort: participants who, during the course of the study, have received only a single dose of the Ad26.COV2.S vaccine and received a booster vaccination under PA6, preferably within 6 to 12 months after the initial vaccination, with a minimum of 3 months after the initial vaccination with Ad26.COV2.S. The number of days between first Ad26.COV2.S vaccination and second Ad26.COV2.S vaccination must be a minimum of 71 days to qualify for the booster dose cohort.

With PA7, requirements for COVID-19 episode reporting are changed, ie, a passive surveillance approach is adopted, defined as following up on new COVID-19 episodes during scheduled phone calls with the participants. Participants will enter this phase on the date of site approval of PA7. The data collected in the passive follow-up phase will be analyzed separately from the open-label active follow-up phase and the efficacy analysis will be described in a separate section within this SAP. For efficacy the same study cohorts as in the open-label active phase are used. Efficacy following a COVID-19 vaccination given outside of the study will not be assessed. The safety data after PA7 approval will also be presented separately from the safety data under the active follow-up. The same vaccination groups are used as for the open-label active follow-up phase.

2. STATISTICAL HYPOTHESES

There is no study hypothesis for the open-label phase of the study.

3. SAMPLE SIZE DETERMINATION

3.1. Efficacy (Total Sample Size)

There is no sample size determination for the open-label phase of the study.

3.2. Immunogenicity Subset

In the double-blind phase, for a total of approximately 400 participants in the Immunogenicity Subset, blood will be collected for analysis of humoral immune responses before each vaccination, 28 days after the 1st vaccination and 14 days after the second vaccination.

In the open-label phase, for participants from the Immunogenicity Subset who did not receive a booster dose, blood will be collected at 6 months, 1 year, 18 months, and 2 years after the second vaccination.

All participants in the Immunogenicity Subset will be enrolled from Study Stage 2. Participants in the Immunogenicity Subset in the double-blind phase and in the open-label phase will be divided into 4 groups as presented in Table 3.

Table 3 Sample Size and Distribution of the Immunogenicity Subset Between Active and Placebo Groups

Study Vaccine	Subset 1a	Subset 1b	Subset 2a	Subset 2b
Ad26.COV2.S (5×10^{10} vp)/Ad26.COV2.S (5×10^{10} vp)	50	50	50	50
Placebo/placebo	50	50	50	50
Total	**100**	**100**	**100**	**100**

vp = virus particles
Subset 1a: healthy participants ≥18 years to <60 years of age without relevant comorbidities, enrolled during Stage 2.
Subset 1b: healthy participants ≥60 years of age without relevant comorbidities, enrolled during Stage 2.
Subset 2a: participants ≥18 to <60 years of age with relevant comorbidities, enrolled during Stage 2.
Subset 2b: participants ≥60 years of age with relevant comorbidities, enrolled during Stage 2

All participants will have a blood sample taken at the time of the unblinding visit (before open-label vaccination) and at the Booster Vaccination Visit (before booster vaccination) for analysis of serum antibodies against SARS-CoV-2 nucleocapsid (N_protein), regardless of whether they were part of the Immunogenicity subset in the double-blind phase.

4. ANALYSIS SETS FOR ANALYSIS

Vaccine assignment will be analyzed according to the *as-treated* principle. The analysis sets that are used for the analysis of safety and immunogenicity for the open-label active phase and the open-label passive phase are described in Table 4.

The safety analysis will include the data from the double-blind phase combined with the open-label active follow-up phase and will be performed using the full analysis set (FAS). The safety data collected after PA7 approval will be presented similarly but separately from the active follow-up. The analysis set used for the passive follow-up is the subset of participants of the FAS who are still active on the day that their site approves PA7 (FAS7).

Analyses of immunogenicity will be performed on the per protocol immunogenicity analysis set (PPI).

Table 4: Analysis Sets

Analysis Sets	Description
Enrolled	The enrolled analysis set includes all participants who signed the informed consent form (ICF) and who were not screen failures.
Randomized	The randomized analysis set includes all enrolled participants who were randomized in the study.
Full Analysis Set (FAS)	All randomized participants with at least one documented study vaccine and met inclusion criterion 1, regardless of the occurrence of protocol deviations and serostatus at enrollment.
Full Analysis Set under PA7 (FAS7)	All randomized participants that are part of the FAS that are still active once the site approves PA7.
Per Protocol Immunogenicity Analysis Set (PPI)	All randomized and vaccinated participants (receiving two doses of Ad26.COV2.S at Day 1 and Day 57), including those who are part of the Immunogenicity Subset and for whom immunogenicity data are available, excluding samples after major protocol deviations (MPD) expected to impact the immunogenicity outcomes (such as administration of COVID-19 vaccine outside the study). In addition, for participants who experience a SARS-CoV-2 event (molecularly confirmed and/or confirmed by N-serology), samples taken after the event and samples taken outside protocol windows will not be taken into account in the assessment of the immunogenicity. The PPI population is the primary immunogenicity population. For key tables, sensitivity immunogenicity analyses will also be performed on the FAS, including participants who are part of the Immunogenicity Subset for whom immunogenicity measures are available. Excluded samples might be taken into account as well in the sensitivity analysis.

The analysis sets that are used for the descriptive evaluations of efficacy in the open label active follow-up phase of the study include the participants from the full analysis set who are at risk to develop an endpoint within the observational period. These sets can be considered as risk sets. The observational period and the definition of the risk sets differ per study dose cohort. All details on the efficacy analysis risk sets are explained in Section 5.2.2. The population used for the analysis in the open-label passive follow-up phase is the full analysis set who are still active in the study at the time the site approves PA7 (FAS7). The same vaccination groups as the open-label active phase are presented.

Descriptive evaluations of efficacy will be performed on the risk set for the study cohort.

5. STATISTICAL ANALYSES

5.1. General Considerations

No efficacy evaluations nor group comparisons will be done in the open-label part of the trial. The data will not fit the purpose of comparing groups.

Efficacy endpoints and safety data will be presented descriptively as the number of cases or safety events and as incidence rates per 100 person years of follow-up within the relevant period per vaccination group.

The vaccination groups presented in the safety analysis and in the efficacy analysis differ. Details for the safety analysis are presented in Section 5.4 and for the efficacy analysis are presented in Section 5.2 and Section 5.3.

5.1.1. Scope of Analysis of the Open-Label Active Follow-up Phase

5.1.1.1. Setting

Unblinding due to availability of other authorized/approved COVID-19 vaccines

In the double-blind phase of the study, investigators may receive requests to unblind study participants who become eligible to receive other COVID-19 vaccines if/when these are authorized/licensed for use. In these cases, the investigator will discuss with the participant available options and ramifications, including whether they are eligible to receive the Ad26.COV2.S vaccine in the study during the unblinding study visit. If the participant is eligible for a licensed vaccine according to local immunization guidelines or recommendation and if the participant wishes to proceed with the unblinding, the investigator will follow the unblinding procedures. The reason for the unblinding request should be documented. The name and date(s) of administration of the other COVID-19 vaccine should be recorded.

Participants who opt for enrollment in an Expanded Access Program or a Phase 3b study (eg, Sisonke/TOGETHER in South Africa) may be unblinded upon their request and will be encouraged to continue in the VAC31518COV3009 study.

When unblinding, if it is determined that the participant received the Ad26.COV2.S vaccine (and not placebo), the participant will be informed that there are no data on the safety of receiving two different COVID-19 vaccines and no further study vaccination would be permitted in the event he/she chooses to receive the vaccine outside the study. Unblinded participants, whether in the vaccine or control group, will be asked to continue to be followed in this study in line with the schedule of activities. Safety, efficacy, and immunogenicity evaluations will be identical for all participants, including participants that are unblinded to obtain an authorized/licensed COVID-19 vaccine and who remain in the study.

Unblinding due to cross-over for Janssen Vaccine

Section 6.4 from the latest protocol details the procedures to unblind participants at the Unblinding visit and offer participants who received placebo a single dose of Ad26.COV2.S vaccine.

If participants decide to continue the study at the Unblinding visit, participants will continue to be followed up and data will be collected as detailed further below.

As the study was still ongoing and recruiting new participants, there are 3 scenarios that could happen after approval of Clinical Trial Protocol Amendment 4 (CTPA4) which introduced cross-over vaccination and when the open-label unblinding visit occurs:

1. New participants that are enrolled after CTPA4 approval will go directly into the open-label phase of the study and will be included in the analysis of the open-label phase.
2. Already enrolled participants who have their open-label unblinding visit after receiving their 1st vaccination but before getting their 2nd vaccination will be included in the analysis of the open-label phase. All data (including data from the double-blind phase) will be included in the analysis of the open-label phase of the study.
3. Already enrolled participants who have their open-label unblinding visit after receiving both vaccinations will be included in the analysis of the open-label phase. All data (including data from the double-blind phase) will be included in the analysis of the open-label phase of the study.

