Janssen Vaccines & Prevention B.V.*

Supplemental Statistical Analysis Plan for the Relative Vaccine Efficacy Analysis

A Randomized, Double-blind, Phase 2 Study to Evaluate the Immunogenicity, Reactogenicity and Safety of Ad26.COV2.S Administered as Booster Vaccination in Adults 18 Years of Age and Older Who Have Previously Received Primary Vaccination with Ad26.COV2.S or BNT162b2.

ENSEMBLE 2

Protocol VAC31518COV2008; Phase 2
AMENDMENT 6

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: Supplemental SAP Version History Summary

Supplemental SAP Version	Approval Date	Change	Rationale
1		Not Applicable	Initial release

1. INTRODUCTION

This supplemental statistical analysis plan (SAP) describes the methods for exploratory efficacy analyses conducted after the primary analysis. Assessments of relative vaccine efficacy (rVE) analysis of booster vaccination with Ad26.COV2.S of the (i) heterologous booster compared to homologous booster vaccination at the same dose level; (ii) within each Cohort, dose levels (Ad26.COV2.S $5x10^{10}$ vp and $2.5x10^{10}$ vp) versus the lower dose level (Ad26.COV2.S $1x10^{10}$ vp) will be conducted.

This SAP is based on Clinical Trial Protocol (CTP) VAC31518COV2008 Amendment 6. For main SAP please refer to document EDMS RIM-462169 dated 15Dec2021. Data Presentation Specification (DPS) documents that further detail the planned statistical outputs are available.

1.1. Objectives, Endpoints

The objectives for the exploratory analysis are:

Exploratory Objectives	Endpoints
To explore the relative vaccine efficacy (rVE) of Ad26.COV2.S heterologous booster vaccination in the prevention of SARS-CoV -2 infection (severe/critical, moderate, moderate to severe/critical, mild, symptomatic, and asymptomatic infections, that are serologically and/or molecularly confirmed) compared to Ad26.COV2.S homologous booster vaccination at the same dose level (5×10^{10}vp, 2.5×10^{10}vp and 1×10^{10}vp).	• Asymptomatic cases of COVID-19, as determined by seropositivity for the SARSCoV-2 N protein. • SARS-CoV-2 infections as detected by molecular testing (RT-PCR or equivalent). • COVID-19 cases meeting the US FDA Harmonized COVID-19 case definition, with onset at least 14 days post vaccination in COV2008. • COVID-19 cases meeting the criteria for "moderate, moderate and severe/critically ill" COVID-19, with onset at least 14 days post vaccination in COV2008, if sufficient data are available.
To explore the rVE of different dose levels of Ad26.COV2.S homologous booster vaccination in the prevention of SARS-CoV-2 infection (severe/critical, moderate, moderate to severe/critical, symptomatic, and asymptomatic infections, that are serologically and/or molecularly confirmed) as follows: – 5×10^{10}vp versus 1×10^{10}vp dose level – 2.5×10^{10}vp versus 1×10^{10}vp dose level	• Asymptomatic cases of COVID-19, as determined by seropositivity for the SARSCoV-2 N protein. • SARS-CoV-2 infections as detected by molecular testing (RT-PCR or equivalent). • COVID-19 cases meeting the US FDA Harmonized COVID-19 case definition, with onset at least 14 days post vaccination in COV2008. • COVID-19 cases meeting the criteria for "moderate, moderate and severe/critically ill" COVID-19, with onset at least 14 days

Exploratory Objectives	Endpoints
	post vaccination in COV2008, if sufficient data are available.
To explore the rVE of different dose levels of Ad26.COV2.S heterologous booster vaccination in the prevention of SARS-CoV-2 infection (severe/critical, moderate, moderate to severe/critical, symptomatic, and asymptomatic infections, that are serologically and/or molecularly confirmed) as follows: – 5×10^{10}vp versus 1×10^{10}vp dose level – 2.5×10^{10}vp versus 1×10^{10}vp dose level	• Asymptomatic cases of COVID-19, as determined by seropositivity for the SARS-CoV-2 N protein. • SARS-CoV-2 infections as detected by molecular testing (RT-PCR or equivalent). • COVID-19 cases meeting the US FDA Harmonized COVID-19 case definition, with onset at least 14 days post vaccination in COV2008. • COVID-19 cases meeting the criteria for "moderate, moderate to severe/critical and severe/critically ill" COVID-19, with onset at least 14 days post vaccination in COV2008, if sufficient data are available.
If feasible, to investigate the effect of post booster cellular responses, mRNA profiles, neutralizing responses and/or other functional antibody responses on the probability of experiencing a COV ID-19 event, moderate and moderate to severe/critically ill COVID-19 disease, or asymptomatic SARS-CoV-2 infection.	• Serological response to vaccination and antibody titers as measured by virus neutralization assay (VNA) titers against the reference strain and/or SARS-CoV-2 variants, by EL ISA/MSD and/or other functional antibody assays, 14 days, 6 months and 1 year after homologous or heterologous booster vaccination with • Ad26.COV2.S, if sufficient data are available. • Cellular response to vaccination as measured by flow cytometry, ELISPOT and/or transcriptomics, 14 days, 6 months and 1 year after homologous or heterologous booster vaccination with Ad26.COV2.S, if sufficient data are available. • COVID-19 cases meeting the US FDA Harmonized COVID-19 case definition, with onset at least 14 days post booster vaccination in study COV2008, if sufficient data are available. • COVID-19 cases meeting the criteria for "moderate and moderate to severe/critically ill" COVID-19, with onset

Exploratory Objectives	Endpoints
	at least 14 days post vaccination in COV2008, if sufficient data are available. • Asymptomatic SARS-CoV-2 infection, with onset at least 14 days post vaccination in COV2008, if sufficient data are available. • Analysis of gene expression by RNA transcript profiling and correlation with humoral and cellular immune responses.

1.2. Study Design

Refer to CTP; section 4.

2. STATISTICAL HYPOTHESES

The statistical hypotheses to be tested are described in the main SAP.

3. SAMPLE SIZE DETERMINATION

Samples size determination and power calculations are detailed in the main SAP.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

The analysis set used for the exploratory analyses are described in Table 2.

Table 2: Analysis Sets

Analysis Sets	Description
Per Protocol Efficacy Analysis Set (PPE)	All vaccinated participants who are SARS-COV-2 seronegative at baseline and who have no major protocol deviations (listed in Appendix 4 of main SAP) expected to impact the efficacy outcomes.

All analyses of exploratory rVE endpoints will be performed based on PPE Analysis Set.

Follow-up time and COVID-19 cases within 14 days after booster vaccination are excluded from the analysis.

5. STATISTICAL ANALYSES

5.1. General Considerations

Unless otherwise indicated, all analyses will pool data across ages and independent of comorbidity status for evaluation without stratification.

The rVE analysis of booster vaccination with Ad26.COV2.S will include efficacy data collected during the entire study, i.e., with an onset date of the event (or censoring date) up to the database cut-off or until study discontinuation of the participant.

5.1.1. Study Phases

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

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).

5.1.2. Phase Definitions

For phase definitions refer to main SAP (EDMS RIM-462169); Section 5.1.2.

5.1.3. Scope of Analysis of the Relative Vaccine Efficacy

The rVE analysis is planned to compare heterologous to homologous vaccination with same dose level, and within each cohort the two higher dose levels (i.e., Ad26.COV2.S 5×10^{10}vp and 2.5×10^{10}vp) to the lower dose level (i.e., 1×10^{10}vp). The analysis will include efficacy data collected during the study until database cut-off or study discontinuation of the participant.

5.1.4. Correlates of Risk Analysis

If feasible and data are available, further exploratory analyses may be conducted to investigate the effect of the immunogenicity responses in various assays on the probability of experiencing a COVID-19 event (eg., moderate to severe/critical; FDA harmonized; Asymptomatic/undetected cases) using correlates of risk analysis. Correlates of risk analysis will be detailed in a separate document.

5.2. COVID-19 case and SARS-CoV-2 Infection Classification

Initial COVID-19 classification is based on a programmed algorithm (see section 5.2.2). Following algorithmic assignment, all COVID-19 episodes and/or SARS-CoV-2 infections (symptomatic and asymptomatic/undetected) will be assessed (case by case or with a sample approach as explained in the Clinical Severity Adjudication Charter) independently by a Clinical Severity Adjudication Committee (CSAC, see Section 5.5.1). This committee will independently evaluate the severity of the COVID-19 cases, confirm the onset date as proposed by the algorithm or adapt the onset date based on clinical judgement through objective findings.

Severity classification will be based on the highest degree of severity during the observation period. CSAC determination of severity is considered the final classification.

The process of adjudication is described in Case classification details are described in section 5.2.2. of this SAP.

5.2.1. Identification of COVID-19 Cases for Adjudication

All COVID-19 episodes and/or SARS-CoV-2 infections from the start of the study will be identified using a programmed algorithm described in the section 5.2.2. Fatalities that occur within the study for which COVID-19 could be a contributory or an underlying cause of death will be sent for adjudication, including fatalities not identified by the programmed algorithm. In addition, cases may be flagged for adjudication using other sources such as the Global Medical Safety database.

All cases identified by the algorithm (Tier I-V)[a] will be sent for adjudication for review.

Participants identified by the algorithm as asymptomatic/undetected infections based on a PCR positive result during their participation in the study and/or based on having seroconverted during their time on study will be sent for adjudication only when the algorithm captures the presence of COVID-19 symptoms at any point up to 7 days prior to the onset of an algorithmic asymptomatic SARS-CoV-2 infection or prior to seroconversion.

Cases will be considered ready for adjudication at the time of case resolution and when the data have been cleaned. Case resolution is defined as two consecutive negative RT-PCRs and two consecutive days without symptoms. Alternatively, a case can be considered resolved when 30 days have elapsed since its onset. In either situation, a case is considered valid for adjudication when the critical factors related to the case definition have been cleaned. Cases that have not resolved and/or been cleaned may be adjudicated when necessary to comply with regulatory filing requirements (e.g., interim analysis or Biologics License Application (BLA)).

5.2.2. COVID-19 Case Classification Relevant Definitions

Definitions relevant to COVID-19 case classification are listed below.

- **Episode** (of COVID-19): An episode of COVID-19 is defined as the period of the onset of (COVID-19) symptoms up until resolution of the episode. The severity of a COVID-19 will be determined based on the maximum severity observed across the episode.
- **Onset of (**COVID-19) **symptoms:** This is the date when any sign(s) or symptom(s) suggesting possible COVID-19. It will be called Day 1 of an episode. It is the earliest date the first symptom of an episode entered on the electronic Clinical Outcome Assessment (eCOA) or on the CRF if entered by the site ("*If a participant records in the eCOA or informs the site that he/she experienced any signs or symptoms suggesting possible COVID-19, this will be considered COVID-19 Day 1 (day of onset of signs and symptoms).*" CTP) or the AE onset date if linked to COVID-19. The COVID-19 Standardized MedDRA Query (SMQ) narrow scope is used to select AEs linked to COVID-19. [Day 1 will be derived based on the first symptoms that are entered in the eCOA before the first swab is taken. In case there are multiple days with symptoms entered in the eCOA before the first swab, Day 1 is the earliest Day of

[a] Tier definitions: Tier I: severe cases, Tier II moderate cases with at least one flag=Y (SpO2 <=93%, heart rate >=125 beats/minute, respiratory rate >= 30 breaths/minute, medically attended/MA-COV), Tier 3: moderate cases with >=3 symptoms, Tier IV: moderate cases with <=2 symptoms, Tier V: mild cases.

all consecutive Days with signs or symptoms that are at least mild. Days without symptoms within 7 days before the first swab will be ignored in the evaluation of consecutive days.]

- **Resolution of an episode:** Resolution of the COVID-19 episode is defined as having 2 consecutive SARS-CoV-2 negative nasal swabs and 2 consecutive days with no COVID-19-related signs or symptoms. [The date taken will be the first of the 2 consecutive negative swabs, OR the first day with no COVID-19 related signs or symptoms, whichever comes last. For this determination, all sources of information will be used (eCOA, eCRF or an AE linked to COVID-19). In case of missing days, it will depend on if those are before or after the first day of the two consecutive SARS-CoV-2 negative nasal swabs. If before days with missing data have no consequence. If after, it is assumed that if days with missing data are after a day with no symptoms, the subsequent days also were without symptoms. If days with missing data are after a Day with symptoms, the assumption depends on the data of subsequent Days. If there are no more than 2 Days without data and the next Day does have (at least mild) symptoms, the missing days will be assumed to also have had symptoms. In all other cases it will be assumed that days with missing data were without symptoms and the rule to determine the resolution of symptoms will be applied.]
- **Molecularly confirmed case:** Events for which at least one SARS-CoV-2 PCR positive test was obtained by the nasal swab PCR test.
- **A suspected COVID-19 case** is a case which meets any of the symptomatic COVID-19 definitions according to the CSAC without a documented PCR positive result (any source) or a positive serology test.

5.2.3. Assigning Case Definition

The case definitions for mild, moderate, and severe/critical COVID-19 are provided in the CTP Section 8.2. This section provides guidance on how these will be applied.

- Information on symptoms is to be collected from the eCOA (see Appendix 5 of the CTP) and from the eCRF (including AEs linked to COVID-19). If the sources of information contain discordant data, (i.e., on a single calendar Day one source records the symptom and another source does not record that same symptom) the symptom is considered to have been present on that day.
- A sign or symptom is considered as absent or present for a COVID-19 episode: any sign or symptom is considered present if observed in the eCOA or eCRF for the COVID-19 episode, and absent if not.
- Signs or symptoms occurring at any time during the episode are used for the application of the case definitions.
- Application of the criteria is independent of duration; if a sign or symptom is present at any time, the sign or symptom is considered to be present. [Note that for a suspected COVID-19 case to be tested, at least one symptom of suspected COVID-19 must be present for 24 hours, and not otherwise explained (Section 8.1.1. of the CTP: “New onset or worsening of any 1 of these symptoms, which lasts for at least 24 hours, not otherwise explained”). For case classification the information from the eCOA and eCRF is taken independent of duration or alternative explanations.

- Fever will be assessed independent of anatomical site of assessment (oral, armpit, ear, or rectal).
- The definitions of mild, moderate, and severe/critical are mutually exclusive, where the most severe category takes priority.

5.2.4. Symptomatic COVID-19 Case Derivation

Some symptoms lead to suspicion of a COVID-19 episode and are used as triggers to proceed with home-collection of the nasal swabs for SARS-CoV-2 testing. The list of symptoms used as triggers for testing are provided in Section 8.1.1 of the CTP. A triggering symptom may lead to a (confirmed) positive SARS-CoV-2 test, even though the case may fail to reach the mild case definition during the episode. These cases are not considered symptomatic. In other words, symptomatic COVID-19 cases are those that are at least of mild severity as defined below.

The derivations for mild, moderate, and severe/critical are given below.

5.2.4.1. Mild COVID-19 Case Derivation

A case will be considered of mild COVID-19 severity if one (or more) of the following symptoms is observed, if not satisfying the definition of a moderate or severe/critical disease severity [black, terminology from eCOA or blue, terminology from the eCRF]:

- Fever (≥38.0°C or ≥100.4°F) or eCRF
- Sore throat / Sore throat
- Loss of appetite / Malaise
- Feeling generally unwell (run down) / Malaise
- Fatigue (tiredness) / Malaise
- Physical Weakness / Malaise
- Headache / Headache
- Muscle aches/pains / Myalgia
- Diarrhea / Gastrointestinal Symptoms
- Vomiting / Gastrointestinal Symptoms
- Nausea / Gastrointestinal Symptoms
- Abdominal/stomach pain / Gastrointestinal Symptoms
- Cough / Cough
- Chest congestion (mucus in chest)
- Runny nose
- Wheezing
- Skin rash

- Eye irritation/discharge
- Chills
- Uncontrollable body shaking/shivering /Shaking chills or rigors
- Decreased sense of smell / Anosmia (olfactory or taste disorders)
- Decreased sense of taste / Anosmia (olfactory or taste disorders)
- Red or bruised looking feet or toes / Chilblains/pernio (red or bruised looking feet or toes)

5.2.4.2. Moderate COVID-19 Case Derivation

For the definition of moderate COVID-19 severity there are two separate criteria, either if met would be sufficient to be considered as moderate (if not satisfying the criteria of severe/critical disease):

1. At least one **sign** or symptom (as derived from the Medically-attended COVID-19 Form (MA-COV) form or other CRF source *or eCOA*):
   - Respiratory Rate ≥ 20 breaths/minute or vital signs CRF
   - Abnormal saturation of oxygen (SpO2) but still >93% on room air at sea level or vital signs CRF (=94%)
   - Clinical or radiologic evidence of pneumonia or AE preferred term "COVID-19 PNEUMONIA"
   - Radiologic evidence of deep vein thrombosis (DVT)
   - *Shortness of breath (difficulty breathing)*

OR

2. Two (or more) signs or symptoms from of the following (black, terminology from eCOA or blue, terminology from the eCRF):
   - Highest temperature was ≥38.0 ºC or ≥100.4 ºF or CRF
   - Heart rate ≥ 90 beats/minute or vital signs CRF
   - Chills or Uncontrollable body shaking/shivering /Shaking chills or rigors
   - Sore throat / Sore throat
   - Cough / Cough
   - At least one from [Loss of appetite, Feeling generally unwell (run down), Fatigue (tiredness), Physical Weakness] / Malaise
   - Headache / Headache
   - Muscle aches/pains / Myalgia
   - At least one from [Diarrhea, Vomiting, Nausea, Abdominal/stomach pain] / Gastrointestinal Symptoms

- Decreased sense of smell or Decreased sense of taste / Anosmia (olfactory or taste disorders)
- Red or bruised looking feet or toes / Chilblains/pernio (red or bruised looking feet or toes)

5.2.4.3. Severe/Critical COVID-19 Case Derivation

A case will be considered severe/critical if (black, terminology from the Medically-attended COVID-19 Form (MA-COV) or blue, terminology from the eCRF):

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths/minute, heart rate ≥125 beats/minute, oxygen saturation (SpO2) ≤93% on room air at sea level, or partial pressure of oxygen/fraction of inspired oxygen (PaO2/FiO2) <300 mmHg)
- Respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation [ECMO])
- Shock (defined as systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or requiring vasopressors)
- Significant acute renal or hepatic dysfunction
- Numbness, tingling, or weakness face or limbs (neurologic dysfunction)
- Difficulty speaking or forming speech (neurologic dysfunction)
- Difficulty understanding speech (neurologic dysfunction)
- Feelings of confusion (neurologic dysfunction)
- Admission to the ICU (Medical Encounters eCRF)
- Death (SAE form)

In addition, severe/critical cases can be identified through the use of the following vital signs:

- $SpO_2 \leq 93\%$
- Heart rate ≥125 beats/minute
- Respiratory Rate ≥30 breaths/minute

5.2.4.4. US FDA Harmonized COVID-19 Case Derivation

A case will be considered satisfying the FDA harmonized COVID-19 case criteria if at least one of the following symptoms was recorded during a COVID-19 episode (black, terminology from eCOA or blue, terminology from the eCRF):

- Fever (≥38.0°C or ≥100.4°F) or CRF
- Cough / Cough
- Chills (or Uncontrollable body shaking/shivering) /Shaking chills or rigors
- Sore throat / Sore throat

- Shortness of breath (difficulty breathing)
- Fatigue (tiredness) / Malaise
- Muscle aches/pains / Myalgia
- Headache / Headache
- Decreased sense of smell / Anosmia (olfactory or taste disorders)
- Decreased sense of taste / Anosmia (olfactory or taste disorders)
- Chest congestion (mucus in chest)
- Nasal congestion (stuffy nose)
- Runny nose
- Joint aches/pains
- Diarrhea / Gastrointestinal Symptoms
- Vomiting / Gastrointestinal Symptoms
- Nausea / Gastrointestinal Symptoms

The FDA harmonized COVID-19 case definition is independent of the case definition above.

5.2.5. Asymptomatic or Undetected SARS-COV-2 Infection

5.2.5.1. Definition

If a participant does not fulfil the criteria for suspected COVID-19 based on signs and symptoms which would classify them as mild, moderate, or severe by the definitions,

AND

has a SARS-CoV-2 positive RT-PCR or molecular test result from any available respiratory tract sample (e.g., nasal swab sample, sputum sample, throat swab sample, saliva sample) or other sample

OR

determined by seropositivity for the SARS-CoV-2 N protein,

then, the participant will be considered to have experienced asymptomatic or undetected COVID-19.

A positive RT-PCR for SARS-CoV-2 will need to be captured in the eCRF.

5.2.5.2. Classification

Asymptomatic infections or undetected cases will be classified using a similar algorithmic approach. Cases will then be reviewed and classified by the CSAC.

Relevant definitions for programmed algorithm

Identification of potential asymptomatic SARS-CoV-2 infections via PCR: Cases with a positive PCR will be reviewed for the presence of signs and/or symptoms of COVID-19 employing the definitions of onset and resolution of section 5.2.2. In the absence of signs and/or symptoms, the case will be classified per algorithm as asymptomatic.

Identification of potential asymptomatic or undetected SARS-CoV-2 infections through seroconversion:

- **SARS-CoV-2 seroconversion by N-serology with onset Day >14** is based on the available data from Day 71, Month 6. If positive at any timepoint while the subject was seronegative at baseline (and at Day 15 for the PPE analysis after day 14), a subject is considered to have seroconverted. If Day 14 is missing or not available, the subject is considered to be negative on that day.
- **SARS-CoV-2 seroconversion by N-serology from Day 1 to Day 14**, is based on the available data on day 14. If positive at day 14 while the subject was seronegative at baseline or missing, a subject is considered to have seroconverted between day 1 and day 14.
- A **seroconverted participant** is a subject with serological conversion without an earlier SARS-CoV-2 positive RT-PCR or molecular test result from any available respiratory tract sample.

Upon algorithmic classification, cases will be evaluated as being an "Asymptomatic SARS-CoV-2 infection" by the Clinical Severity Adjudication Committee as follows:

- Asymptomatic SARS-CoV-2 infections or seroconverted participants as assigned via the programmed algorithm will be reviewed for the presence of possible COVID-19 signs and symptoms from baseline up to 7 days prior to the first positive PCR or up to the day of the first positive serology test.
- If no presence of signs/symptoms, the algorithm will be accepted and no further review by the CSAC and the case classified as Asymptomatic SARS-CoV-2 infection.
- If at least one sign or symptom is present, those cases will be sent to the CSAC for review for a possible undetected symptomatic COVID-19 illness.
    - If reviewed by the CSAC as asymptomatic SARS-CoV-2 infections, cases will be classified as asymptomatic infection.
    - Seroconverted cases reviewed by the CSAC as symptomatic will be classified as **serologically confirmed COVID-19** (by N-serology) and evaluated according to the accepted/reviewed severity and onset date.
    - PCR positive cases reviewed by the CSAC as symptomatic will be classified and evaluated according to the accepted/reviewed severity and onset date.

5.2.6. Endpoint Selection for Analysis

Unless mentioned otherwise all clinical endpoints will be analyzed based on the assessment of the CSAC, supported by the algorithmic approach as explained above. Cases that are adjudicated as not a case by the CSAC are excluded from the analysis. Furthermore, for any symptomatic case to be included in this analysis there needs to be at least one SARS-CoV-2 positive RT-PCR or molecular test result from any available respiratory tract sample (e.g., nasal swab sample, sputum sample, throat swab sample, saliva sample) confirmed by the central laboratory.

Supplementary analysis will include:

- An analysis based on the algorithmic classification as assigned above (limiting to centrally confirmed cases)
- An analysis based on any documented positive PCR irrespective of the source (central confirmation, local site, Covance, external to the study) according to the accepted/reviewed severity and onset date by the CSAC
- An analysis will be done including suspected cases adjudicated by the CSAC.

5.3. Exploratory Endpoint(s) Analysis

5.3.1. Definition of Endpoints and Estimands

5.3.1.1. Exploratory endpoint(s)

The exploratory endpoint(s) is defined as a COVID-19 case meeting case definitions, as defined in Sections 5.2.4 and 5.2.5, with onset at least 14 days post last vaccination.

Estimand 1:

What is the relative vaccine efficacy against moderate to severe/critical COVID-19 of Ad26.COV2.S booster vaccination at different dose levels within and between cohorts in adults ≥18 years with or without comorbidities associated with increased risk of progression to severe COVID-19?

Population: Adults ≥18 years with or without comorbidities associated with increased risk of progression to severe COVID-19 cases and who previously received primary vaccination with Ad26.COV2.S or BNT162b2 and subsequently received Ad26.COV2.S boost on the study.

Endpoint: Molecularly confirmed symptomatic moderate to severe/critical COVID-19 Omicron infections with onset ≥14 days after last study vaccination.

Intercurrent Events: Other COVID-19 vaccines.

Data handling for estimators: Cases will be counted from the day after last Ad26.COV2.S vaccination until and including the last available timepoint in the database. Participants with a SARS-CoV-2 infection (symptomatic or asymptomatic) prior to 14 days post last study vaccination will be excluded from the risk set.

A subject will be censored:

- If no event of interest to the analysis was experienced during the considered observation period
- On the date of receipt of another authorized/approved COVID-19 vaccine outside of the study, the date of study discontinuation or the last available date (data lock point), whichever occurred first.

The above defined Estimand approach will be used for following interventions and summary measures:

Estimand	**Interventions**	**Summary Measures[1]**
Within each Cohort: (Cohort 1 and 2 separately)		
Estimand 1.1	Ad26.COV2.S $5x10^{10}$ vp and Ad26.COV2.S $1x10^{10}$ vp	Relative VE = 100 x (1-hazard ratio of Ad26.COV2.S $5x10^{10}$ vp / Ad26.COV2.S $1x10^{10}$ vp)%
Estimand 1.2	Ad26.COV2.S $2.5x10^{10}$ vp and Ad26.COV2.S $1x10^{10}$ vp	Relative VE = 100 x (1-hazard ratio of incidence Ad26.COV2.S $2.5x10^{10}$ vp / Ad26.COV2.S $1x10^{10}$ vp)%
Between Cohorts:		
Estimand 1.3	Ad26.COV2.S $5x10^{10}$ vp (Cohort 1) and Ad26.COV2.S $5x10^{10}$ vp (Cohort 2)	Relative VE = 100 x (1-hazard ratio of Cohort 1 Ad26.COV2.S $5x10^{10}$ vp / Cohort 2 Ad26.COV2.S $5x10^{10}$ vp)%
Estimand 1.4	Ad26.COV2.S $2.5x10^{10}$ vp (Cohort 1) and Ad26.COV2.S $2.5x10^{10}$ vp (Cohort 2)	Relative VE = 100 x (1-hazard ratio of Cohort 1 Ad26.COV2.S $2.5x10^{10}$ vp / Cohort 2 Ad26.COV2.S $2.5x10^{10}$ vp)%
Estimand 1.5	Ad26.COV2.S $1x10^{10}$ vp (Cohort 1) and Ad26.COV2.S $1x10^{10}$ vp (Cohort 2)	Relative VE = 100 x (1-hazard ratio of Cohort 1 Ad26.COV2.S $1x10^{10}$ vp / Cohort 2 Ad26.COV2.S $1x10^{10}$ vp)%

[1]Relative VE and associated 95% CI will be calculated from Cox Proportional hazards model**.**

5.3.2. Analysis Method

Exploratory analysis will be done on the PPE analysis set including only baseline seronegative subjects. The analysis will focus on the Omicron variant, as this is presumed to be the dominant variant during the observation period.