Booster Vaccination

Section 6.5 from the latest protocol details the procedures to offer participants who received only a single vaccination with Ad26.COV2.S a single booster dose of Ad26.COV2.S vaccine ($5x10^{10}$ vp). Participants who already received 2 vaccinations with Ad26.COV2.S at the $5x10^{10}$ vp dose level or any COVID-19 vaccinations outside the study (including the Janssen vaccine) at the time of local approval of Protocol amendment 6 are not eligible to receive a booster vaccination with Ad26.COV2.S. The booster vaccination will be administered in the open-label phase of the study, preferably within 6 to 12 months after the participant's first Ad26.COV2.S vaccination in the study. If this is not possible, the booster vaccination should not occur earlier than 3 months after the participant's first Ad26.COV2.S vaccination.

5.1.1.2. Analysis Scope

The analysis of safety will include safety data collected from the beginning of the study until study site approval of PA7 for each participant. The vaccination groups that will be presented are: placebo, Ad26.COV2.S, non-mRNA (any number of doses) + Ad26.COV2.S booster or mRNA (any number of doses) + Ad26.COV2.S booster, and mixed schedule group. The safety data will be presented in three separate layouts: layout 1a covers the safety data after Ad26.COV2.S and placebo only, up until receipt of another COVID-19 vaccine; layout 1b covers the safety data after Ad26.COV2.S when given as a booster on top of mRNA vaccinations or on top of non-mRNA vaccinations, layout 2 covers all other safety data after outside vaccinations or any other order

mixing outside vaccination with Ad26.COV2.S vaccination (eg: Ad26.COV2.S + mRNA vaccination).

The efficacy analysis planned for the open-label active phase, comparing the different study cohorts, will include efficacy data from the date of unblinding up to 30 days prior to study site approval of PA7. This 30 day window is chosen to assure that the active surveillance took place for the full duration of the COVID-19 episode and no symptoms would be missed. A separate listing will be provided to include the COVID-19 events within 30 days prior to study site approval of PA7. There are 3 study cohorts: one dose schedule; two-dose schedule and booster dose schedule. These cohorts are described in more detail in Section 5.2.1.

5.1.2. Scope of the Analysis of the Open-Label Passive Follow-up Phase

After implementation of PA7, the active follow-up of suspected COVID-19 is replaced by a passive follow-up (from study site approval of PA7 up to end of study).

The safety data of the open-label passive follow-up phase will be presented similarly as for the open-label active phase, however the data will be presented separately. All data collected during the study from study site approval of PA7 until study end will be included.

For efficacy in the open-label passive follow-up phase, the COVID-19 events are based on the reporting of adverse events. The COVID-19 events will be summarized descriptively for the 1 dose schedule, 2 dose schedule and the booster dose schedule.

5.1.3. Participant Dispositions

Participant information will be shown for the full analysis set by randomized treatment group and by the vaccination groups used in the safety analysis, presented in Section 5.4.4.

The number of participants in the following disposition categories will be summarized throughout the study by vaccination group and overall:

- participants in the FAS
- participants in the FAS7
- participants randomized
- participants vaccinated at day 1 and not randomized
- participants randomized, not vaccinated at day 1
- participants randomized and vaccinated at day 1
- participants vaccinated at day 1 with incorrect treatment
- participants vaccinated at day 1 with correct treatment
- participants who discontinued study (and reasons for discontinuation)
- participants who discontinued study before PA7 site approval

Additionally, the disposition of the efficacy risk sets (explained in Section 5.2.2) will be provided including the reasons why subjects are excluded from the risk set starting from the initial study vaccination received in the FAS. The efficacy risk set will be presented for the 1 dose cohort, 2 dose cohort and booster dose cohort. Note that subjects from the 1 dose cohort can also be included in the 2 dose or booster dose cohort and therefore can be part of multiple risk sets.

5.2. Efficacy Analysis of the Open-Label Active Follow-up Phase

Note that no hypothesis testing and no efficacy evaluations will be performed. All endpoints will be evaluated using descriptive statistics. These descriptive summaries can not support any comparisons between groups or any interpretation regarding difference between groups.

The efficacy analyses will be based on a subset of the participants of the FAS, ie the participants who are at risk to develop an endpoint in the open-label active phase. These subsets are called risk sets and depend on the vaccination schedule the participants received as indicated in Table 5 and explained in Sections 5.2.1 and Section 5.2.2.

As only the data under the open-label active follow-up is considered, an observational period is defined for each of the vaccination groups (Table 5 and explained in Section 5.2.3). Only the efficacy data within this observational period will be summarized. Efficacy endpoints for the vaccination groups outside of this observational period, ie within 30 days prior to the PA7 site approval, will be listed.

Table 5: Risk set and observational period

Risk set	Start of observational period	Censoring End of observational period	Inclusion criteria	Exclusion criteria
One dose cohort	Maximum of • Unblinding date • First dose of Ad26.COV2.S	Minimum of • Endpoint observed • Outside vaccination • Second Ad26.COV2.S vaccination • Discontinuation • PA7 site approval – 30 days	At least 1 dose of Ad26.COV2.S prior to PA7 site approval – 30 days and prior to study discontinuation	Prior to the observational period • SARS-CoV-2 infection • Discontinued • Outside vaccination
Two dose cohort	Maximum of • Unblinding date • Second dose of Ad26.COV2.S	Minimum of • Endpoint observed • Outside vaccination • Third Ad26.COV2.S vaccination • Discontinuation	At least 2 doses of Ad26.COV2.S prior to PA7 site approval – 30 days and prior to study discontinuation	Prior to observational period • SARS-CoV-2 infection • Discontinued • Outside vaccination • More than 70 days between first and second

Table 5: Risk set and observational period

Risk set	Start of observational period	Censoring End of observational period	Inclusion criteria	Exclusion criteria
		• PA7 site approval – 30 days		Ad26.COV2.S vaccination
Booster dose cohort	Maximum of • Unblinding date • Second dose of Ad26.COV2.S	Minimum of • Endpoint observed • Outside vaccination • Third Ad26.COV2.S vaccination • Discontinuation • PA7 site approval – 30 days	At least 2 doses of Ad26.COV2.S prior to PA7 site approval – 30 days and prior to study discontinuation	Prior to observational period • SARS-CoV-2 infection • Discontinued • Outside vaccination • 70 days or less between first and second Ad26.COV2.S vaccination

5.2.1. Study dose cohorts

Participants will be allocated to the study dose cohorts, if they are part of the risk sets and if they have follow-up time within the observational period, as follows:

- One-dose schedule cohort: participants who only received a single dose of the Ad26.COV2.S vaccination. Participants who received a further Ad26.COV2.S vaccination remain in this cohort until they received their second vaccination.

- Two-dose schedule cohort: participants who received two doses of the Ad26.COV2.S vaccination with a maximum gap between doses of 70 days.

- Booster dose schedule cohort: participants who received two doses of the Ad26.COV2.S vaccination with a minimum gap between doses of 71 days.

5.2.2. Risk sets

The risk set for each study dose cohort will include adults ≥18 years with or without comorbidities associated with increased risk of progression to severe COVID-19 who do not discontinue or receive another COVID-19 vaccination or have a SARS-CoV-2 infection (positive PCR result or positive serology test) prior to the start of the observation period (ie before their follow-up is counted under the relevant dose cohort). Subjects where the date of unblinding is unknown will also be excluded from the risk sets since it is not possible to accurately determine the start of the open-label observational period.

Additionally, for the one-dose cohort, subjects that are unblinded and receive a second Ad26.COV2.S vaccination on the same day as unblinding will be excluded from the risk set, since they are not considered to contribute one whole day of follow-up.

An overview of the risk sets and the in and exclusion criteria are presented in Table 5.

5.2.3. Observational period

The start of the observational period differs per dose cohort as follows: for subjects in the one-dose schedule cohort the observation period starts at the date of unblinding. If the date of the first Ad26.COV2.S vaccination is after the date of unblinding, then the observational period starts at the date of first Ad26.COV2.S vaccination. For subjects in the two-dose schedule cohort and subjects in the booster dose schedule cohort the observation period starts at the date of the second dose. If the date of the second dose is prior to unblinding then the observational period will start from the date of unblinding. Note that the first 28 days after vaccination, named the blackout period, are excluded. The start of the observational period is presented by dose cohort in Table 5.

The end of the observational period is also different per dose cohort. The observational period ends when the participants experience an endpoint of interest, or the observational period is censored when an outside vaccination is received, 30 days prior to the site approval of PA7 or when the participant discontinued. Additionally for the one-dose cohort the observational period is censored when a second Ad26.COV2.S vaccination is received, and for the two-dose cohort and the booster dose cohort the observational period is censored when a third Ad26.COV2.S vaccination is received.

The calculation of follow-up time is described in section 5.2.5.