Analysis will be performed if there are at least 6 cases available for the analysis of interest.

i) Calendar-Based Time Scale Method:

For the exploratory efficacy endpoints, follow-up time will be expressed on a calendar time scale, and is defined as time since study start (i.e., 08 August 2021) to adjust for changing incidence over time. Follow-up time will begin on the date of administration of the first dose of Janssen COVID-19 vaccine (within study COV2008), expressed on a calendar time scale as time since study start,

although follow-up time and events occurring within 14 days post vaccination with first dose of Janssen COVID-19 vaccine will be ignored.

The follow-up time is the time to first occurrence of moderate to severe disease, with an onset at any time at least 14 days post vaccination of previously received Janssen COVID-19 vaccine. 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 iii) the last available date, whichever occurred first.

Vaccine efficacy will be summarized by relative vaccine efficacy measures and the associated 95% confidence intervals (CI) using time-dependent Cox Proportional hazards models , stratified by the following factors to account for i) changing incidence over calendar time, ii) potential confounding by age [18 - <60 years (as reference category), >= 60 years], co-morbidities [Y/N (as a reference category)] and geographical region in which the site is located (cf. Section 5.4.1).

One model will be fit estimating VE under the assumption of constant relative vaccine efficacy (Fintzi et al, 2020), comparing:

- Within each Cohort, from higher dose levels (i.e. Ad26.COV2.S $5x10^{10}$ vp and $2.5x10^{10}$ vp) to lower dose level (Ad26.COV2.S $1x10^{10}$ vp).
- Heterologous booster (Cohort 2) to homologous booster (Cohort 1) vaccination at same dose level.

Models that do not converge will be omitted and reported as non-convergent. The method for tabulating relative VE and 95% CI will be detailed in DPS.

Estimand 2:

What is the relative vaccine efficacy against moderate COVID-19 of Ad26.COV2.S booster vaccination at different dose levels within and between cohorts in adults ≥18 years with or without comorbidities associated with increased risk of progression to moderate COVID-19?

Population: Adults ≥18 years with or without comorbidities associated with increased risk of progression to severe COVID-19 cases and who previously received primary vaccination with Ad26.COV2.S or BNT162b2 and subsequently received Ad26.COV2.S boost on the study.

Endpoint: Molecularly confirmed symptomatic moderate COVID-19 Omicron infections with onset ≥14 days after last study vaccination.

Intercurrent Events: Other COVID-19 vaccines

Data handling for estimators: Cases will be counted from the day after last Ad26.COV2.S vaccination until and including the last available timepoint in the database. Participants with a SARS-CoV-2 infection (symptomatic or asymptomatic) prior to 14 days post last study vaccination will be excluded from the risk set.

A subject will be censored:

- If no event of interest to the analysis was experienced during the considered observation period
- On the date of receipt of another authorized/approved COVID-19 vaccine outside of the study, the date of study discontinuation or the last available date (data lock point), whichever occurred first.

The above defined Estimand approach will be used for following interventions and summary measures:

Estimand	**Interventions**	**Summary Measures**[1]
Within each Cohort: (Cohort 1 and 2 separately)		
Estimand 2.1	Ad26.COV2.S $5x10^{10}$ vp and Ad26.COV2.S $1x10^{10}$ vp	Relative VE = 100 x (1-hazard ratio of Ad26.COV2.S $5x10^{10}$ vp / Ad26.COV2.S $1x10^{10}$ vp)%
Estimand 2.2	Ad26.COV2.S $2.5x10^{10}$ vp and Ad26.COV2.S $1x10^{10}$ vp	Relative VE = 100 x (1-hazard ratio of incidence Ad26.COV2.S $2.5x10^{10}$ vp / Ad26.COV2.S $1x10^{10}$ vp)%
Between Cohorts:		
Estimand 2.3	Ad26.COV2.S $5x10^{10}$ vp (Cohort 1) and Ad26.COV2.S $5x10^{10}$ vp (Cohort 2)	Relative VE = 100 x (1-hazard ratio of Cohort 1 Ad26.COV2.S $5x10^{10}$ vp / Cohort 2 Ad26.COV2.S $5x10^{10}$ vp)%
Estimand 2.4	Ad26.COV2.S $2.5x10^{10}$ vp (Cohort 1) and Ad26.COV2.S $2.5x10^{10}$ vp (Cohort 2)	Relative VE = 100 x (1-hazard ratio of Cohort 1 Ad26.COV2.S $2.5x10^{10}$ vp / Cohort 2 Ad26.COV2.S $2.5x10^{10}$ vp)%
Estimand 2.5	Ad26.COV2.S $1x10^{10}$ vp (Cohort 1) and Ad26.COV2.S $1x10^{10}$ vp (Cohort 2)	Relative VE = 100 x (1-hazard ratio of Cohort 1 Ad26.COV2.S $1x10^{10}$ vp / Cohort 2 Ad26.COV2.S $1x10^{10}$ vp)%

[1]Relative VE and associated 95% CI will be calculated from Cox Proportional hazards model**.**

Analysis method will be repeated as explained in Section 5.3.2.

Estimand 3:

What is the relative vaccine efficacy against severe/critical COVID-19 of Ad26.COV2.S booster vaccination at different dose levels within and between cohorts in adults ≥18 years with or without comorbidities associated with increased risk of progression to severe COVID-19?

Population: Adults ≥18 years with or without comorbidities associated with increased risk of progression to severe COVID-19 cases and who previously received primary vaccination with Ad26.COV2.S or BNT162b2 and subsequently received Ad26.COV2.S boost on the study.

Endpoint: Molecularly confirmed symptomatic severe/critical COVID-19 Omicron infections with onset ≥14 days after last study vaccination.

Intercurrent Events: Other COVID-19 vaccines

Data handling for estimators: Cases will be counted from the day after last Ad26.COV2.S vaccination until and including the last available timepoint in the database. Participants with a SARS-CoV-2 infection (symptomatic or asymptomatic) prior to 14 days post last study vaccination will be excluded from the risk set.

A subject will be censored:

- If no event of interest to the analysis was experienced during the considered observation period
- On the date of receipt of another authorized/approved COVID-19 vaccine outside of the study, the date of study discontinuation or the last available date (data lock point), whichever occurred first.

The above defined Estimand approach will be used for following interventions and summary measures:

Estimand	Interventions	Summary Measures[1]
Within each Cohort: (Cohort 1 and 2 separately)		
Estimand 3.1	Ad26.COV2.S $5x10^{10}$ vp and Ad26.COV2.S $1x10^{10}$ vp	Relative VE = 100 x (1-hazard ratio of Ad26.COV2.S $5x10^{10}$ vp / Ad26.COV2.S $1x10^{10}$ vp)%
Estimand 3.2	Ad26.COV2.S $2.5x10^{10}$ vp and Ad26.COV2.S $1x10^{10}$ vp	Relative VE = 100 x (1-hazard ratio of incidence Ad26.COV2.S $2.5x10^{10}$ vp / Ad26.COV2.S $1x10^{10}$ vp)%
Between Cohorts:		
Estimand 3.3	Ad26.COV2.S $5x10^{10}$ vp (Cohort 1) and Ad26.COV2.S $5x10^{10}$ vp (Cohort 2)	Relative VE = 100 x (1-hazard ratio of Cohort 1 Ad26.COV2.S $5x10^{10}$ vp / Cohort 2 Ad26.COV2.S $5x10^{10}$ vp)%
Estimand 3.4	Ad26.COV2.S $2.5x10^{10}$ vp (Cohort 1) and Ad26.COV2.S $2.5x10^{10}$ vp (Cohort 2)	Relative VE = 100 x (1-hazard ratio of Cohort 1 Ad26.COV2.S $2.5x10^{10}$ vp / Cohort 2 Ad26.COV2.S $2.5x10^{10}$ vp)%
Estimand 3.5	Ad26.COV2.S $1x10^{10}$ vp (Cohort 1) and Ad26.COV2.S $1x10^{10}$ vp (Cohort 2)	Relative VE = 100 x (1-hazard ratio of Cohort 1 Ad26.COV2.S $1x10^{10}$ vp / Cohort 2 Ad26.COV2.S $1x10^{10}$ vp)%

[1]Relative VE and associated 95% CI will be calculated from Cox Proportional hazards model**.**

Analysis method will be repeated as explained in Section 5.3.2.

Estimand 4:

What is the relative vaccine efficacy against US FDA Harmonized COVID-19 of Ad26.COV2.S booster vaccination at different dose levels within and between cohorts in adults ≥18 years with or without comorbidities associated with increased risk of progression to severe COVID-19?

Population: Adults ≥18 years with or without comorbidities associated with increased risk of progression to severe COVID-19 cases and who previously received primary vaccination with Ad26.COV2.S or BNT162b2 and subsequently received Ad26.COV2.S boost on the study.

Endpoint: Molecularly confirmed symptomatic US FDA Harmonized COVID-19 Omicron infections with onset ≥14 days after last study vaccination.

Intercurrent Events: Other COVID-19 vaccines

Data handling for estimators: Cases will be counted from the day after last Ad26.COV2.S vaccination until and including the last available timepoint in the database. Participants with a SARS-CoV-2 infection (symptomatic or asymptomatic) related to US FDA Harmonized COVID-19 prior to 14 days post last study vaccination will be excluded from the risk set.

A subject will be censored:

- If no event of interest to the analysis was experienced during the considered observation period
- On the date of receipt of another authorized/approved COVID-19 vaccine outside of the study, the date of study discontinuation or the last available date (data lock point), whichever occurred first.

The above defined Estimand approach will be used for following interventions and summary measures:

Estimand	**Interventions**	**Summary Measures[1]**
Within each Cohort: (Cohort 1 and 2 separately)		
Estimand 4.1	Ad26.COV2.S $5x10^{10}$ vp and Ad26.COV2.S $1x10^{10}$ vp	Relative VE = 100 x (1-hazard ratio of Ad26.COV2.S $5x10^{10}$ vp / Ad26.COV2.S $1x10^{10}$ vp)%
Estimand 4.2	Ad26.COV2.S $2.5x10^{10}$ vp and Ad26.COV2.S $1x10^{10}$ vp	Relative VE = 100 x (1-hazard ratio of incidence Ad26.COV2.S $2.5x10^{10}$ vp / Ad26.COV2.S $1x10^{10}$ vp)%
Between Cohorts:		
Estimand 4.3	Ad26.COV2.S $5x10^{10}$ vp (Cohort 1) and Ad26.COV2.S $5x10^{10}$ vp (Cohort 2)	Relative VE = 100 x (1-hazard ratio of Cohort 1 Ad26.COV2.S $5x10^{10}$ vp / Cohort 2 Ad26.COV2.S $5x10^{10}$ vp)%
Estimand 4.4	Ad26.COV2.S $2.5x10^{10}$ vp (Cohort 1) and Ad26.COV2.S $2.5x10^{10}$ vp (Cohort 2)	Relative VE = 100 x (1-hazard ratio of Cohort 1 Ad26.COV2.S $2.5x10^{10}$ vp / Cohort 2 Ad26.COV2.S $2.5x10^{10}$ vp)%
Estimand 4.5	Ad26.COV2.S $1x10^{10}$ vp (Cohort 1) and Ad26.COV2.S $1x10^{10}$ vp (Cohort 2)	Relative VE = 100 x (1-hazard ratio of Cohort 1 Ad26.COV2.S $1x10^{10}$ vp / Cohort 2 Ad26.COV2.S $1x10^{10}$ vp)%

[1]Relative VE and associated 95% CI will be calculated from Cox Proportional hazards model**.**

Analysis method will be repeated as explained in Section 5.3.2.

Estimand 5:

What is the relative vaccine efficacy against asymptomatic/undetected COVID-19 of Ad26.COV2.S booster vaccination at different dose levels within and between cohorts in adults ≥18 years with or without comorbidities associated with increased risk of progression to severe COVID-19?

Population: Adults ≥18 years with or without comorbidities associated with increased risk of progression to severe COVID-19 cases and who previously received primary vaccination with Ad26.COV2.S or BNT162b2 and subsequently received Ad26.COV2.S boost on the study.

Endpoint: Asymptomatic/undetected COVID-19 Omicron infections with onset ≥14 days after last study vaccination.

Intercurrent Events: Other COVID-19 vaccines

Data handling for estimators: Cases will be counted from the day after last Ad26.COV2.S vaccination until and including the last available timepoint in the database. Participants with a SARS-CoV-2 infection (asymptomatic/undetected) prior to 14 days post last study vaccination will be excluded from the risk set.

A subject will be censored:

- If no event of interest to the analysis was experienced during the considered observation period
- On the date of receipt of another authorized/approved COVID-19 vaccine outside of the study, the date of study discontinuation or the last available date (data lock point), whichever occurred first.

The above defined Estimand approach will be used for following interventions and summary measures:

Estimand	**Interventions**	**Summary Measures[1]**
Within each Cohort: (Cohort 1 and 2 separately)		
Estimand 5.1	Ad26.COV2.S $5x10^{10}$ vp and Ad26.COV2.S $1x10^{10}$ vp	Relative VE = 100 x (1-hazard ratio of Ad26.COV2.S $5x10^{10}$ vp / Ad26.COV2.S $1x10^{10}$ vp)%
Estimand 5.2	Ad26.COV2.S $2.5x10^{10}$ vp and Ad26.COV2.S $1x10^{10}$ vp	Relative VE = 100 x (1-hazard ratio of incidence Ad26.COV2.S $2.5x10^{10}$ vp / Ad26.COV2.S $1x10^{10}$ vp)%
Between Cohorts:		
Estimand 5.3	Ad26.COV2.S $5x10^{10}$ vp (Cohort 1) and Ad26.COV2.S $5x10^{10}$ vp (Cohort 2)	Relative VE = 100 x (1-hazard ratio of Cohort 1 Ad26.COV2.S $5x10^{10}$ vp / Cohort 2 Ad26.COV2.S $5x10^{10}$ vp)%

Estimand	Interventions	Summary Measures[1]
Estimand 5.4	Ad26.COV2.S $2.5x10^{10}$ vp (Cohort 1) and Ad26.COV2.S $2.5x10^{10}$ vp (Cohort 2)	Relative VE = 100 x (1-hazard ratio of Cohort 1 Ad26.COV2.S $2.5x10^{10}$ vp / Cohort 2 Ad26.COV2.S $2.5x10^{10}$ vp)%
Estimand 5.5	Ad26.COV2.S $1x10^{10}$ vp (Cohort 1) and Ad26.COV2.S $1x10^{10}$ vp (Cohort 2)	Relative VE = 100 x (1-hazard ratio of Cohort 1 Ad26.COV2.S $1x10^{10}$ vp / Cohort 2 Ad26.COV2.S $1x10^{10}$ vp)%

[1]Relative VE and associated 95% CI will be calculated from Cox Proportional hazards model**.**

Analysis method will be repeated as explained in Section 5.3.2.

5.3.3. Graphical Displays

The time to onset of the first occurrence of SARS-CoV-2 COVID-19 will be graphically summarized using Kaplan-Meier methods for the PPE analysis set, seronegative subjects only with onset at least 14 days after last vaccination for each cohort.

- These graphs will be prepared regardless of severity according to the case definitions mild, moderate, severe and US FDA harmonized and for asymptomatic/undetected case definition.

5.4. Other Analyses

5.4.1. Definition of Subgroups

Selected descriptive statistics will be provided by vaccination dose groups in each cohort for the following subgroups:

- sex
- age group (18 - ≤59 & ≥60 years)
- presence of baseline comorbidity (yes/no)
- sites
- higher geographical region (West; Midwest; Northeast and South): Categorization of regions by pooling of US states as are described in Table 3 (based on U.S. Department of Commerce Economics and Statistics Administration U.S. Census Bureau).

Table 3: Geographical Regions

CTMS Site #	City, State	Region
PPD	North Charleston, SC	South
	Peoria, IL	Midwest
	Houston, TX	South
	Rochester, NY	Northeast
	Lenexa, KS	Midwest
	Lexington, KY	South
	Long Beach, CA	West
	Mount Pleasant, SC	South
	Tucson, AZ	West
	Phoenix, AZ	West
	Metairie, LA	South
	Hallandale Beach, FL	South
	Hollywood, FL	South
	Boston, MA	Northeast
	The Villages, FL	South
	Orlando, FL	South
	Anaheim, CA	West
	West Jordan, UT	West
	N. Hollywood, CA	West
	Denver,CO	West
	Anderson, SC	South
	Boston, MA	Northeast

Analysis Methods:

Descriptive analyses/summary will be provided for PPE analysis set for each cohort by dose groups. These analyses may include but are not limited to:

- The number and percentage of severity of SARS-CoV-2 COVID-19 cases
- Number of events and follow-up time for SARS-CoV-2 COVID-19 cases by subgroups
- Based on availability of the data, for COVID-19 requiring medical intervention/ hospitalization, a summary table will be provided by type of intervention (as indicated by the adjudicators, if available) with onset at least 14 days post last vaccination. A severity adjusted analysis will be done on the medical intervention endpoint (such as composite endpoint of hospitalization, ICU admission, mechanical ventilation, and ECMO, linked to objective measures such as decreased oxygenation, X-ray or CT findings

5.4.2. 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 by part 1, part 2 and part 3, scored separately for PPE analysis set.

SIC Analysis:

- Part 1 (25 symptoms): Each symptom is present or absent (0), and if present rated on a 10 point scale from 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 area under the curve (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 ^{o}C or ≥100.4 ^{o}F 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, i.e., interpolation will be used in the calculation of the AUC.)

The fever score will also be coded using FDA grades for fever.

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 till 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'.

5.4.3. SARS-CoV-2 Viral Genome Sequence Analysis

SARS-CoV-2 viral genome sequence analysis will be performed using Next Generation Sequencing (NGS) using the SWIFT Biosciences to evaluate the presence of polymorphisms and variations at the amino acid level.

Sequence results will be presented only for the spike protein and is focused on a predefined list of amino acid positions of interest. Data are transferred as the consensus sequence from the sample (i.e. no minority variants or mutation frequencies are transferred for this analysis). A separate virology report will be prepared.

Time Points and Samples

Samples for viral sequencing are taken throughout the T&E schedule. An attempt is made to sequence the sample closest to the onset of symptoms, but sequencing is triggered at the discretion of the virologist considering the SARS-CoV-2 viral load levels and the limitations of the sequencing assays.

Definitions

Polymorphisms, ie genetic variations, are defined as amino acid changes from the SARS-CoV-2 Wuhan-Hu1 Reference Sequence.

Wild type: If at certain position the amino acid in the participant sequence matches the reference sequence, that is no genetic variation is present at that position, the virus is considered to be wild type at that position.

Positions & Genetic Variations of Interest

Amino acid level:

In the SARS-CoV-2 spike protein, based on changes in the N-terminal or receptor binding domains, and changes observed in naturally occurring variants

- S13I, L18F, T20N, P26S, 69del + 70del, D80A, L98F, D138Y, Y144del, W152C, R190S, D215G, L242H, 242del + 243del + 244del, R246I, K417N, K417T, N439K, V445A, L452R, Y453F, S477N, S477R, E484K, N501Y, A520S, A570D, D614G, H655Y, P681H, A701V, T761I, S982A, T1027I, D1118H

Variants (lineage-WHO label-defining mutations):

Lineage	WHO label	Defining mutations	Additional rule
B.1.1.7	Alpha	H69del,V70del,Y144del,N501Y,A570D,D614G,P681H,S982A,T716I,D1118H	
B.1.351	Beta	K417N,E484K,N501Y,D614G, A701V	
B.1.617.2/AY.x	Delta	T19R,L452R,T478K,D614G,P681R	
B.1.427/429	Epsilon	W152C,L452R,D614G	
B.1.525	Eta	E484K,D614G,Q677H,F888L	
P.1/P.1.x/P.1.x.x	Gamma	D614G,H655Y,V1176F,T1027I,L18F,P26S,T20N,N501Y,K417T,E484K	
B.1.526	Iota	L5F,T95I,D253G,D614G	
B.1.617.1	Kappa	L452R,E484Q,D614G,P681R	does not contain T478K
C.37/C.37.1	Lambda	L452Q,F490S,D614G,T859N	
P.3	Theta	D614G,P681H,E1092K,H1101Y,V1176F	
P.2	Zeta	E484K,D614G,V1176F	NOT P.1, NOT P.3
B.1.621/B.1.621.1	Mu	D614G,P681H,R346K,T95I,N501Y	
BA.x	Omicron	G339D,N969K	
B.1/B.1.2/B.1.1/B.1.1.214		D614G	NOT any other variant
C.36.3/C.36.3.1		D614G,A899S,Q677H,L452R	
R.1		G769V,D614G,E484K,W152L	
B.1.1.519		D614G,P681H,T732A	
Other+E484K		E484K	NOT any other variant
Reference		D614G	NOT any other variant
Other			NOT any other variant

Omicron variant definitions are based on various subvariants as follows:

OMICRON	BA.4/5	BA.1	BA.3	BA.2
G142D	OMICRON	OMICRON	OMICRON	OMICRON
D614G	L452R	ins214EPE	NOT BA.1	NOT BA.1
H655Y	F486V	S371L	T95I	NOT BA.3
N679K		G496S	V143del	NOT BA.4/5
P681H		T547K	Y144del	T19I
D796Y		N856K	Y145del	V213G
Q954H		L981F	N211del	S371F
N969K			L212I	T376A
				D405N
				R408S

Note: Variants are defined in this order (left to right from the above table). For example, to define BA.2 the sequence should not be BA.3, BA.1 and BA.4/5.

Analysis Methods

Frequencies and percentages will be presented for the specified parameters. The denominator is the number of subjects with a COVID-19 episode with sequencing data.

5.4.4. Viral Load (VL)

SARS-CoV-2 viral RNA load was determined by first available positive nasal swab sample per participant during the COVID-19 episode.

Values below the lower limit of quantification (LLOQ) will be imputed with 1 when detected and with 0 when not detected.

Similar methods will be used for the analysis of VL based on saliva samples (if available).

Analysis Methods

VL for the first available positive swab will be descriptively summarized (n, mean, median, SD, SE, range) for PPE analysis set by cohorts, dose groups and COVID-19 severity (mild, moderate and severe/critical).

To assess the correlation between VL and number/intensity of symptoms, the following scatter plots will be provided by severity (mild, moderate and severe/critical):

- Log_{10} Viral Load versus number of symptoms over the molecularly confirmed symptomatic COVID-19 Episode with Onset at least 14 days after booster vaccination in each cohort.
- Log_{10} Viral Load versus AUC symptom over the molecularly confirmed symptomatic COVID-19 Episode with Onset at least 14 days after booster vaccination in each cohort.

5.5. Interim Analyses

Interim analyses may be performed for exploratory endoints. Data will be collected based on molecularly confirmed SARS-CoV-2 infections, SARS-CoV-2 asymptomatic infection (by measurement of nucleocapsid binding antibodies), moderate, moderate to severe/critical COVID-19 disease, medical intervention/hospitalization and COVID-19-like signs and symptoms. The analysis of the exploratory vaccine efficacy endpoints will evaluate the rVE measures and the associated 95% CIs will be estimated. The analysis will be based on the Cox proportional hazards model, using the calendar-based time scale. If feasible, the model may stratify for age groups, co-morbidities, site or a higher-level geographical region, to account for potential differences in geographical exposure.

5.5.1. 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 Section 0, 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. More details will be provided in the revised charter of the Clinical Severity Adjudication Committee. 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 in 5.2.1. Readjudication will occur if new information becomes available. The last adjudication for a given case will determine the status of the case for analysis. The Clinical Severity Adjudication Committee's assessment will be considered the definitive classification of the case.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

AE	adverse event
AUC	area under the curve
BLA	biologics license application
BMI	body mass index
CI	confidence interval
COVID-19	coronavirus disease-2019
CRF	case report form
CSAC	clinical severity adjudication committee
CTP	clinical trial protocol
DPS	Data presentation specifications
DVT	deep vein thrombosis
ECMO	extracorporeal membrane oxygenation
eCOA	electronic clinical outcome assessment
ELISA	enzyme-linked immunosorbent assay
FAS	full analysis set
FDA	Food and Drug Administration
LLOQ	lower limit of quantification
MSR	modelling and simulation report
PPE	per protocol efficacy analysis set
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
SIC	symptoms of infection with coronavirus-19
SMQ	standardized MedDRA query
SpO2	saturation of oxygen
US	United States
rVE	relative vaccine efficacy
VE	vaccine efficacy
VL	viral load
VNA	virus neutralization assay
vp	virus particle

6.2. Appendix 3 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.

7. REFERENCES

Bretz F, et al. A graphical approach to sequentially rejective multiple test procedures. Stat in Med, 2009; 28:586-.

Robins, James. A new approach to causal inference in mortality studies with a sustained exposure period—application to control of the healthy worker survivor effect. *Mathematical Modelling* 7.9-12 (1986): 1393-1512.

Van der Laan, Mark J., and Susan Gruber. Targeted minimum loss based estimation of causal effects of multiple time point interventions. (2012) *The International Journal of Biostatistics* 8.1.

Van der Laan, Mark J., Eric C. Polley, and Alan E. Hubbard. "Super learner." *Statistical applications in genetics and molecular biology* 6.1 (2007).

Zeng, Donglin. Estimating marginal survival function by adjusting for dependent censoring using many covariates. *The Annals of Statistics* 32.4 (2004): 1533-1555.

Nauta J. *Statistics in Clinical Vaccine Trials*. Springer. (2011).Section 7.4.2.

Assessing Vaccine Durability in Randomized Trials Following Placebo Crossover Jonathan Fintzi and Dean Follmann, Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases Rockville, Maryland, U.S.A.

Janssen Research & Development

Statistical Analysis Plan

A Randomized, Double-blind, Phase 2 Study to Evaluate the Immunogenicity, Reactogenicity and Safety of Ad26.COV2.S Administered as Booster Vaccination in Adults 18 Years of Age and Older Who Have Previously Received Primary Vaccination with Ad26.COV2.S or BNT162b2

Protocol VAC31518COV2008; Phase 2

VAC31518 (JNJ-78436735 [Ad26.COV2.S]))

Status: Approved
Date: 15Dec 2021
Prepared by: Janssen Vaccines & Prevention B.V.
Document No.: EDMS RIM-462169

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

TABLE OF CONTENTS

VERSION HISTORY

Table [xx] – SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1		Not Applicable	Initial release

1. INTRODUCTION

This Statistical Analysis Plan (SAP) specifies definitions of analysis sets, key derived variables, and the statistical analysis methods for the pre-planned Interim Analysis (to be confirmed), Primary Analysis and Final Analysis of immunogenicity, reactogenicity, and safety data of the study. This SAP is based on Clinical Protocol VAC31518COV2008. One or more Data Presentation Specification Documents (DPS) could be available to further detail the statistical outputs that will be generated

1.1. Objectives and Endpoints

Refer to Clinical Trial Protocol (CTP); section 3.