5.2.4. Efficacy endpoints

Details on the COVID-19 case classification are described in the SAP for the double-blind phase. As described in that SAP, COVID-19 classifications are performed by two methods: one consisting of a programmed algorithm and one consisting of an assessment by the CSAC. Of note, as described in the introduction, the clinical development program has moved from “Development” to a “Life cycle management” phase. Hence the scope and the extent of the open-label analysis have been reduced. No efficacy analysis will be assessed during the open-label phase of the trial. No relative vaccine efficacy nor group comparisons will be calculated. The efficacy endpoints will be presented descriptively per dose cohort. Note that since July 8 2022, no suspected COVID-19 cases were sent for adjudication. Additionally some suspected COVID-19 cases that were sent prior to July 8 2022 were never adjudicated. Therefore, in the open-label phase, not all COVID-19 cases will have an evaluation of severity by the CSAC. Therefore all tables, figures and listings presenting the COVID-19 cases that occurred during the open-label phase are assessed by the programmed algorithm only.

For each of the endpoints listed below, the number of cases and incidence per 100 person-years will be presented for each study dose cohort by month. Cumulative incidence plots per endpoint by calendar time for each study dose cohort will be provided. For the endpoint of moderate to severe/critical COVID-19 this plot will be repeated by region and by country.

1. Molecularly confirmed moderate to severe/critical COVID-19 infection at least 28 days after last vaccination

2. Molecularly confirmed severe/critical COVID-19 infection at least 28 days after last vaccination

3. Molecularly confirmed symptomatic COVID-19 infection at least 28 days after last vaccination

4. Molecularly confirmed COVID-19 infection requiring medical intervention at least 28 days after last vaccination

5. COVID-19 related death at least 28 days after last vaccination

5.2.4.1. Programmed algorithm for molecularly confirmed COVID-19 infection requiring medical intervention

A COVID-19 infection is considered to require medical intervention if the subject has one of the following recorded as a medical encounter in the CRF for a molecularly confirmed COVID-19 episode:

- “HOSPITAL INPATIENT DEPARTMENT"
- "MECHANICAL VENTILATION USE"
- "INTENSIVE CARE UNIT"

5.2.4.2. Programmed algorithm for COVID-19 related death

A COVID-19 infection is considered to be a COVID-19 related death if the participant had a fatal AE related to COVID-19 with a molecularly confirmed PCR test.

5.2.5. Follow-up for Efficacy Endpoints

Median, minimum, maximum, and interquartile range of the follow-up time in the observational period will be provided by study dose cohort of the efficacy risk set. The reason for the end of follow-up will also be included in the table.

For subjects in the one-dose schedule cohort the follow-up time is calculated from date of unblinding. If the date of the first dose is after the date of unblinding, then the follow-up time will start at the date of first dose. For subjects in the two-dose schedule cohort and subjects in the booster dose schedule cohort the follow-up time starts from the date of the second dose. If the date of the second dose is prior to unblinding then the follow-up time will start from the date of unblinding. The first 28 days after vaccination are excluded. Additionally follow-up time from first study vaccination and follow-up time from last Ad26.COV2.S vaccination will also be presented by study dose cohort of the efficacy risk set.

The follow-up time for an individual will be censored at i) the date of receipt of another authorized/approved COVID-19 vaccine, including the Janssen COVID-19 vaccine if received outside of the study, ii) the date of study discontinuation or completion, iii) 30 days prior to the date of study site approval for PA7, or iv) the date the endpoint was observed, whichever occurred first. Additionally, for subjects in the single-dose schedule cohort the date of a second

Ad26.COV2.S vaccination will be considered as a reason for censoring and for subjects in the two-dose and the booster dose cohorts, the date of a third Ad26.COV2.S vaccination will be considered as a reason for censoring.

Kaplan-Meier (KM) plots will be produced for the follow-up time in the observational period for each study dose cohort in the efficacy risk set for each endpoint overall and by country. KM plots of follow-up time from first study vaccination and for follow-up time from last Ad26.COV2.S vaccination will also be produced for each study dose cohort in the efficacy risk set for each endpoint overall. Additionally, a graph using calendar time will be produced to present the number of subjects at risk for moderate to severe/critical COVID-19 during the observational period in each study dose cohort overall and by country and by region. Also a graph using calendar time for the full set of participants from the FAS, including participants who were not part of the risk set, will be produced to present the number of subjects at risk for moderate to severe/critical COVID-19 from the start of the study by vaccination group.

5.2.6. Subgroups

For each of the endpoints listed in section 5.2.4 the number of cases and incidence rates per 100 person-years will be presented by month and the following subgroup:

- Country and/or region

5.2.7. Supportive Analysis

Demographics and baseline characteristics

Demographic tables including baseline characteristics comparing the study dose cohort risk sets.

Severity ratio

The severity ratio will be calculated as the ratio between severe cases and both severe and moderate cases. This ratio will be presented for each of the study dose cohorts.

Long COVID-19 ratio

The long COVID-19 ratio will be calculated as the ratio between long COVID-19 cases and both long and short cases. This ratio will be presented for each of the study dose cohorts. An episode lasting more than 28 days is considered to be a long COVID-19 case and an episode lasting 28 days or less a short COVID-19 case.

5.2.8. Patient-Reported Outcomes

5.2.8.1. Symptoms of Infection with Coronavirus-19 (SIC)

The SIC is a disease-specific patient-reported outcome (PRO) instrument that is completed by the participant, self-administered. The SIC has a total of 30 items assessing signs and symptoms of COVID-19. The first 25 items, the participant indicates “yes” or “no” if they have a symptom and if “yes” report a severity from 0 (none) to 10 (worst possible). The second part has the participant

enter their temperature, and the third part has the participant record "yes" or "no" (absence or presence of additional signs and symptoms). The analyses are conducted in two ways, by part 1, part 2 and part 3, scored separately, and also grouped into related categories for composite scoring.

SIC Analysis Approach One:

- Part 1 (25 symptoms): Each symptom is present or absent (0), and if present rated on a 10 point scale ranging from 0 (None) to 10 (Worst possible).

The **symptom score** is the mean score of all items on the SIC for each day, during the COVID-19 episode.

The **symptom duration** is the period from the first day of symptoms till the last day with symptoms in Days (calculated as last day with symptoms – first day of symptoms + 1).

The **symptom AUC** is the area under the curve for the complete COVID-19 episode.

The **peak symptom score** is the maximum of all the symptom scores during the COVID-19 episode.

- Part 2: Fever/ temperature.

Fever will be scored (fever score) as the maximum recorded temperature for each day during the COVID-19 episode.

Fever will be coded as 'Present' if the fever score is ≥38.0 ºC or ≥100.4 ºF and 'Absent' otherwise.

The **total fever days** is the number of days with fever present during the COVID-19 episode.

Fever duration will be the period from the first day with fever till the last day with fever in Days (calculated as last day with fever – first day of fever + 1).

The **peak fever** is the maximum fever score during the COVID-19 episode.

The **fever AUC is** the AUC of fever score during the total of fever days of the COVID-19 episode. (For the AUC if there is a single missing day between days with fever the missing day will be ignored, ie, interpolation will be used in the calculation of the AUC.)

- Part 3: Each of the 3 specific symptoms is either present (1) or absent (2).

The **specific symptom score** is the mean of all scores during the COVID-19 episode.

The **specific symptom duration** is the duration of specific symptoms during the COVID-19 episode from the first day with a specific symptom until the last day with a specific symptom in Days (calculated as last day with a specific symptom – first day of a specific symptom + 1).

The **total specific reported symptom score** is the mean of all scores during the COVID-19 episode at which a subject has reported at least one specific symptom.

Note 1: For Part 1, total scores will be calculated based on the number of assessments completed by the participant per day and in cases where more than 75% of the items needed to calculate the score is not collected (reported as no answer to the part 1 Yes/No possibility AND no severity rate), then the value for that score will be set to missing. For example, if a participant has responded to 7 or more out of the 25 symptom scale questions the score will be the mean of the available questions. If the participant has only completed 6 or less of the questions then the symptom score will be set to missing, unless a subject has only provided responses 'Yes' to all of the answered questions (then it is assumed that the subject only noted the pertinent symptoms for that day). In case of missing severity rate and the answer was 'yes' the rate will be imputed by '5'.

SIC Analysis Approach Two: Composite Scoring

For the purpose of computing the SIC composite scores, the 25 SIC symptom items with severity ratings (part 1) are scored such that item scores range from 0 ("No," ie, not experienced; or "None") to 10 ("Worst possible"). Except for the Sensory score, SIC composite scores are computed as the average of the symptom severity ratings for each set of items (Constitutional [where C7 = 0 if NO, 10 if YES], Gastrointestinal, Musculoskeletal, Neurological, Respiratory, Upper Respiratory, Lower Respiratory). The average composite score is a number between 0 and 10 (inclusive). Because all SIC composite scores are in the same metric as the item-level severity ratings, this links the interpretation of the SIC composite scores to the items, with higher scores reflecting worse symptoms.