1.2. Study Design

Refer to Clinical Trial Protocol (CTP); section 4.

2. STATISTICAL HYPOTHESES

Refer to Clinical Trial Protocol (CTP); section 9.1.

3. SAMPLE SIZE DETERMINATION

Refer to Clinical Trial Protocol (CTP); section 9.2.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

For vaccine studies, study intervention assignment will follow the *as treated principle* i.e., all analyses will be presented by the vaccine actually received.

Population	**Description**
All screened participants (ALL)	The "all screened participants" set includes all participants who were screened, regardless of whether they were enrolled and/or randomized.
All randomized participants (ALL RANDOMIZED)	The "all randomized participants" set includes all participants who were randomized to one of the treatment groups.
Full Analyses Set (FAS)	The full analysis set includes all participants with documented study vaccine (Ad26.COV2.S) administration.
Per Protocol Immunogenicity Set (PPI)	The per protocol immunogenicity analysis set includes all vaccinated participants for whom post-baseline immunogenicity data are available and excludes participants with major protocol deviations expected to impact immunogenicity outcomes. In addition, samples obtained after natural SARS-CoV-2 infection will be excluded from this analysis set.
Non-Inferiority Analysis Set (NI)	The non-inferiority analysis set includes all PPI participants who are SARS-COV-2 seronegative at baseline.

Pfizer BNT162b2 external samples	The Pfizer BNT162b2 external samples analysis set includes individuals, selected from biobanks or clinical studies, who received 2 doses of Pfizer BNT162b2 vaccine as primary vaccination and for whom blood samples are available between 2 weeks and 2 months post primary vaccination series with Pfizer BNT162b2 vaccine.

5. STATISTICAL ANALYSES

5.1. General Considerations

5.1.1. Study phases

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

The safety analysis will present all results by phase (cf. section 5.1.1 below for phase definitions). Immunogenicity results will be presented per scheduled timepoint as appropriate. Listings will be shown per phase and timepoint.

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).

5.1.2. Phase definitions

The phases in the study will be constructed as detailed in Table 1.

Table 1: Phase Definitions

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
Regimen	2	Post-dose 1	1	Date and time of first vaccination in this study	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of database cut-off in case of interim analysis c) 23:59 on 28 days after the first vaccination (23:59 of day of vaccination + 28 days)
Follow-up 1	3			One minute after end of Post dose 1 period	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of database cut-off in case of interim analysis c) 23:59 at the date of last visit

Note: the end date of the regimen phase should be the end date of the last post dose period.

Adverse Events and selected other tables may display AEs (or other counts) by period.

For some tables, e.g. SAE tables, a period termed "Entire study" will be defined. This will be a combination of Post-dose 1 and Follow-up 1, so that it covers the time window from vaccination 1 up to and including the end of the study for each participant.

5.1.3. Visit Windows

Refer to CTP section 1.3. Visit windows will be taken into account for the analysis of immunogenicity results (see section 5.7.1).

5.2. Participant Dispositions

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

- Participants screened
- Participants who screen failed (and main reason for screen failure)
- Participants who received study intervention (i.e. participants in the FAS)
- Participants vaccinated and not randomized
- Participants randomized and not vaccinated
- Participants in the PPI
- Participants in the FAS but not in the PPI (and reasons for not being in the PPI)
- Participants in the NI
- Participants who discontinued study
- Reasons for termination of study

Listings of participants will be provided for the following categories:

- Screen failures
- Participants who terminated study prematurely
- Participants who were randomized and did not receive study intervention.
- Participants who received study intervention and were not randomized

5.3. Primary Endpoint(s) Analysis

5.3.1. Definition of Endpoint(s)

The endpoints related to the primary objectives of this study, are:

Primary Objective 1a:

- Serological response to vaccination and antibody titers as measured by virus neutralization assay (VNA) titers against the original strain, 14 days after Ad26.COV2.S booster vaccination (5×10^{10} vp dose level) after completing 1-dose primary vaccination with Ad26.COV2.S (5×10^{10} vp dose level).

- Serological response to vaccination and antibody titers (VNA) against the original strain, 28 days after Ad26.COV2.S (5×10^{10} vp dose level) single-dose primary vaccination.

Primary Objective 1b:

- Serological response to vaccination and antibody titers as measured by virus neutralization assay (VNA) titers against the leading variant of high consequence or concern*, 14 days after Ad26.COV2.S booster vaccination (5×10^{10} vp dose level) after completing 1-dose primary vaccination with Ad26.COV2.S (5×10^{10} vp dose level).
- Serological response to vaccination and antibody titers (VNA) against the leading variant of high consequence or concern*, 28 days after Ad26.COV2.S (5×10^{10} vp dose level) single-dose primary vaccination.

Primary Objective 1c:

- Serological response to vaccination and antibody titers as measured by virus neutralization assay (VNA) titers against the original strain, 14 days after Ad26.COV2.S booster vaccination (2.5×10^{10} vp dose level) after completing 1-dose primary vaccination with Ad26.COV2.S (5×10^{10} vp dose level).
- Serological response to vaccination and antibody titers (VNA) against the original strain, 28 days after Ad26.COV2.S (5×10^{10} vp dose level) single-dose primary vaccination

Primary Objective 1d:

- Serological response to vaccination and antibody titers as measured by virus neutralization assay (VNA) titers against the original strain, 14 days after Ad26.COV2.S booster vaccination (1×10^{10} vp dose level) after completing 1-dose primary vaccination with Ad26.COV2.S (5×10^{10} vp dose level).
- Serological response to vaccination and antibody titers (VNA) against the original strain, 28 days after Ad26.COV2.S (5×10^{10} vp dose level) single-dose primary vaccination.

Primary Objective 2a:

- Serological response to vaccination and antibody titers as measured by virus neutralization assay (VNA) titers against the original strain, 14 days after Ad26.COV2.S booster vaccination (5×10^{10} vp dose level) after completing 2-dose primary vaccination with Pfizer BNT162b2
- Serological response to vaccination and antibody titers (VNA) against the original strain in serum samples of approximately 300 individuals, collected 2 weeks to 2 months after

completing 2-dose primary vaccination with Pfizer BNT162b2 (further referred to as Pfizer BNT162b2 external samples).

Primary Objective 2b:

- Serological response to vaccination and antibody titers as measured by virus neutralization assay (VNA) against the leading variant of high consequence or concern* 14 days after Ad26.COV2.S booster vaccination (5×10^{10} vp dose level) after completing 2-dose primary vaccination with Pfizer BNT162b2
- Serological response to vaccination and antibody titers as measured by virus neutralization assay (VNA) against the leading variant of high consequence or concern* in Pfizer BNT162b2 external samples

Primary Objective 2c:

- Serological response to vaccination and antibody titers as measured by virus neutralization assay (VNA) titers against the original strain, 14 days after Ad26.COV2.S booster vaccination (2.5×10^{10} vp dose level) after completing 2-dose primary vaccination with Pfizer BNT162b2.
- Serological response to vaccination and antibody titers (VNA) against the original strain, in Pfizer BNT162b2 external samples.

Primary Objective 2d:

- Serological response to vaccination and antibody titers as measured by virus neutralization assay (VNA) titers against the original strain, 14 days after Ad26.COV2.S booster vaccination (1×10^{10} vp dose level) after completing 2-dose primary vaccination with Pfizer BNT162b2.
- Serological response to vaccination and antibody titers (VNA) against the original strain, in Pfizer BNT162b2 external samples

5.3.2. Estimand

Not applicable

5.3.3. Analysis Methods

Refer to section 0.

5.4. Secondary Endpoint(s) Analysis

The secondary endpoints include:

- To assess the safety and reactogenicity of Ad26.COV2.S as booster vaccinations in adults.
  - Solicited local and systemic adverse events (AEs) for 7 days after booster vaccination.
  - Unsolicited AEs for 28 days after booster vaccination.
  - Serious adverse events (SAEs) and adverse events of special interest (AESIs) throughout the study (from booster vaccination until end of the study).

- To assess the neutralizing and binding antibody response to the original strain, leading variant of high consequence or concern* and other relevant variants of concern, induced by booster vaccination in adults who have previously completed single-dose primary vaccination with Ad26.COV2.S at the 5×10^{10} vp dose level.

  - Serological response to vaccination and antibody titers, as measured by VNA, against the original strain, leading variant of high consequence or concern* AND other relevant variants of concern, 14 days and 28 days after Ad26.COV2.S booster vaccination.
  - Antibodies binding to SARS-CoV-2 relevant variants of concern or individual SARS-CoV-2 proteins (eg, S and/or receptor-binding domain [RBD] proteins from the SARS-CoV-2 variants of concern) by ELISA and/or MSD.
  - Antibodies binding to the SARS-CoV-2 nucleocapsid (N) protein at Day 1 (N-serology).

- To assess the neutralizing and binding antibody response to the original strain, leading variant of high consequence or concern* and other relevant variants of concern, induced by booster vaccination in adults who have previously completed primary vaccination with Pfizer BNT162b

  - Same endpoints as above

5.5. Tertiary/Exploratory Endpoint(s) Analysis

Refer to Clinical Trial Protocol (CTP section 3).

5.6. Safety Analyses

All safety analyses will be based on the FAS based on actual intervention received, unless otherwise specified.

All continuous safety variables, descriptive statistics by intervention group will include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by vaccination group using frequency counts and percentages. All safety data summary will be presented by Cohort where Cohort 1 includes participants who received Ad26.COV2.S as primary vaccination; and Cohort 2 includes those who received BNT162b2 as primary vaccination, unless specified otherwise. In addition, selected safety results will be presented in the same output with both cohorts.

5.6.1. Extent of Exposure

The number of participants who receive study intervention will be summarized.

5.6.2. Adverse Events

5.6.2.1. Definitions

Solicited AEs shown in the tables are extracted from the investigator assessment pages (CE) of the CRF. For unsolicited AEs, only the AEs within the 28-day period following vaccination will be presented in the safety tables except for SAEs and AEs of Special Interest (AESI) which will be captured and tabulated in the outputs covering the whole study period. All other collected unsolicited adverse events will be presented through listings.

By definition, solicited administration site symptoms are considered to be related to the study vaccine.

The severity of AEs will be classified as grade 1 to 4. Solicited events that are graded less than grade 1 are not considered AEs. If grade is not present, grading is assigned based on the grading list in Appendix 11.

Respiratory tract infections due to SARS-CoV-2 infection will be tabulated and listed separately. Respiratory tract infections not due to SARS-CoV-2 infection will be reported as AEs by System Organ Class and Preferred Term if they occur between the time of vaccination through the following 28 days. Respiratory tract infections recorded as AEs in the eCRF will be excluded from AE analysis if the molecular test result for that event is positive for SARS-CoV-2. In general, any (S)AEs caused by molecularly confirmed SARS-CoV-2 infection will be removed at the analysis level from the (S)AE listings and tables and presented separately.

This study defines thrombosis with thrombocytopenia syndrome (TTS) as an AE of Special Interest (AESI), cf. protocol sections 8.3.1 and 8.3.7.1. Suspected AESIs will be adjudicated by a committee to determine whether they fulfill the definition(s) for TTS (and consequently, whether they are confirmed AESIs).

If additional information (e.g. adjudicated cases, associated lab tests) becomes available in the clinical database, additional statistical analyses may be specified in the DPS.

5.6.2.2. Analysis of Adverse Events

Number and percentage of participants with at least one particular AE (unsolicited/solicited) will be tabulated. Solicited AEs will be summarized by class (administration site/systemic) and Preferred Term. Unsolicited AEs will be summarized by System Organ Class and Preferred Term.

For solicited AEs, the following tables will be provided: summary; by worst severity grade; at least grade 3; related (systemic only); time to onset (in days); and duration (in days) for most frequent events and body temperature. Note: Duration is defined as number of days from the start of the event until resolution of the event. The time to first onset is defined as (date of first onset – reference date + 1). The reference date is the start date of the vaccination period.

For unsolicited AEs, the following tables will be provided: summary table (including SAE, fatal outcome, and discontinuation); all events; most frequent; at least grade 3; permanent stop of vaccine; related; and SAE.

Tables will be provided to summarize the occurrence of TTS. These tables will cover the entire study period, post-dose 1 (booster) and follow-up 1 (similar to SAE tables). The following summary tables will be provided on suspected and probable suspected AE of Special Interest (AESI) by vaccine group:

1. Number of Suspected AEs of Special Interest (AESI) (as reported by Investigator) by SMQ and Preferred Term
   Note: Suspected AESI as reported by investigator and presented by: Embolic and thrombotic events (SMQ); Haematopoietic thrombocytopenias (SMQ) (broad) or HLT Thrombocytopenias; Other SMQ.
2. Number of Suspected AEs of Special Interest (AESI) (identified through SMQ search) by SMQ and Preferred Term
   Note: Suspected AESI: Embolic and thrombotic events (SMQ), Haematopoietic thrombocytopenias (SMQ) (broad) or HLT Thrombocytopenias
3. Number of Probable AEs of Special Interest (AESI) qualified for assessment by SMQ and Preferred Term
   Note1: Probable AESI qualified for assessment: [Embolic and thrombotic events (SMQ)] and [Haematopoietic thrombocytopenias (SMQ) (broad) or HLT Thrombocytopenias or platelet count below normal ranges per local or central laboratory report or platelet count < 150 × 10E9/L]

Platelet counts will be prospectively collected for AESIs (in LB domain). These will be used to identify participants who will be reported in 3 above and will be presented in participant narratives.

Anti-PF4 data may be presented as table or listing as appropriate.

Details on TTS is specified in section 8.3.7.1 of the CTP. The list of thrombotic events to be reported to the sponsor as an AESI is provided Appendix 14of the CTP. AEs meeting the AESI criteria will be flagged as such in the SDTM database.

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

5.6.2.3. Phase allocation of Adverse Events

Solicited events are always allocated to the respective Post Dose period.

Step 1: Allocation of events to the periods:

Adverse events in the 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 (i.e. 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, 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 trial. In case of a completely missing start date, the event is allocated to the first active treatment phase (post dose 1 period), except if the end date of the AE falls before the start of the first active treatment phase (post dose 1 period).

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 (i.e. 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 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.

5.6.2.4. Missing Data

Missing AE data will not be imputed. Participants who do not report an AE will be considered as participants without an adverse event. An AE with missing severity or relationship will be considered as the reported AE, 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.

5.6.3. Additional Safety Assessments (if applicable)

Not Applicable

5.6.3.1. Clinical Laboratory Tests

Protocol-Required Safety Laboratory Assessments are documented in Appendix 2 of the CTP. A listing of all laboratory values (abnormal or graded, when available) will be made, restricted to participants with at least one laboratory abnormality.

An abnormality (toxicity grade or abnormality based on normal ranges) will be considered as emerging in a particular period if it is worse than the baseline value. If the baseline is missing, the abnormality is always considered emerging. A shift from 'abnormally low' at baseline to 'abnormally high' post baseline (or vice versa) is also emerging. If a laboratory test result is censored (no numeric value is available, but only a verbatim term), a numeric value will be imputed by a value exceeding the cut-off value with one unit. (<x: subtract 1 unit from x, >x: add 1 unit to x; <3.45 is imputed with 3.44).

If no toxicity grades are defined for a test, the abnormalities (above/below normal range) will be used. In determining toxicity grades, the following rules are applied:

- Worst grades/abnormalities are determined over the whole observational period for each trial period separately, including all post-baseline measurements of that period.
- The abnormalities 'abnormally low' and 'abnormally high' are considered equally important, i.e. if a participant has as well an abnormally low as an abnormally high value post-baseline, both abnormalities are shown in the tables. (This means that the sum of the percentages can be more than 100%)
- The grading scale for some parameters in the grading table contains gaps (zones where no toxicity grade definition exists). In these cases, laboratory results falling in these gap zones will be allocated to the adjacent worst-case grade.
- If a lab value falls within the grading as specified in the grading table but also within the local lab normal limits, the value is considered normal.

No distinction will be made in grading for sample test results obtained under fasting and non-fasting conditions. If limits under fasting and non-fasting conditions differ, the limits of the condition (fasting/non-fasting) of scheduled visits as planned in the CTP will be used. The same applies to samples obtained under a different condition (e.g. samples of withdrawal visits).

5.6.3.2. Vital Signs and Physical Examination Findings

Physical examination findings will be summarized at baseline. A listing of the abnormalities will be made.

Vital signs including body temperature, pulse/heart rate, respiratory rate, and blood pressure (systolic and diastolic) will be summarized over time, using descriptive statistics. Abnormalities emerging after vaccination will be tabulated by worst abnormality grade using the FDA table in appendix 10.

A listing of participants with pyrexia/fever according to the FDA grading table will be provided. In addition, temperature measurements (whether obtained from the diary or from on-site assessments) will be allocated to predefined temperature intervals (from 37.5° C to 40°C, in half degree increments, e.g., <37.5; 37.5 to <38; 38 to <38.5; … >40, and tabulated.

5.6.3.3. Other Safety Parameters

Not Applicable.

5.7. Other Analyses

Not applicable

5.7.1. Immunogenicity

5.7.1.1. Immunogenicity Analysis

The analysis of immunogenicity will use the PPI and NI analyses sets. Selected immunogenicity analyses may also be done on the FAS. Within each Cohort (Cohort 1 (Ad26.COV2.S primary vaccination); Cohort 2 (BNT162b2 primary vaccination)), data will be analyzed by vaccine group, and by vaccine group and participant seropositivity status at screening. Data will be presented by scheduled time point. Selected results will be presented in the same output with both cohorts.

For the PPI analysis, samples taken outside of the allowed window will be excluded from the tables and graphs (but will be included in the listings and clearly marked as results not included in the PPI analyses). For the FAS analysis, samples taken outside of the window will be included.

5.7.1.2. Parameters

Planned humoral and cellular immune assays are listed in the CTP section 8.1.4. However, not all assays might be available for all immunogenicity analyses covered by this SAP. Further information on which assays will be analyzed in each of the analyses, will be included in the corresponding DPS document(s).

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

Missing immune response data will not be imputed.

Values below the lower limit of quantification (LLOQ) or limit of detection (LOD) will be handled as follows:

- Calculation of geometric mean and median:
  - o values <LLOQ(or LOD) are imputed with LLOQ(or LOD)/2.
- Calculation of fold increases from baseline or other reference timepoint:
  - o values <LLOQ(or LOD) are imputed with LLOQ(orLOD).

Values above the upper limit of quantification (ULOQ) will be handled as follows:

- Calculation of geometric mean and median:
  - o Values >ULOQ are imputed with ULOQ.
- Calculation of fold increases from baseline or other reference timepoint:
  - o Values >ULOQ are imputed with ULOQ.

5.7.1.4. Handling of changes in assay status throughout the study conduct

In case of changes in assay status, from "qualified" to "validated", the LLOQ and ULOQ are likely to change as well. If this should happen, then the SDTM database will contain records pertaining to the assay in the qualified status and records pertaining to the validated status, and the LLOQ and ULOQ values will also differ.

The statistical analysis will use the LLOQ and ULOQ values associated with the validated assay and will retrospectively apply these on all the data pertaining to the assay, including the data obtained while the assay status was "qualified". This may imply that data received, statistically analyzed, and presented at an earlier time may change. Graphical displays will show the eventually used LLOQ and ULOQ values. Graphs and tables will have an additional footnote that reflects the assay status. Immune Response Analysis

5.7.1.5. NI Analysis – Success Criterion and Statistical method

Formal NI testing in Cohort 1 will be conducted as a "within-participants" analysis, in which participants' VNA data are considered matched pairs across the two time points. However, the formal NI testing in Cohort 2 will be conducted as between participant analysis comparing COV2008 Pfizer cohort (cohort 2) vs. the external Pfizer samples VNA data.

For each Primary objective in Cohort 1 and Cohort 2, the NI tests will be performed on the NI analysis set and must be demonstrated on both co-primary endpoints as well as on the GMR estimate criterion to conclude NI:

- GMR
- Responder rate for Cohort 1 and seropositivity rate for cohort 2
- An estimated GMR (GMT Day 15 post-booster/GMT post primary regimen) of >0.8

The primary responder definition (FDA) (see section 5.7.1.6.2.1) will be used for the NI assessment of the primary objectives.

Furthermore, hierarchical testing will be applied to the NI hypotheses in the cohorts (see CTP section 9.1; Figure 3: Decision Tree-based Hypothesis Testing).

In addition to the hierarchical NI hypotheses testing results, forest plot of responder rate (cohort 1) and seropositivity rate (cohort 2) differences and GMRs associated with the NI Hypotheses will be presented by cohort. The forest plots will also be presented by age group (see section 5.7.2).

The success criterion and the corresponding statistical methods to be used are as described below for each cohort.

Remark: Note that, in general, the lower bound of a 2-sided $100 * (1 - 2 * \alpha)\%$ CI (where α= 1-sided significance level) is equivalent to the lower bound of the 1-sided $100 * (1 - \alpha)\%$ CI which is needed for the NI hypothesis testing.

5.7.1.5.1. Cohort 1 (primary objectives 1a,1b,1c and 1d)

To assess the 4 NI hypotheses related to Cohort 1 (CTP section 9.1), the neutralizing antibody response 14 days post Ad26.COV2.S booster vs the neutralizing antibody response 28 days post primary vaccination with Ad26.COV2.S will be used.

For the NI analysis, define the following groups:

1 = Ad26.COV2.S $5x10^{10}$ vp booster after Ad26.COV2.S (original virus)
2 = Ad26.COV2.S $5x10^{10}$ vp booster after Ad26.COV2.S (leading variant of high consequence or concern*), if feasible
3 = Ad26.COV2.S $2.5x10^{10}$ vp booster after Ad26.COV2.S (original virus)
4 = Ad26.COV2.S $1x10^{10}$ vp booster after Ad26.COV2.S (original virus)

R1 = Ad26.COV2.S 5×10^{10} vp primary vaccination (original strain) – (Reference group 1)

R2 = Ad26.COV2.S 5×10^{10} vp primary vaccination (leading variant of high consequence or concern*), if feasible (Reference group 2)

Success Criterion 1:

The responder rate induced in group k (k = 1, 3, or 4) is NI as compared to the responder rate induced in group R1 using a NI margin of -10%. Similarly, the responder rate induced in group k (k = 2) is NI as compared to the responder rate induced in group R2, using a NI margin of -10%

Statistical method:

Objectives 1a and 1b (evaluated at the interim (if conducted) and primary analysis), 1c and 1d (evaluated only at the primary analysis).

To compute the differences in responder rates and associated Agresti-Min confidence intervals, let the dichotomous response post booster and post primary vaccination (reference) summary data be presented in a 2x2 table as follows.

Table 1: Paired Data Study Design Responses

	Post Booster		
Post Primary	Success	Failure	Total
Success	a	b	a + b
Failure	c	d	c + d
Total	a + c	b + d	n

Where,

a = Number of participants responding favorably on both the post primary and on the booster
b = Number of participants responding favorably on the post primary but unfavorably on the booster
c = Number of participants responding unfavorably on the post primary but favorably on the booster
d = Number of participants responding unfavorably on both the post primary and on the booster

Let $d = \left(\hat{P}_{Boost} - \hat{P}_{Primary}\right)$ = Post booster responder rate – Post primary responder rate.

Then,

$$d = \frac{(a+c)}{n} - \frac{(a+b)}{n} = \frac{(c-b)}{n}$$

Based on the data structure given in Table 1, the Agresti-Min (Agresti, A. & Min, Y. (2005).) point estimate and confidence interval (for the population responder difference rates, $\delta = \left(P_{Boost} - P_{Primary}\right)$) lower and upper bounds are computed as follows:

$$Lower\ limit = \frac{(c^* - b^*)}{n^*} - Z_{\alpha/2}\sqrt{\left[(b^* + c^*) - \frac{(c^* - b^*)^2}{n^*}\right]/n^*}$$

$$Upper\ \ limit = \frac{(c^* - b^*)}{n^*} + Z_{\alpha/2}\sqrt{\left[(b^* + c^*) - \frac{(c^* - b^*)^2}{n^*}\right]/n^*}$$

Where $b^* = b + \frac{1}{2}, c^* = c + \frac{1}{2}, and\ n^* = n + 2$

For the NI assessment with respect to responder rates, in each group k (k = 1, 3, or 4) compared to the reference group R1 and in group k=2 compared to the reference group R2, the Agresti-Min (Agresti 2005) method, as described above, will be used to estimate the "within-participant" responder rate differences (i.e., booster vaccination after Ad26.COV2.S (original virus or leading variant of high consequence or concern*) minus primary vaccination (original strain or leading variant of high consequence or concern*) and its associated 2-sided $100 * (1 - 2 * \alpha)\%$ CI (where α= 1-sided significance level).This method was chosen because of its well-behaved Coverage Probability (CP) properties compared to other methods for the analysis of matched pairs data (Reed

2009). Coverage probability is generally used to evaluate (1 – α) CIs where α is the Type I error rate.

If an interim analysis is done (objectives 1a and 1b) with alpha spent = 0.0003 (1-sided) at the interim, based on the O'Brien-Fleming group sequential method assuming information fraction of 1/3, then the Agresti-Min method will result in the estimated responder rate difference and associated CI of 99.94% at the Interim analysis and 95.02% (for alpha=0.0249 (1-sided)) at the primary analysis, respectively. If at the time of the interim analysis, the assumption of 1/3 for information fraction is found not to be true, then the O'Brien-Fleming adjustments will be recalculated.

The estimated responder rate difference and associated 97.5% CI for Objectives 1c and 1d will be evaluated only at the primary analysis.

Remark: If no interim analysis is carried out, then the Agresti-Min method will result in the estimated responder rate difference and its 95% CI (objectives 1a and 1b) and 97.5% CI (objectives 1c and 1d) at the PA, respectively.

Success Criterion 2:

Note: success criterion 2 will only be tested if success criterion 1 was met successfully for the hypothesis under consideration.

The GMT induced in group k (k = 1, 3, or 4) is NI as compared to the GMT induced in group R1 using a NI margin of 2/3. Similarly, the GMT induced in group k (k = 2) is NI as compared to the GMT induced in group R2 using a NI margin of 2/3

Statistical method:

Objectives 1a and 1b (evaluated at the interim and primary analysis), 1c and 1d (evaluated only at the primary analysis)

The NI analysis on the GMR, in each group k (k = 1, 3, or 4) compared to the reference group R1 and in group k=2 compared to the reference group R2 , will, respectively, use a paired t-test to estimate the within participant mean differences (i.e., booster vaccination after Ad26.COV2.S (original virus or leading variant of high consequence or concern*) minus primary vaccination (original strain or leading variant of high consequence or concern*) log10 transformed data, or equivalently change from primary on log10 transformed data) and its associated $100 * (1 - 2 * \alpha)\%$ CI (where α= 1-sided significance level). The estimated differences and its CIs will be back transformed to yield the GMR and its associated CI.

Similarly, if an interim analysis is done (objectives 1a and 1b) with alpha spent = 0.0003 (1-sided) at the interim, based on the O'Brien-Fleming group sequential method assuming information fraction of 1/3, then the back transformation of the log10 transformed data, will result in the

estimated GMR difference and associated 99.94% CI at the Interim analysis and 95.02% (for alpha=0.0249 (1-sided)) at the primary analysis, respectively. If at the time of the interim analysis, the assumption of 1/3 for information fraction is found not to be true, then the O'Brien-Fleming adjustments will be recalculated.