Constitutional. The SIC includes 7 Constitutional items, 2 of those items use a dichotomous response scale (C6: Fever, C7: Uncontrollable body shaking/shivering). The constitutional score includes C7 as well as the 5 Constitutional items that use the 11-point severity rating scale (C1: Feeling generally unwell, C2: Fatigue (tiredness), C3: Chills, C4: Skin rash, C5: Eye irritation/discharge). To allow scoring in the 0-10 item metric, a "Yes" to C7 was re-coded to a value of 10 given the severe nature of rigors. The SIC Constitutional score is the equally weighted average of 6 Constitutional items (excluding C6). Fever as described above is analyzed on its own (part 2 of SIC Analysis Approach1):

Constitutional = average of (C1, C2, C3, C4, C5, C7) *where C7* = 0 if NO, 10 if YES

Gastrointestinal. The SIC Gastrointestinal score is an equally weighted average of the severity ratings of all 5 SIC items related to Gastrointestinal symptoms (G1: Diarrhea, G2: Vomiting, G3: Nausea, G4: Abdominal/stomach pain, G5: Loss of appetite):

Gastrointestinal = average of (G1, G2, G3, G4, G5)

Musculoskeletal. The SIC Musculoskeletal score is an equally weighted average severity ratings of 3 items (M1: Physical weakness, M2: Muscle aches/pains, M3: Joint aches/pains):

Musculoskeletal = average of (M1, M2, M3)

Neurological. The SIC Neurological score is an equally weighted average severity ratings of 3 items (N1: Headache, N2: Feeling faint, N3: Problems thinking clearly/brain fog):

Neurological = average of (N1, N2, N3)

Sensory. Two SIC items (N4: Decreased sense of smell, N5: Decreased sense of taste) are a 2-item Sensory composite score with 3 possible values:

Sensory = 0 if NO to both N4: Decreased sense of smell and N5: Decreased sense of taste

= 5 if YES to only one of the 2 items (and NO to the other item)

= 10 if YES to both items

Respiratory. The SIC Respiratory score is an equally weighted average severity rating of all 9 Respiratory items (R1: Cough, R2: Shortness of breath, R3: Sore throat, R4: Nasal congestion, R5: Wheezing, R6: Runny nose, R7: Sneezing, R8: Chest congestion, R9: Chest pain/pressure/tightness):

Respiratory = average of (R1, R2, R3, R4, R5, R6, R7, R8, R9)

In addition, separate Lower Respiratory and Upper Respiratory SIC scores were computed:

Lower Respiratory = average of (R1, R2, R5, R8, R9)

Upper Respiratory = average of (R3, R4, R6, R7)

For each composite the following analysis will be conducted:

The **<Composite name> symptom score** is the mean of all scores for each day, during the COVID-19 episode.

The **<Composite name> symptom duration** is the period from the first day of symptoms till the last day with symptoms in Days (calculated as last day with symptoms – first day of symptoms + 1).

The **<Composite name>symptom AUC** is area under the curve for the complete COVID-19 episode.

The **<Composite name> peak symptom score** is the maximum of all the symptom scores during the COVID-19 episode.

After completing the SIC, each day the participant completed a Patient Global Assessment of Severity, asking them to rate the severity of their symptoms in the last 24 hours with responses of “No Symptoms”, “Mild”, “Moderate” or “Severe”

5.2.8.2. Analysis Methods

SIC scores will be analyzed for participants with any COVID-19 episode, based on the programming algorithm, for each study dose cohort.

For continuous variables, either boxplots or plots of means with standard errors by time point (starts since onset of COVID-19 episode) will be presented per study dose cohort of the risk set. A barchart of the peak SIC score will also be provided per study dose cohort of the risk set.

5.3. Efficacy Analysis of the Open-Label Passive Follow-up Phase

Since PA7, suspected COVID-19 cases are followed up in a passive manner. There are no nasal swabs and no signs and symptoms collected for suspected COVID-19. Suspected COVID-19 cases are collected via a passive safety reporting of adverse events.

The efficacy analysis of the open-label passive follow-up phase includes all COVID-19 data collected as adverse events from the date that the site approves PA7 until study end date. The endpoints of interest are: symptomatic COVID-19, severe COVID-19, COVID-19 requiring medical intervention, and COVID-19 related death.

Under PA7, the definition of symptomatic COVID-19 is adverse events with a preferred term that is included in the narrow scope of the SMQ of "COVID-19". Severe COVID-19, is defined by serious adverse events with a preferred term that is included in the narrow scope of the SMQ of "COVID-19". COVID-19 requiring medical intervention is defined by hospitalized adverse events with a preferred term that is included in the narrow scope of the SMQ of "COVID-19". COVID-19 related death is defined by the WHO assessment from the Global Medical Safety group.

The population used for the analysis in the open-label passive follow-up phase is the full analysis set who are still active in the study at the time the site approves PA7 (FAS7). Same study dose cohorts as the open-label active follow-up phase are presented (Section 5.2.1).

Similarly as for the open-label active follow-up analysis, a demographic table will be provided for the FAS7 population.

For each of the COVID-19 cases as defined above, the number of cases and incidence per 100 person-years will be presented for each study dose cohort. The denominator for the incidence rates is the number of person years in the considered period for a certain regimen (incidence per 100 person years/period). The follow-up time included for the participants will end at the period end date (study end or discontinuation date). Note that participants can have multiple COVID-19 events within the same period.

5.4. Safety Analyses

All safety analyses will be performed on the FAS or FAS7.

The presentation of the safety data is divided into 2 parts, one set of tables will be created for the entire active follow-up period covering the double blind and open-label active phase until site approval of PA7 and another set of tables will be created for the passive follow-up period covering

the safety data from site approval of PA7 until study end. The first set of tables covering the active follow-up is performed on the FAS and the second set of tables covering the passive follow-up is performed on FAS7.

No formal statistical testing of safety data is planned. All safety analyses will be presented overall and no presentations by subgroups are planned.

5.4.1. Safety data collected

The following information will be collected for:

- All participants in the FAS during the entire study (including the passive follow-up phase):
  - Serious adverse events (SAEs) and medically-attended adverse events (MAAEs) leading to study discontinuation after each vaccination
  - AEs of Special Interest (AESI)
  - Selected AEs of interest (AEI), see Appendix 6 for details
- All participants in the FAS until 6 months after last vaccination:
  - MAAEs after each study vaccination

5.4.2. Study Phases

A baseline (or reference) value will be defined as the value of the last available assessment prior to the first study vaccination on Day 1.

The safety analyses will present all results by study phase (see Section 5.4.3).

Study day or relative day is defined as follows:

- Study Day = visit date – date of Day 1 + 1; if visit date >= date of Day 1 (date of first vaccination).
- Study Day = visit date – date of Day 1; if visit date < date of Day 1 (date of first vaccination).

5.4.3. Phase Definitions

COVID-19 vaccinations given outside of the study reported under the concomitant medications will be included in the phase definitions as active vaccinations together with the study vaccinations. Subjects that have COVID-19 vaccinations on the same day or before the date of informed consent will not have a screening phase. Their first phase/period will be post-dose 1 starting from the first COVID-19 vaccination given outside of the study. Note, placebo vaccination between active vaccinations will be ignored.

For the safety data after PA7 approval, no separate phase will be created. Events that occurred in the passive follow-up phase will be flagged, and follow-up in the passive phase is calculated separately starting from the PA7 study site approval date until end of the phase or end of study.

The phases in the study will be constructed as follows:

Table 6: Phase Definitions for Safety Analysis

Phase	Phase #	Period	Period #	Interval	
				From	To
Screening	1			Date and time of signing the informed consent form	One minute prior to start of post dose 1 period
Post Dose	2	Post dose 1	1	Date and time of first vaccination	Minimum of a) 23:59 at the date of last contact (for early discontinuation or completion) b) 23:59 at the date of database cut-off date c) 23:59 on 28 days after the first vaccination (23:59 of day of vaccination + 28 days) d) One minute prior to date and time of next vaccination
Follow-up 1 (D30-M6)	3			One minute after post-dose 1 period ends	Minimum of: a) 23:59 at the date of last contact (for early discontinuation or completion) b) 23:59 at the date of database cut-off date c) 23:59 at the date of Month 6 (date of vaccination + 6 months) d) One minute prior to date and time of next vaccination
Follow-up 1 (M6-End)	4			One minute after follow-up 1 (D30-M6) ends	Minimum of: a) 23:59 at the date of database cut-off b) One minute prior to date and time of next vaccination c) maximum of: 1. 23:59 at the date of last contact (for early discontinuation or completion) 2. 23:59 at the date of last visit (for completion)
Post Dose	2	Post dose 2	2	Date and time of second vaccination	Minimum of a) 23:59 at the date of last contact (for early discontinuation or completion) b) 23:59 at the date of database cut-off date c) 23:59 on 28 days after the second vaccination (23:59 of day of vaccination + 28 days) d) One minute prior to date and time of next vaccination
Follow-up 2 (D30-M6)	5			One minute after post-dose 2 period ends	Minimum of: a) 23:59 at the date of last contact (for early discontinuation or completion) b) 23:59 at the date of database cut-off date c) 23:59 at the date of Month 6 (date of vaccination + 6 months) d) One minute prior to date and time of next vaccination