The estimated GMR difference and associated 97.5% CI for Objectives 1c and 1d will be evaluated only at the primary analysis.

Remark: If no interim analysis is carried out, then the estimated differences and its CIs will be back transformed to yield the GMR and its 95% CI (objectives 1a and 1b) and 97.5% CI (objectives 1c and 1d) at the PA, respectively.

5.7.1.5.2. Cohort 2 (primary objectives 2a,2b 2c, and 2d)

Serum samples of approximately 300 individuals collected 2 weeks to 2 months after completion of the 2-dose primary vaccination with Pfizer BNT162b2 obtained from external sources will be used to assess NI of the neutralizing antibody response 14 days post Ad26.COV2.S booster vs the neutralizing antibody response 2 weeks to 2 months after completion of the 2-dose primary vaccination with Pfizer BNT162b2 in the 4 hypotheses related to Cohort 2 (CTP section 9.1).

For the NI analysis, define the following groups:

5 = Ad26.COV2.S 5×10^{10} vp booster vaccination after Pfizer (original virus)
6 = Ad26.COV2.S 5×10^{10} vp booster vaccination after Pfizer (leading variant of high consequence or concern*), if feasible
7 = Ad26.COV2.S 2.5×10^{10} vp booster vaccination after Pfizer (original virus)
8 = Ad26.COV2.S 1×10^{10} vp booster vaccination after Pfizer (original virus)
R3 = 2-dose Pfizer BNT162b2 primary vaccination (original strain) (referred to as Pfizer BNT162b2 external samples) (Reference group 3)

R4 = 2-dose Pfizer BNT162b2 primary vaccination (leading variant of high consequence or concern*), if feasible (referred to as Pfizer BNT162b2 external samples) (Reference group 4)

Success Criterion 1:

The Seropositivity rate induced in group k (k = 5, 7, or 8) is NI as compared to the Seropositivity rate induced in group R3, using a NI margin of -10%. Similarly, the Seropositivity rate induced in group k (k = 6) is NI as compared to the Seropositivity rate induced in group R4, using a NI margin of -10%

Statistical method:

The $100 * (1 - 2 * \alpha)\%$ CI (where α= 1-sided significance level) for differences in Seropositivity rate between each group 5, 7, 8 and R3 (Reference group 3) and between group 6 and R4 (Reference group 4) will, respectively, be computed using the Farrington & Manning Likelihood Score Test method.

The rate will be converted to percentage and if the lower limit of the CI is > - 10, then it will be concluded that success criterion 1 for the given hypothesis has been met. In that case, success criterion 2 will be tested for the hypothesis under consideration. Otherwise, the testing will be ended, and it will be concluded that NI has not been demonstrated for the hypothesis under consideration.

Success Criterion 2:

Note: success criterion 2 will only be tested if success criterion 1 was met successfully for the hypothesis under consideration.

The GMT induced in group k (k = 5, 7, or 8) is NI as compared to the GMT induced in group R3 using a NI margin of 2/3. Similarly, the GMT induced in group k (k = 6) is NI as compared to the GMT induced in group R4 using a NI margin of 2/3

Statistical method:

Objectives 2a, 2b, 2c and 2d: evaluated only at the primary analysis

The NI analysis on the GMR, in each group g (g = 5, 7, or 8) compared to the reference group R3 and in group k=6 compared to the reference group R4, will, respectively, be assessed by first constructing the 2-sided (1- 2*α) % confidence interval for the difference in means (i.e., booster vaccination after Ad26.COV2.S (original virus or leading variant of high consequence or concern*) minus primary vaccination (original strain or leading variant of high consequence or concern*) log10 transformed data) based on the sampling distribution of two independent normal distributions with variances that are unknown but assumed equal.

Let $X_g = \log_{10} Y_g \sim N(\mu_g, \sigma_g)$, normally distributed with true population mean and standard deviation, μ_g and σ_g respectively and where X_g is the log-transformed ($\log_{10}$ scale) virus neutralization assay (VNA) titers for Cohort 2 booster vaccine groups, $g = 5,6,7,8$ (so defined to reflect the hypotheses in Figure 3 Refer to Clinical Trial Protocol (CTP); section 9.1).

Let $X_R = \log_{10} Y_R \sim N(\mu_R, \sigma_R)$, where X_R $(R = R_3 \; or \; R_4)$ is the log-transformed ($\log_{10}$ scale) virus neutralization assay (VNA) titers for the 2-dose Pfizer BNT162b2 primary vaccination (original strain) (Reference group 3) or the 2-dose Pfizer BNT162b2 primary vaccination (leading variant of high consequence or concern*), if feasible (Reference group 4)

It can be shown that the log-transformed ($\log_{10}$ scale) virus neutralization assay (VNA) titers mean differences between the vaccine groups g, $(\overline{X_g} - \overline{X_R})$, is equal to the log-transformed ($\log_{10}$ scale) ratio of the corresponding geometric means, i.e., $\log_{10}(GMT_g/GMT_R)$

Hence, back transforming yields, $GMT_g/GMT_R = 10^{(\overline{X_g} - \overline{X_R})}$ as the geometric mean ratio estimates.

Next, we can construct the (1- 2*α)% confidence interval (2-sided) (where α= 1-sided significance level), for the geometric mean ratios, by first constructing the confidence interval on the difference on the means, $(\overline{X_g} - \overline{X_R})$.

Assuming unknown equal variances for the population cohort 2 booster vaccine groups g and the reference group, R, and log-transformed ($\log_{10}$ scale) virus neutralization assay (VNA) titers, the (1- 2*α) % confidence interval (2-sided), (where α= 1-sided significance level), estimate for the population mean differences, is given by,

$$\left(\overline{X_g} - \overline{X_R}\right) \pm t_{(1-2*\alpha/2\,;v_p)} S_p \sqrt{\left(\frac{1}{n_g} + \frac{1}{n_R}\right)}$$

Where the *pooled variance estimate*, $S_p^2 = \frac{(n_g-1)S_g^2+(n_R-1)S_R^2}{n_g+n_R-2}$ and $v_p = n_g + n_R - 2$ is the degrees of freedom for the t-distribution and $\alpha = 0.025$.

Since log transformation is monotone, back transforming confidence intervals for the difference in means in the log10 scale gives a confidence interval for the ratio of the geometric means. Hence, the lower and upper bounds of the 2-sided $(1 - 2 * \alpha)\%$ (i.e.,97.5% since α= 0.0125 (1-sided)) confidence interval for the GMT ratios are as follows:

$$\left((GMT\ Ratio)\right)_{Lower\ Limit} = 10^{\left((\overline{X_g}-\overline{X_R}) - t_{(1-\alpha/2\,;v_p)} S_p \sqrt{\left(\frac{1}{n_g}+\frac{1}{n_R}\right)}\right)}$$

$$\left((GMT\ Ratio)\right)_{Upper\ Limit} = 10^{\left((\overline{X_g}-\overline{X_R}) + t_{(1-\alpha/2\,;v_p)} S_p \sqrt{\left(\frac{1}{n_g}+\frac{1}{n_R}\right)}\right)}$$

If the assumptions of the unknown equal variances for the independent normal distributions of cohort 2 booster vaccine groups g and the reference group, R, do not hold (i.e., test of equality variances shows that the variances are significantly different), then an approximate t-distribution with Satterthwaite approximated degrees of freedom will be used instead (Casella, G & Berger L.R (1990).

For each of the booster vaccine groups, g comparisons, NI will be demonstrated if $\left((GMR\ Ratio)\right)_{Lower\ Limit} > \frac{2}{3}$, where the lower limit corresponds to a 97.5% 2-sided confidence interval.

SAS v 9.4 will be used in implementing the NI comparisons.

5.7.1.5.3. Sensitivity NI Analysis (cohort 1 objectives) – Statistical method

A sensitivity analysis, for the primary objectives 1a, 1c and 1d in cohort 1, will be conducted by pooling the 28 days post-dose 1 VNA data across the three study arms and comparing it to the 14 days post booster VNA data in the study arm of interest. That is, for primary objectives 1a, 1c and 1d by pooling all VNA data in Reference group 1 (R1) and comparing it to each of the groups 1, 3 and 4 (see section 5.7.1.5.1), respectively.

For each vaccination group 1,2 and 3, the pooled and each vaccination group 14 days post booster VNA data will jointly constitute repeated measures data collected at two time points, Day 0 and Day 15 which are correlated by design. Day 0 refers to the day the primary vaccination (cohort 1) was collected. Each vaccination group repeated measures data will be analyzed using appropriate statistical model that accounts for the correlation of the repeated measures data.

For the analysis of each vaccination group repeated measures correlated binary response VNA data, Generalized Estimating Equations (GEEs) (Liang and Zeger (1986)) method will be used. This approach provides a non-likelihood based or quasi-likelihood approach for modeling correlated responses by specifying one of a variety of possible working correlation matrix structures to account for the within-participant correlations. PROC GENMOD in SAS will be used to fit the Generalized Estimating Equation (GEE) model. The random effects model will include the binary response variable as the dependent variable, day as fixed effects and subject as the random (repeated measures) effect. Unstructured variance-covariance matrix will be used in the model and the model will fit the probability that the response variable is equal to '1'.

Within each vaccination group, Day 15 minus Day 0 responder rate differences will be estimated by transforming the model LSMEAN (in SAS) estimates on the logit scale to probability estimates. The associated 2-sided confidence intervals (95% CI for primary objective 1a and 97.5% CI for primary objectives 1c and 1d) will be determined using the bootstrap Percentile Confidence Interval method. A bootstrap sample of 10,000 will be generated with replacement from the original data to accomplish this. NI will then be declared if the within each vaccination group, lower limit of the 2-sided confidence intervals (95% CI for primary objective 1a and 97.5% CI for primary objectives 1c and 1d) of the responder rate (Day 15 – Day 0) difference is greater than -10% (see DPS for some guidance in coding).

Similarly, for the analysis each vaccination group repeated correlated continuous VNA data, Mixed Effects model method will be used. The random effects model will include the continuous log VNA (log_{10} scale) variable as the dependent variable, day as fixed effects and subject as the random (repeated measures) effect. Unstructured variance-covariance matrix will be used in the model. PROC Mixed (in SAS) will be used to fit the model.

Within each vaccination group, Day 15 minus Day 0 mean differences (log_{10} scale) and associated 2-sided confidence intervals (95% CI for primary objective 1a and 97.5% CI for primary objectives 1c and 1d) will be determined from the appropriate LSMESTIMATE (in SAS) of the vaccine day fixed effect in the model.

The GMRs (booster/primary) and associated confidence intervals will then be estimated by back transforming the differences in means (log10 scale) and associated confidence intervals, respectively. NI, within a vaccination group, will then be declared if the lower limit of the 2-sided confidence interval (95% CI for primary objective 1a and 97.5% CI for primary objectives 1c and 1d) of the GMR (booster/primary) is greater than 2/3 (see DPS for some coding guidance).

Remark: Sensitivity analysis will only be conducted at the primary analysis.

5.7.1.6. Immunogenicity against the insert

5.7.1.6.1. Humoral assays

5.7.1.6.2. Responder Definition and Data Summary

For neutralizing and binding antibodies to the reference SARS-CoV-2 strain and variants:

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

Two responder definitions, as defined below, are considered in the study.

5.7.1.6.2.1. Primary Responder Definition (FDA):

- For Pre-booster time points (Day 29): responder if at least one of the following conditions is satisfied:
    - If pre-dose 1 titer < LLOQ, then post-vaccination titer ≥ 4xLLOQ
    - If pre-dose 1 titer > LLOQ, then post-vaccination titer ≥ 4x pre-dose 1 titer
- For Post-booster time points: responder if at least one of the following conditions is satisfied:
    - If pre-booster titer < LLOQ, then post-booster titer ≥ 4xLLOQ
    - If pre-booster titer > LLOQ, then post-booster titer ≥ 4x pre-booster titer

Note: In the above definitions, “pre-dose 1” refers to the COV3001 dose 1 and "pre-booster" refers to the COV2008 pre-dose 1.

This definition represents the core definition to be used for the NI assessment of the primary objectives and will be applied to outputs related to psVNA, ELISA, and MSD assays.

5.7.1.6.2.2. Exploratory Responder Definition (Janssen, based on other COVID19 studies):

- A post-baseline sample will be considered a responder if at least one of the following conditions is satisfied:
    - If pre-dose 1 titer < LLOQ, then post-booster titer ≥ LLOQ
    - If pre-dose1 titer > LLOQ, then post-booster titer ≥ 4x pre-dose 1 titer

This definition will be used for exploratory/supplementary analyses to match the responder definition used in other COV studies and will also be applied to outputs related to psVNA, ELISA, and MSD assays.

For SARS-CoV-2 neutralization **VNA**, the following statistics will be calculated: N, geometric mean and corresponding 95% CI of the actual values, fold increase from baseline.

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.

As exploratory analysis, post-booster GMT and responder rate data will be summarized by pre-boost timepoint low vs. high titers (low [≤400 ID50] vs. high [>400 ID50] titers defined based on COV1001 cohort 2a data). An optimal threshold for defining low vs high will also be explored. The R package "OptimalCutpoints" (Lopez-Raton el. al (2014)) could be implemented to determine the optimal threshold.

Actual values will be 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, 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.

Reverse distribution curves of the actual values are provided for selected time points.

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

Further details and/or updated rules may be provided in the DPS.

For **S-ELISA/MSD (if available)**, the same as above applies.