Table 6: Phase Definitions for Safety Analysis

Phase	Phase #	Period	Period #	Interval	
				From	To
Follow-up 2 (M6-End)	6			One minute after follow-up 2 (D30-M6) ends	Minimum of: a) 23:59 at the date of database cut-off b) One minute prior to date and time of next vaccination c) maximum of: 1. 23:59 at the date of last contact (for early discontinuation or completion) 2. 23:59 at the date of last visit (for completion)
Post Dose[a]	2	Post dose 3	3	Date and time of third vaccination	Minimum of a) 23:59 at the date of last contact (for early discontinuation or completion) b) 23:59 at the date of database cut-off date c) 23:59 on 28 days after the third vaccination (23:59 of day of vaccination + 28 days) d) One minute prior to date and time of next vaccination
Follow-up 3 (D30-M6)[a]	7			One minute after post-dose 3 period ends	Minimum of: a) 23:59 at the date of last contact (for early discontinuation or completion) b) 23:59 at the date of database cut-off date c) 23:59 at the date of Month 6 (date of vaccination + 6 months) d) One minute prior to date and time of next vaccination
Follow-up 3 (M6-End)[a]	8			One minute after follow-up 3 (D30-M6) ends	Minimum of: a) 23:59 at the date of database cut-off date b) One minute prior to date and time of next vaccination c) maximum of: 1. 23:59 at the date of last contact (for early discontinuation or completion) 2. 23:59 at the date of last visit (for completion)

(a) In case a treatment sequence has more than 3 vaccinations, the phases need to be added accordingly (Post-dose 4, Follow-up 4 (D30-M6). Follow-up 4 (M6-End), etc)

All vaccinations will have post-dose and follow-up phases as appropriate. The study phases are used to prepare the ADaM datasets, however for reporting purposes, some periods and phases will be combined and others will be renumbered. Specifically, after a COVID-19 vaccination outside the study, the post-dose and follow-up phases will be combined so that data after an outside vaccination can be presented as an overall period. The numbering of a post-dose period after an Ad26.COV2.S vaccination will be restarted at 1 in case that previous vaccinations were only outside vaccinations (only mRNA or only non-mRNA vaccinations) or were only placebo injections. Additionally, data following an Ad26.COV2.S vaccination will be censored at the date and time of a COVID-19 vaccination given outside of the study. Also for participants that receive

placebo after an active vaccination, the placebo injection will not be counted as a study vaccination.

When the time of the first study vaccination is missing and it occurred on the same day as the randomization, the time of vaccination will be imputed with the time of randomization. Otherwise, if the date of first vaccination is available, then the time will be imputed with 00:00 before applying the phase and period derivation rules.

In case the time of the vaccination outside the study is missing then time will be imputed with 00:00 if the date is available. In case of a partial date, then the available info will first be compared to the unblinding date and, if no imputation can be done, then the available info will be compared to the date of informed consent. If the month and year are available and they are the same as the unblinding month and year then the day is imputed with the day of unblinding, else if the month and year are the same as the informed consent month and year then the day is imputed with the day of informed consent, otherwise the day is imputed with the first day of that month. If the month and day are missing then the year will be compared with the year of unblinding. If the year is the same then the month and day are imputed with the day and month of the unblinding date, else if the year is the same as the informed consent year then the month and day are imputed with the day and month of informed consent, otherwise the other vaccine date is imputed with the first of January of that year. If the date and time of the outside vaccination is fully missing, then the date is imputed with the ICF date.

For subjects that initially receive placebo and subsequently receive active vaccinations, separate post-dose periods will be created for the placebo injections and the active vaccinations. For subjects that receive placebo after an active vaccination, no post-dose period or follow-up periods for the placebo injection will be created.

5.4.4. Vaccination groups

All safety analyses will be tabulated by vaccination group according to the *as treated* principle. The COVID-19 vaccinations received outside of the study are considered as well. Participants can be present in more than 1 vaccination group as described below. Safety data by vaccination group will be analyzed descriptively.

The following vaccination groups will be presented:

A. Layout 1a:
   1. Placebo
      All participants who received as first vaccination a placebo injection. All safety data will be reported here until the participant receives an active COVID-19 vaccination (Ad26.COV2.S or outside vaccination).
   2. Ad26.COV2.S
      All participants who received as first active COVID-19 vaccination Ad26.COV2.S until the participant receives an outside COVID-19 vaccination. This includes participants who initially received placebo and subsequently received Ad26.COV2.S, however only the safety data after the Ad26.COV2.S vaccination until the participant receives an outside

COVID-19 vaccination (if applicable) will be presented here. The safety data of participants who received 2 or more Ad26.COV2.S vaccinations will be presented by post-dose 1, post-dose 2, etc.

B. Layout 1b:
   1. mRNA/non-mRNA vaccination + Ad26.COV2.S
      All participants who received as first active COVID-19 vaccination one or more outside mRNA vaccinations or one or more outside non-mRNA vaccinations and subsequently also received an Ad26.COV2.S booster vaccination. Only the safety data after the Ad26.COV2.S vaccination until the participant receives another outside COVID-19 vaccination (if applicable) will be presented here. The safety data of participants who received 2 or more Ad26.COV2.S vaccinations after being primed with non-mRNA/mRNA will be presented by post-dose 1, post-dose 2, etc.

C. Layout 2:
   1. Mixed schedule
      The safety data after all other vaccination schedules will be included here. This includes safety data after receipt of only outside vaccinations, after outside vaccinations when primed with Ad26.COV2.S, after outside vaccinations prior to first Ad26.COV2.S vaccination, or any other combination switching between outside vaccinations and Ad26.COV2.S. Note that participants who have a vaccination given outside of the study on the same day as the first study vaccination will have all safety data presented in the mixed schedule vaccination group.

Subjects that switch between Ad26.COV2.S vaccinations and COVID-19 vaccinations given outside of the study (and vice versa) will be presented in the relevant vaccination group depending on the actual vaccination sequence. For example:

1. Vaccination sequence: Ad26.COV2.S, outside COVID-19 vaccination, Ad26.COV2.S

Safety data for subjects following this sequence will have data following the first Ad26.COV2.S vaccination up to the date of the outside COVID-19 vaccination presented in the outputs showing first active vaccination is Ad26.COV2.S (layout 1a). All data following the outside COVID-19 vaccination will be presented in the outputs for the mixed schedule vaccination group (layout 2).

2. Vaccination sequence: outside COVID-19 vaccination, Ad26.COV2.S, outside COVID-19 vaccination

Safety data for subjects following this sequence will have data following the first outside COVID-19 vaccination up to the date of the Ad26.COV2.S vaccination presented in the outputs for the mixed schedule vaccination group (layout 2). The data following the Ad26.COV2.S vaccination up to the date of the second outside COVID-19 vaccination will be presented in the outputs for Ad26.COV2.S after a COVID-19 vaccination given outside of the study (layout 1b) so long as the previous outside vaccinations were always mRNA or always non-mRNA. The data following the second outside COVID-19 vaccination will be presented in the outputs for the mixed schedule vaccination group (layout 2).

For outputs using layout 1a or 1b, all tables will be produced by study phases and periods per vaccination group, ie post-dose, follow-up D30-M6, follow-up M6-end. For the mixed schedule vaccination group (layout 2) only the AE summary table will be produced presenting data for the entire study period, ie not presented by study phases.

The safety analyses will be performed for the combined double-blind and open-label active phase for the FAS.

5.4.5. Safety data for the Passive Follow-up Phase

The safety data collected after PA7 approval encompass SAEs, AEIs, AESIs and MAAEs.

Safety data after the study site approval of PA7 will be presented in separate tables from the active follow-up. All participants of the full analysis set are included who are still active at the time of the study site PA7 approval (FAS7). The same vaccination groups will be presented as in Section 5.4.4 and the same phases as in Section 5.4.2 are used. If subjects received an outside vaccination under PA7 then they are additionally counted in the relevant vaccination group. For example: if a participant received 2 doses of Ad26.COV2.S during the open-label active follow-up and received one additional outside vaccine in the passive follow-up, then they are counted under layout 1a; and not under the mixed schedule group for the active follow-up tables, but they are counted under layout 1a and under the mixed schedule group for the passive follow-up tables.

5.4.6. Adverse Events

5.4.6.1. Definitions

SAEs, AESIs, AEIs, and MAAEs leading to study discontinuation, will be tabulated in the outputs covering the active follow-up period (the active follow-up, including the double-blind phase and open-label active phase and separately for the passive follow-up), and MAAEs (including new onset of chronic diseases) will be tabulated in the outputs covering the 6 months after last vaccination period for all participants in the FAS and FAS7 respectively.

An overall summary table for the entire study period (combined double-blind phase, open-label active phase, and open-label passive phase) will also be produced for subjects that received at least 1 dose of Ad26.COV2.S presenting the number and percentage of subjects with events.

The severity of the AEs will be classified as grade 1 to 4 by the investigator.

The AEIs (selected adverse events of interest) are presented by customized group term and MedDRA preferred term as detailed in Appendix 6 Adverse Events of Interest (AEI).

For AESI analyses, the following subcategories are defined:

- Suspected AESIs as identified by the investigator in the database
- Suspected AESIs selected programmatically

  Those include all reported AEs that are identified by the selection rule:

  - SMQ = "EMBOLIC AND THROMBOTIC EVENTS (SMQ)" or
  - (SUB_SMQ1 = "HAEMATOPOIETIC THROMBOCYTOPENIA (SMQ)" and SCOPE in ("BROAD", "NARROW")) or HLT (higher level term)="Thrombocytopenias"

- Qualified for assessment AESIs are thromboembolic events which are reported within 42 days of thrombocytopenia/low platelet counts reported concurrently for the same participant. These events have risk levels assessed by one of the following three criteria:

  - Brighton Collaboration Level (Level 1-5)
  - Center for Disease Control and Prevention (CDC) Tier (non-tier 1/ 2, tier 1, tier 2)
  - Pharmacovigilance Risk Assessment Committee (PRAC) criteria (confirmed, possible, probable, unlikely, criteria not met)

5.4.6.2. Analysis of Adverse Events

The number and percentage of participants with at least one particular AE will be tabulated with exact 95% CI, when appropriate. Additionally the incidence rate will also be derived as number of participants with at least one particular AE per 100 person years of follow-up. Unsolicited AEs will be summarized by System Organ Class and Preferred Term.

Denominator for the percentages is the number of participants in the considered population and phase for a certain vaccination group (incidence per 100 participants/phase). Denominator for the incidence rates is the number of person years in the considered population and phase for a certain vaccination group (incidence per 100 person years/phase).

For unsolicited AEs, the following tables will be provided: summary table (including SAEs, SAEs related to study vaccine, MAAEs, MAAEs leading to study discontinuation, MAAEs related to study vaccine, AEs with fatal outcome, AEs related to study vaccine with fatal outcome, AEs related to study vaccine leading to study discontinuation, and AEs leading to study discontinuation), all events, AEs at least grade 3, AEs related to study vaccination, AEs at least grade 3 and related to study vaccination, AEs leading to study discontinuation, SAEs related to study vaccination, SAE (overall, associated with COVID, not associated with COVID), MAAE, selected AEs of interest, fatal AEs, and AESI.

Listings and/or participant narratives will be provided as appropriate, for those participants who die, discontinue study due to an AE, or experience a serious AE.

5.4.6.3. Phase Allocation of Adverse Events

Step 1: Allocation of events to the periods:

Adverse events in the study data tabulation model (SDTM) database are allocated to periods based on their start date/time. If the start date/time of an event falls between (or on) the start and stop date/time of a period, the AE is attributed to that period (treatment-emergent principle).

- In case of partial start or stop dates (ie time and/or day and/or month and/or year missing), the events are allocated to the periods using the available partial information on start and end date; no imputation will be done. If, for instance, for the AE start date only month and year are available, these data are compared to the month and year information of the periods. This rule may lead to multiplication of the event as a consequence of its assignment to multiple periods.

- In case of a completely missing end date, the date is imputed by the cut-off date of the analysis for participants still ongoing in the study, and by the end date of the last period for participants who discontinued or completed the study. In case of a completely missing start date, the event is allocated to the first active treatment phase (post dose period 1), except if the end date of the AE falls before the start of the first active treatment phase (post dose period 1).

Step 2: Combination of events:

Overlapping/consecutive events are defined as events of the same participant with the same preferred term which have at least 1 day overlap or for which the start date of an event is 1 day after the end date of the preceding event. Overlapping/consecutive events may be combined into one AE or not, according to the following rules:

1. If overlapping/consecutive events start in one of the following periods - Screening or post dose extension (ie non-active periods) - followed by an AE in - post-dose period (active period) - they are allocated to their respective periods and are considered as separate events.
2. In case overlapping/consecutive events start within a single period, they are considered as one and the same AE. The individual events which contribute to this AE are retained as individual records in the Analysis Data Model (ADaM) database but are assigned the same onset, period, and total duration. All related attributes to the AE/phase/period should also be consistent with the new event.
3. In case overlapping/consecutive events start in both an active period followed by a non-active period, they are allocated to the active period only and are considered as one and the same AE. The individual events which contribute to this AE are retained as individual records in the ADaM database but are assigned the same onset, treatment period, and total duration. All related attributes to the AE/phase/period should also be consistent with the new event.
4. In case an active period is followed by another active period, and the overlapping/consecutive events start in both periods, they are allocated to their respective period and are considered as separate AEs. The same rule applies for 2 non-active periods.

Remarks:

1. Events can only be combined into one and the same AE if their start and stop dates are known.

2. In case the completely missing end date is imputed (for period allocation), this date is also considered as a complete date.
3. Time is not considered when determining overlap of events.

5.4.6.4. Missing Data

Missing data will not be imputed. Participants who do not report an event/concomitant medication will be considered as participants without an event/concomitant medication. An AE with a missing severity or relationship will be considered as an AE reported, but will be considered as not reported for the severity or relationship. For example, an AE with missing severity will be considered as an AE reported for the analysis of any grade, but will be considered as not reported for the analysis of at least grade 3.

5.4.7. Vital Signs

For all participants, weight and height (and BMI) at baseline will be summarized using descriptive statistics.

No other presentations of vital signs are planned.

5.4.8. Follow-up of Safety data

Median, minimum, maximum, and interquartile range of the follow-up time from first study vaccination for each of the vaccination groups (except the mixed schedule group) of Section 5.4.4 will be provided for the FAS. Separate tables will be produced for the combined double-blind, open-label active, and open-label passive phase and for the combined double-blind and open-label active phase.

For the tables covering the combined double-blind and open-label active phase:

The follow-up time for an individual who initially received placebo will be censored at i) the date of receipt of Ad26.COV2.S or a vaccination given outside of the study, ii) the date of study discontinuation, iii) the date of study site approval for PA7, or iv) the date of database cutoff, whichever occurred first. The follow-up time for an individual whose first active vaccination was Ad26.COV2.S will be censored at i) the date of receipt of a vaccination given outside of the study, ii) the date of study discontinuation, iii) the date of study site approval for PA7, or iv) the date of database cutoff, whichever occurred first. For the vaccination groups that received first an mRNA or non-mRNA vaccination and then an Ad26.COV2.S vaccination, the follow-up will start from the first Ad26.COV2.S vaccination and will be censored at i) the date of receipt of a vaccination given outside of the study, ii) the date of study discontinuation, iii) the date of study site approval for PA7, or iv) the date of database cutoff, whichever occurred first.

For the tables covering the combined double-blind, open-label active phase, and open-label passive phase the follow-up time is not censored at the date of study site approval of PA7.

5.5. Immunogenicity

5.5.1. Immunogenicity (Double-Blind Phase)

Blood will be collected from all participants for humoral immunogenicity assessments before the 1st vaccination (for subjects enrolled during the double-blind phase of the study), at the open-label unblinding visit (prior to vaccination, where applicable), at the booster vaccination visit (prior to vaccination) and also at Day 71 (visit 5) or Week 32 (visit 7).

During a COVID-19 episode, blood will be collected on COVID-19 Day 3-5 and on COVID-19 Day 29 and immunogenicity assessments may be performed, including the assays summarized in Table 7.

No immunogenicity analyses will be performed for the combined double-blind and open-label active phase. Immunogenicity analyses for the double-blind phase have already been reported.

Table 7: Overview of Immunogenicity assessments

Humoral Assays	Purpose
Supportive of Secondary Objectives	
SARS-CoV-2 binding antibodies to S protein (ELISA)	Analysis of antibodies binding to SARS-CoV-2 S protein
SARS-CoV-2 seroconversion based on antibodies to N protein (ELISA and/or SARS-CoV-2 immunoglobulin assay)	Analysis of antibodies binding to SARS-CoV-2 N protein
Supportive of Exploratory Objectives	
SARS-CoV-2 neutralization (VNA)	Analysis of neutralizing antibodies to the wild-type or variant virus, and/or pseudovirion expressing S protein
SARS-CoV-2 binding antibodies to S protein (MSD)	Analysis of antibodies binding to SARS-CoV-2 S protein (different than the assays supportive of the secondary objectives) and the receptor-binding domain (RBD) of SARS-CoV-2 S protein
Functional and molecular antibody characterization	Analysis of antibody characteristics including, but not limited to, avidity, Fc-mediated viral clearance, Fc characteristics, Ig subclass, IgG isotype, antibody glycosylation, and assessment of antibody repertoire
Adenovirus neutralization (VNA)	Adenovirus neutralization assay to evaluate neutralizing antibody responses against the Ad26 vector
Binding antibodies to other coronaviruses (MSD)	Analysis of antibodies binding to coronaviruses other than SARS-CoV-2

Ad26 = adenovirus type 26; ELISA = enzyme-linked immunosorbent assay; Fc = crystallizable fragment; Ig(G) = immunoglobulin (G); MSD = Meso Scale Discovery; N = nucleocapsid; RBD = receptor-binding domain; S = spike; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; VNA = virus neutralization assay.
*N-serology used for assessment of asymptomatic SARS-CoV-2 assessment, rather than immunogenicity of Ad26.COV2.S as SARS-CoV-2 nucleocapsid is not included as antigen in the vaccine

5.5.2. Immunogenicity (Open-Label Passive Phase)

During the open-label passive phase (following study site approval of PA6 and PA7), for participants who are not part of the Immunogenicity Subset, no samples for assessment of immunogenicity will be taken. For a total of approximately 200 participants from the on-active

group of the Immunogenicity Subset (double-blind phase), blood will be collected for analysis of humoral immune responses at Week 32 (visit 7), Week 60 (visit 8), Week 86 (visit 9), and Week 112 (visit 10).

The analysis of immunogenicity will use the PPI set.

Humoral immunogenicity data will be analyzed according to the as-treated principle by vaccine regimen (2-doses of Ad26.COV2.S), by vaccine regimen and participant seropositivity status at screening, by vaccine regimen and age and comorbidity (with/without) strata, and by vaccine regimen and region.

Correlate of immunity will not be assessed in this study.

5.5.2.1. Parameters

The following humoral immune responses are measured by immunogenicity against the insert using humoral immune responses, including titers of neutralizing antibodies and S-ELISA titers, functional and molecular antibody characterization and RBD antibodies and N-ELISA positivity. Immunogenicity against the vector may be explored using an adenovirus neutralization assay to assess neutralizing antibody responses against the vector.

5.5.2.2. Handling of Missing and/or Unquantifiable Immune Response Data

Missing immune response data will not be imputed.

- Values will be imputed based on the type of analysis. For the calculation of the geometric mean titer, values below LLOQ will be imputed to LLOQ/2. While for the calculation of the fold increase from baseline, values below LLOQ will be imputed to LLOQ. The LLOQ values per assay are available in the database.

Values above the upper limit of quantification (ULOQ) will be imputed with the ULOQ for both the calculation of geometric mean and fold increase from baseline.

In case a LOD is reported, the same rules as described above for LLOQ are applied.

5.5.2.3. Immune Response Analysis

No formal hypothesis on immunogenicity will be tested.

5.5.2.4. Immunogenicity Against the Insert:

5.5.2.4.1. Humoral assays

For VNA (both wild-type virus and pseudovirion expressing S protein, as available), S-ELISA, and ADCP assays, the following results will be calculated: N, geometric mean[a§] and corresponding

[a] calculate the mean and corresponding 95% CI of the $\log_{10}$ transformed values, back-transform this mean [i.e. 10^mean] and CI [i.e. 10^CI].

95% CI of the actual values and fold increases from baseline will be tabulated and graphically presented.

For the calculation of the geometric mean and its corresponding 95% CI, the arithmetic mean and its corresponding 95% CI are calculated on the $\log_{10}$ transformed values. These values are back transformed to provide the geometric mean and its corresponding 95% CI.

For wild type, pseudovirion VNA, S-ELISA, and ADCP separately:

• A sample will be considered positive if its value is strictly greater than the LLOQ (>LLOQ).

• Responder definition. A post-baseline sample will be considered a responder if at least one of the following conditions is satisfied:

- The baseline sample value is less than or equal to the LLOQ (≤LLOQ) and the post-baseline sample is strictly greater than the LLOQ (>LLOQ)
- The baseline sample value is strictly greater than the LLOQ (>LLOQ) and the post-baseline sample value represents an at least 4-fold (≥4-fold) increase from the baseline sample value.

Actual values are tabulated and shown as box plots with the corresponding geometric mean, 95% CI per time point and minimum and maximum are shown for each assay. For the Immunogenicity Subset actual values are tabulated and shown as dot plots with dots for participant values, and the corresponding geometric mean and 95% CI per time point for each assay.

In addition, geometric mean titer (GMT) plots over time, combining the regimens in one graph (without individual participant dots) will also be generated.

Participant profiles of the actual values over time will be graphically presented for Covid-19 cases.

Correlation plots between humoral assay results will be performed for selected time points.

In graphs, original values will be displayed on a $\log_{10}$ scale.

Further details may be provided in the DPS. For the **N-serology** the proportion of participants that are positive will be tabulated.

5.5.2.5. Immunogenicity Against the Vector

For immunogenicity against the Ad26 vector backbone (Adenovirus neutralization by neutralization assay), the following statistics will be calculated if assessment is performed: geometric mean and corresponding 95% CI of the actual values, and number and percentage of participants with a positive sample.

Correlation plots with the Adeno assays versus the assays against the inserts will be provided for the most important time points.

5.6. Interim Analyses

No interim analyses are planned for the open-label phase of the study.

5.6.1. Independent Data Monitoring Committee (IDMC)

The study will be formally monitored by an Independent Data Monitoring Committee (IDMC, also known as a Data Safety Monitoring Board or DSMB). In general, the IDMC will monitor safety data on a regular basis to ensure the continuing safety of the participants. Enrollment (if applicable) will not be paused during regular safety reviews. The IDMC will review unblinded data. The IDMC responsibilities, authorities, and procedures will be documented in the IDMC Charter.

Since the safety of Ad26.COV2.S has been established, in February 2022 the IDMC agreed that there was no need to continue reviewing safety data for this study.

5.6.2. Clinical Severity Adjudication Committee

The Clinical Severity Adjudication Committee will review all cases in the study, except for cases already adjudicated as severe, as a supplement to the algorithm described in the double-blind SAP, as well as those requiring medical intervention (such as a composite endpoint of hospitalization, ICU admission, mechanical ventilation, and ECMO, linked to objective measures such as decreased oxygenation, X-ray or CT findings), including onset of cases, taking into account all available relevant information at the time of adjudication (as explained in the charter). Depending on an algorithmic selection the cases will be sent for adjudication on a case by case basis or on a sample approach, as explained inthe double-blind SAP. Readjudication will occur if new information becomes available. The last adjudication for a given case will determine the status of the case for analysis.

As of 8 July 2022, no further adjudication was performed and no efficacy endpoints will be created based on the CSAC assessment for the analysis of the open-label phase of the study.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

ADaM	Analysis Data Model
AE	adverse event
AESI	Adverse event of special interest
ATC	Anatomical Therapeutic Chemical classification system
BMI	body mass index
CD4	cluster of differentiation 4
CDC	Center for Disease Control and Prevention
CI	confidence interval
COVID-19	coronavirus disease-2019
CRF	case report form
CTP	clinical trial protocol
DD	drug dictionary
DPS	Data presentation specifications
eCOA	electronic clinical outcome assessment
ECMO	extracorporeal membrane oxygenation
ELISA	enzyme-linked immunosorbent assay
FAS	full analysis set
FDA	Food and Drug Administration
GMR	geometric mean ratio
GMT	Geometric Mean Titer
ICF	informed consent form
IDMC	Independent Data Monitoring Committee
LLOD	lower limit of detection
LLOQ	lower limit of quantification
MAAE	medically-attended adverse event
MPD	Major Protocol Deviation
PP	per protocol efficacy analysis set
PPI	per protocol immunogenicity analysis set
PRAC	Pharmacovigilance Risk Assessment Committee
RBD	receptor-binding domain
RNA	ribonucleic acid
RT-PCR	reverse-transcriptase polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDTM	Study Data Tabulation Model
SMQ	Standardized MedDRA Query
ULOQ	upper limit of quantification
US	United States
VE	vaccine efficacy
VNA	virus neutralization assay
vp	virus particle
WHO	World Health Organization

6.2. Appendix 2 Demographics and Baseline Characteristics

The following demographic and baseline characteristics will be summarized.

Table 8 presents a list of the demographic variables that will be summarized by vaccine regimen and overall for the FAS. Demographics will also be summarized for the efficacy risk sets.

Table 8: Demographic Variables

Continuous Variables:	**Summary Type**
Age ([years])	Descriptive statistics (N, mean, standard deviation [SD], median, range [minimum and maximum], and IQ range [first and third quartiles]).
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m^2)	
Categorical Variables	
Age group 1 ([18-≤59, ≥60 years])	Frequency distribution with the number and percentage of participants in each category.
Age group 2 (18-<40, 40-≤59, ≥60 years)	
Age group 3 (18-<40, 40-≤59, 60-≤69, 70-≤79, ≥80 years)	
Age group 4 (18-64, ≥65 years)	
Age group 5 (≥75 years)	
Sex (male, female, unknown, undifferentiated)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple, Unknown, Not reported)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino, Unknown, Not reported)	
BMI ([underweight <18.5 kg/m^2, normal 18.5-<25 kg/m^2, overweight 25-<30 kg/m^2, obese >=30 kg/m^2])	
Region (Europe, Latin America, Philippines, South Africa, United States)	
Country	
SARS-CoV-2 Seropositivity status at baseline (Positive, Negative)	
SARS-CoV-2 PCR positivity status at baseline (Positive, Negative)	
Presence of comorbidity (One or more, None)	
Baseline comorbidity category 1 (None, One, Two, 3 or more)	
Baseline comorbidity category 2 (list of comorbidities taken from the CRF)	
Working Status	
HIV infection (Positive, Negative)	
Childbearing potential for female and undifferentiated participants (Yes, No)	
Breastfeeding (Yes, No)	
Frailty index (frail, pre-frail, non-frail, unknown)[b]	

[a]If multiple race categories are indicated, the Race is recorded as 'Multiple'
[b]refer to the appendix 8 of the double-blind SAP

6.3. Appendix 3 Protocol Deviations

Major protocol deviations (MPD) will be summarized by vaccine regimen for the FAS using the categories below. An additional table will be provided to further specify the MPDs in the 'Other' category.

In general, the following list of major protocol deviations may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study. Participants with major protocol deviations will be identified prior to database lock and the participants with major protocol deviations will be summarized by category.

[Developed withdrawal criteria but not withdrawn]

[Entered but did not satisfy criteria]

[Received a disallowed concomitant treatment]

[Received wrong treatment or incorrect dose]

[Other]

6.4. Appendix 4 Prior and Concomitant Medications

The analysis of concomitant therapies will be done using the World Health Organization (WHO) drug coded terms.

For all participants, concomitant therapies associated with an SAE will be collected and recorded in the eCRF from the moment of first vaccination through the end of the study. Concomitant therapies associated with MAAEs will be collected and recorded in the eCRF from the moment of first vaccination until 6 months after last vaccination. Concomitant therapies associated with MAAEs leading to study discontinuation will be recorded in the eCRF during the entire study. The participants with concomitant medication associated with these SAEs and MAAEs will listed.

For all participants, concomitant therapies associated with COVID-19 will be captured in the eCRF for the duration of the study. The participants with new concomitant medication associated with these cases will belisted. New concomitant medications are defined as medications not available at baseline or medication with an increased dosage (See below, New Concomitant Medications, for details), compared to baseline. Baseline medications are all medications reported prior to and at the day of first double-blind vaccination. In case a baseline medication is reported multiple times then only the last available record reported prior to or at the day of first double-blind vaccination will be used.

Based on their start and stop date, concomitant therapies will be reported in each applicable phase.

If a concomitant therapy record misses components of its start and/or stop dates (time, day and/or month and/or year):

In case of partial start or stop dates, the concomitant therapy records will be allocated to periods using the available partial information, without imputations. If, for example, only month and year are available, these will be compared to the month and the year of the periods, and the concomitant therapy record will be allocated to the period(s) where these date parts match. This rule may lead to assignment to multiple periods. In case it is clear the medication was taken after vaccination, the start will be allocated to the correct phase without the use of the start dates (time, day and/or month and/or year). In case of a completely missing end date, the concomitant therapy will be considered as ongoing at the end of the study.

There will be special attention to any systemic use of analgesics/antipyretics and corticosteroids, started during 8 days following each vaccination (00:00 of day of vaccination + 7 days). The following CMCLASCD (anatomic and therapeutic class (ATC)/DD codes) will be used for analgesics/antipyretics: N02A (OPIOIDS) and N02B (OTHER ANALGESICS AND ANTIPYRETICS), M01A (ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS) and M01B (ANTIINFLAMMATORY/ANTIRHEUMATIC AGENTS IN COMBINATION).

The following CMCLASCD (ATC/DD codes) will be used for corticosteroids H02 (CORTICOSTEROIDS FOR SYSTEMIC USE), M01BA (ANTIINFLAMATORY DRUGS/ANTIINFLAMATORY DRUGS IN COMBINATION WITH CORTICOSTEROIDS),

R03BA (GLUCOCORTICOIDS), and R03AK (SYMPATHOMIMETICS IN COMBINATION WITH CORTICOSTEROIDS OR OTHER AGENTS, EXCLUDING ANTICHOLINERGICS).

The classes will be added in a footnote in all related tables and listings. For the use of analgesics/antipyretics which are taken on the day of vaccination an exception is made in case the time is before vaccination. In this case the concomitant medication is also allocated to the post-dose period.

COVID-19 vaccinations received outside of the study are reported as concomitant medication. COVID-19 vaccinations are identified based on the following selection criteria: all CMDECODs with CMCLAS="COVID-19 VACCINES" except if CMDECOD is in ("OTHER VIRAL VACCINES", "HERPES SIMPLEX 1 VACCINE", "RSV VACCINE", "SMALLPOX VACCINE", "SMALLPOX VACCINE LIVE (MVA-BN)").

COVID-19 vaccinations received outside of the study are classified as mRNA or as non-mRNA as follows: If CMDECOD is in ("COVID-19 VACCINE MRNA" "ELASOMERAN" "TOZINAMERAN") then it is mRNA, else it is non-mRNA.

New Concomitant Medications – Increase in dosage Calculation

In case a participant receives the same medication with the same form at baseline and during a COVID-19 episode, then in order to identify whether there was an increase in dose between baseline and the episode the medication dose will be calculated by multiplying the dosage per administration with the number of administrations per day or per week, as applicable for both timepoints and compared.

This rule applies for the following medication frequencies:

- Four times daily (QID)
- Three times daily (TID)
- Twice Daily (BID)
- Daily (QD)
- Every Other Day (QOD)
- Four Times weekly (4 times per week)
- Three Times weekly (3 times per week)
- Twice weekly (2 times per week)
- Once weekly (1 time per week)
- Every two weeks (Every 2 weeks)
- Twice per Month (BIM)
- Every four weeks (Every 4 weeks)
- Weekly (Every week)
- Once

- Once monthly (QM)
- Every three months (Q3M)
- Once yearly

For frequencies equal to ‘other’ at baseline, any change to one of the above frequencies will be considered an increase, given that the form remains the same. For frequencies equal to ‘as necessary’ (PRN) or ‘occasional’, any change to another frequency or dose will be considered as an increase. A change from ‘as necessary’ (PRN) to ‘occasional’ or ‘other’ will not be considered as an increase.

Moreover, capsule and tablet are considered the same form so to define if there was an increase the dose and the frequency will be used as defined above. The same applies for inhalant and aerosol.

6.5. Appendix 5 Summary of Guidance from CDC Website on Underlying Medical Conditions That Lead or Might Lead to Increased Risk for Severe Illness From COVID-19

People of any age with **certain underlying medical conditions** are at increased risk for severe illness from COVID-19:

People of any age with the following conditions **are at increased risk** of severe illness from COVID-19:

- Cancer
- Chronic kidney disease
- COPD (chronic obstructive pulmonary disease)
- Immunocompromised state (weakened immune system) from solid organ transplant
- Obesity (body mass index [BMI] of 30 or higher)
- Serious heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies
- Sickle cell disease
- Type 2 diabetes mellitus

COVID-19 is a new disease. Currently there are limited data and information about the impact of underlying medical conditions and whether they increase the risk for severe illness from COVID-19. Based on what we know at this time, people with the following **conditions might be at an increased risk** for severe illness from COVID-19:

- Asthma (moderate-to-severe)
- Cerebrovascular disease (affects blood vessels and blood supply to the brain)
- Cystic fibrosis
- Hypertension or high blood pressure
- Immunocompromised state (weakened immune system) from blood or bone marrow transplant, immune deficiencies, HIV, use of corticosteroids, or use of other immune weakening medicines
- Neurologic conditions, such as dementia
- Liver disease
- Pregnancy
- Pulmonary fibrosis (having damaged or scarred lung tissues)
- Smoking
- Thalassemia (a type of blood disorder)
- Type 1 diabetes mellitus

Source: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2 Fcoronavirus% 2F2019-ncov%2Fneed-extra-precautions%2Fgroups-at-higher-risk.html. Accessed: 19 July 2020.

6.6. Appendix 6 Adverse Events of Interest (AEI)

Adverse Event of Interest Group	Adverse Event of Interest	MedDRA Term	MedDRA Search Criteria
Nervous system disorders	Non-infectious CNS inflammatory conditions (Excl. demyelinating diseases)	Noninfectious encephalitis	Noninfectious encephalitis (SMQ), Narrow
	Demyelinating disorders (central and peripheral nervous system)	Demyelination	Demyelination (SMQ), Narrow
		Guillain-Barré Syndrome	Guillain-Barré Syndrome (SMQ), Narrow
		Peripheral neuropathy	Peripheral neuropathy (SMQ), Narrow
	Narcolepsy and catalepsy	Narcolepsy and Hypersomnia	Narcolepsy and Hypersomnia (HLT)
Cardiac disorders	Myocarditis	Noninfectious myocarditis	Noninfectious myocarditis (HLT)
	Pericarditis	Noninfectious pericarditis	Noninfectious pericarditis (HLT)
Vascular disorders	Vasculitides	Vasculitis	Vasculitis (SMQ), Narrow
Blood and lymphatic system disorders	Thrombocytopenia	Haematopoietic thrombocytopenia	Haematopoietic cytopenias (SMQ) Broad, only sub SMQ Haematopoietic thrombocytopenia
		Thrombocytopenias	Thrombocytopenias (HLT)

HLT: MedDRA High Level Term
PT: MedDRA Preferred Term
SMQ: Standardized MedDRA Query