The ratio of binding (S-ELISA/MSD) to neutralizing antibodies (VNA), will be calculated for each time point, and per matching variant between binding and neutralizing antibody assays. Values <LLOQ will be imputed with LLOQ for the calculation of the ratios. In addition, the ratio of the fold increase from baseline in binding antibodies (S-ELISA/MSD) to the fold increase from baseline in the VNA will be calculated for each post-baseline time point. Values <LLOQ will be imputed with LLOQ for the calculation of the fold increase ratios. The following statistics will be calculated and tabulated: N, geometric mean and corresponding 95% CI of the ratio. Graphical displays will also be prepared, showing – for each time point – the geometric mean of the ratio and its 95% CI, together with the individual data points (dot plot).

If a similar assay is performed at different analyzing labs, then separate statistical analyses may be performed.

Scatterplots between humoral assay results will be provided for selected time points. These may include, but are not be limited to:

- Binding antibodies (S-ELISA/MSD) versus neutralizing antibodies (VNA)

If a similar assay is performed at different analyzing labs, then the statistical analyses may distinguish between these and provide separate scatterplots for each analyzing lab versus the other assay of interest. These scatterplots will display the values as analyzed for the geometric mean calculations, with values <LLOQ imputed with LLOQ (if an LLOQ is defined) and values >ULOQ imputed with ULOQ (if an ULOQ is defined). The LLOQ and ULOQ cut-off values per assay will be visualized in the scatterplots. Spearman correlation coefficients will also be provided (one per scatterplot).

5.7.1.6.3. Cellular assays

For **ELISpot**, **if available (assay not selected yet)**, at least the following statistics will be calculated: N, median, first and third quartile, minimum and maximum of the actual values. Additional statistics may be calculated and will be detailed in the DPS. The ELISpot in this study is planned to be two single ELISpot, measuring IFN-g and IL-4. In that case, the statistics will be analyzed for each cytokine separately.

For each cytokine, if available, the following may be defined, depending on the assay selected:

- Sample positivity:
  - For IFN-g: a sample will be considered positive if the value is strictly greater than the LOD (>LOD).
  - For IL-4: a sample will be considered positive if the value is strictly greater than the LOD (>LOD).
- Responder:

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

  For IFN-g:

  - The baseline sample value is less than or equal to the LOD (≤LOD) and the post-baseline sample is strictly greater than the LOD (>LOD)
  - The baseline sample value is strictly greater than the LOD (>LOD) and the post-baseline sample value represents an at least 3-fold (≥3-fold) increase from the baseline sample value.

  For IL-4:

  - The baseline sample value is less than or equal to the LOD (≤LOD) and the post-baseline sample is strictly greater than the LOD (>LOD)
  - 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 2-fold (≥2-fold) increase from the baseline sample value.

The SDTM database will contain the LOD and LLOQ values.

In keeping with the general derivation rules, values <LLOQ are imputed with LLOQ/2 for the calculation of the median and with LLOQ for the calculation of the fold increases from baseline.

ELISpot values available in the database will already be background subtracted. No further background subtraction should be carried out. In case the SDTM data only contain peptide pools 1 and 2, but no combined peptide pool, then the combined peptide pool will be calculated as the sum of both peptide pools.

Tables with the descriptive statistics will be provided.

Participant profiles of the actual values over time will be graphically presented. For the graphs, original values will be displayed on the $\log_{10}$ scale.

For ELISpot, the reported values are spot forming cells per million peripheral blood mononuclear cells (PBMC).

Further details and/or updated rules may be provided in the DPS.

For **ICS**, **if available (assay not selected yet)**, at least the following statistics will be calculated: N, median, first and third quartile, minimum and maximum of the actual values, number and percentage of participants with a positive sample (if available). Additional statistics may be calculated and will be detailed in the DPS.

It is planned to analyze the following cell populations at the time of the full analysis, depending on the panel of antibodies selected for the ICS assessment. The DPS may provide an updated version of this list.

- CD4+:
  - IFN-g or IL2
  - IFN-g or IL2 NOT TH2
  - IL4 and CD40L
  - IL4 or IL5 or IL13 and CD40L
- CD8+:
  - IFN-g or IL2

The data received from the analyzing lab(s) may contain background subtracted values ("immediately reportable values"; i.e. background subtracted[a] percentages of cells expressing the cytokine or cytokine combination). Negative background subtracted values will be imputed with zero prior to further processing.

The data will contain a positivity call for each cell population. Sample positivity should therefore not be further derived at the statistical analysis stage.

Tables will be provided that show the descriptive statistics mentioned above, structured as follows: CD4+/CD8+, peptide pool (as available in the database, e.g.: SARS-Cov2-S, SARS-Cov2-S1, SARS-Cov2-S2), cytokine (combination), and time point.

Participant profiles of the actual values over time will be graphically presented. For the graphs, original values will be displayed on the $\log_{10}$ scale, with values <0.022% imputed with 0.011%

[a] Also known as "mock subtracted"

(only for visual representation; calculations will be based on the actual values). The graphs that show individual participant's data will visually differentiate between positive/negative samples (e.g. different symbols and/or different colors).

The reported values are percentage of cells expressing the cytokine(s).

5.7.1.7. Immunogenicity against the vector

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

If only one time point is available, then actual values at that single time point will be shown as a dot plot. If multiple time points are available, then GMT plots over time, combining the regimens in one graph (without individual participant dots) will also be generated. In addition, participant profiles will then also be created.

5.7.1.8. Antibodies binding to the SARS-CoV-2 nucleocapsid (N) protein

For antibodies binding to the SARS-CoV-2 nucleocapsid (N) protein, the number and percentage of participants with a positive sample at Day 1, Day 29, Day 71, and Day 181will be tabulated. A positive or negative result will be obtained from the assay (qualitative assay).

In contrast to the other immunogenicity analyses, this analysis will be performed only on the FAS.

The definition of the PPI analysis set incorporates the N-serology sample positivity assessment: immunogenicity samples obtained after a positive N-serology sample will be excluded from the PPI analysis.

5.7.2. Definition of Subgroups

Selected safety and immunogenicity analyses will be conducted by the following subgroup.

Subgroup	Definition
Age Group (years)	• ≥18 to <60 • ≥60

5.8. Interim, and Planned Analyses

This SAP applies to all planned analyses of this study per CTP section 9.5 (primary analysis and final Analysis) in addition to the immunogenicity interim analysis that may be conducted on Cohort 1 data.

5.8.1. Interim Analysis

When at least 330 participants (see CTP Section **Error! Reference source not found.**) from Groups 1 to 3 in Cohort 1 have been enrolled and completed the Day 15 visit, it is estimated that immunogenicity data can be obtained from at least 110 participants in Group 1 to potentially

conduct an interim analysis. The planned primary non-inferiority testing of Cohort 1 – Group 1 may be performed on the available data from the Cohort 1 – Group 1 participants.

Scope of the Interim Analysis:

The interim analysis will consist of a statistical immunogenicity analysis of Cohort 1 – Group 1 participants only. Hypotheses 1a and 1b will be tested, in the hierarchical manner as outlined in **Error! Reference source not found.** (see CTP): Hypothesis 1b will only be tested if all success criteria of Hypothesis 1a are met. The other hypotheses (1c, 1d, 2a, 2b and 2c) will only be tested at the primary analysis.

In addition, limited safety/reactogenicity statistical outputs will be generated in a blinded manner, for all available participants (Cohort 1 and Cohort 2, all groups). The same outputs will be generated in an unblinded manner by the independent Statistical Support Group and will be shared only with the IDMC. The unblinded outputs may also be used to respond to questions or requests from Health Authorities. In this case, appropriate channels of communication will be used to keep the Sponsor blinded.

Alpha Spending:

An O'Brien-Fleming adjustment will be used whereby the type I error for the NI test at the interim analysis will be 0.0003 (one-sided). This alpha is calculated based on an estimated interim analysis sample size of 110 Cohort 1 – Group 1 participants (~33% of the total sample size). If immunogenicity data is available for more than 110 Cohort 1 – Group 1 participants at the time of the interim analysis, then the nominal alpha level of the interim analysis will be kept at 0.0003, but the alpha level at the primary analysis will be recalculated. The recalculation will be based on the O'Brien-Fleming adjustment and will take into consideration the alpha spent at the time of the interim analysis and the actual information fraction that was available at the time.

Procedures to maintain the study blind:

This interim analysis will be conducted by an independent Statistical Support Group. Only group-level unblinded immunogenicity statistical outputs and blinded safety/reactogenicity statistical outputs will be available to the Sponsor.

In order to keep the blind at the laboratory, all available Cohort 1 immunogenicity samples, from all groups, will be shipped and analyzed, if operationally feasible. In case a selection of samples is needed for operational reasons, the selection will be made in advance by the independent Statistical Support Group and this selection will include, next to the Cohort1 – Group 1 samples, also at least 20 samples of Cohort 1 – Group 2 and at least 20 samples of Cohort 1 – Group 3.

5.8.2. Planned Analysis

The primary and final analyses of Cohort 1 may be performed before the analyses of Cohort 2.

The primary analysis of safety and immunogenicity in Cohort 1 or Cohort 2 will be performed when all evaluable participants in the respective cohort have completed the visit that takes place 28 days after study vaccination or discontinued earlier. The analysis will include immunogenicity data (VNA, S-ELISA, N-serology) for all evaluable participants through Day 15, and all available safety data. The sponsor will be unblinded for the respective cohort at the time of this primary analysis, but the blind will be maintained at the participant and study site level up to study end.

The final analysis in Cohort 1 or Cohort 2 will be performed when all included participants in the respective cohort have completed their last visit or discontinued earlier.

5.9. Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) has been commissioned to review the safety data of this trial alongside the other COVID-19 trials. Please refer to the associated IDMC Charter.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

Ad26	adenovirus type 26
AE	adverse event
AESI	adverse event of special interest
ALT/SGPT	alanine aminotransferase
ANCOVA	analysis of covariance
AST/SGOT	aspartate aminotransferase
ATC	anatomic and therapeutic class
AUC	area under the curve
BMI	body mass index
BNT162b2	Pfizer mRNA- based SARS-CoV-2 vaccine
BSA	body surface area
CI	confidence interval
COVID-19	coronavirus disease-2019
CRF	case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DMC	Data Monitoring Committee
DPS	Data Presentation Specifications
ECG	electrocardiogram
eCRF	electronic case report form
F (%)	absolute SC bioavailability
FAS	full analysis set
FDA	Food and Drug Administration
GMR	geometric mean ratio
GMC	geometric mean concentration
GMT	geometric mean titer
ICH	International Conference on Harmonisation
IQ	interquartile
IVRS	interactive voice response system
IWRS	interactive web response system
LLOQ	lower limit of quantification
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimum required dilution
NAb	neutralizing antibodies
PD	pharmacodynamic(s)
PI	principal investigator
PK	pharmacokinetic(s)
PP	per protocol
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SMQs	standardised MedDRA queries
TEAE	treatment-emergent adverse event
Tmax	time to maximum concentration
US NCI	United States National Cancer Institute
V	volume distribution
vp	virus particle
Vz	volume of distribution based on terminal phase
Vz/F	apparent volume of distribution based on terminal phase after extravascular administration
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

6.2. Appendix 2 Changes to Protocol-Planned Analyses

6.3. Appendix 3 Demographics and Baseline Characteristics

The following demographic and baseline characteristics will be summarized.
Table 2 presents a list of the demographic and baseline variables that will be summarized by vaccine regimen and overall for the FAS.

Table 2: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m^2)	
Categorical Variables	
Sex (male, female, undifferentiated)	Frequency distribution with the number and percentage of participants in each category.
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
Study center	
SARS-CoV-2 Seropositivity status at screening	
Age (years): • ≥18 to <60 • ≥60	

[a]If multiple race categories are indicated, the Race is recorded as 'Multiple'

6.4. Appendix 4 Protocol Deviations

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

Major protocol deviations which have a potential impact on immunogenicity will be flagged in the listings.

6.5. Appendix 5 Prior and Concomitant Medications

The analysis of concomitant therapies will be done using the WHO drug coded terms.

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 of a completely missing start date, the concomitant therapy will be considered as having started before the trial.
- In case of a completely missing end date, the concomitant therapy will be considered as ongoing at the end of the trial.

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

6.6. Appendix 6 Medical History

Medical history will be listed.

6.7. Appendix 7 Intervention Compliance

Not applicable.

6.8. Appendix 8 Adverse Events of Special Interest

This study defines thrombosis with thrombocytopenia as an AESI, cf. protocol section 8.3.7.1. AESI's will be flagged in the SDTM database. No programmed search (SMQ or otherwise) is currently planned. If this should become necessary, the details may be added in an SAP amendment if still feasible, otherwise they will be provided in the DPS.

6.9. Appendix 9 Medications of Special Interest

Please refer to Appendix 5 for concomitant medications of special interest.

6.10. Appendix 10 Toxicity Grading Scale

Adapted from the FDA Guidance document "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (September 2007) (US DHHS 2007).

A: Tables for Clinical Abnormalities

Local Reaction to Injectable Product	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Pain/Tenderness[#]	Aware of symptoms but easily tolerated; Does not interfere with activity; Discomfort only to touch	Notable symptoms; Requires modification in activity or use of medications; Discomfort with movement	Incapacitating symptoms; Inability to do work, school, or usual activities; Use of narcotic pain reliever	Hospitalization; Pain/tenderness causing inability to perform basic self-care function
Erythema[#]	25 – 50 mm	51 – 100 mm	> 100 mm	Hospitalization; Necrosis or exfoliative dermatitis
Swelling[#]	25 – 50 mm	51 – 100 mm	> 100 mm	Hospitalization; Necrosis

[#] Revised by the sponsor.

Vital Signs *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever (°C) ** (°F)**	38.0 - 38.4 100.4 - 101.1	38.5 - 38.9 101.2 - 102.0	39.0 - 40.0 102.1 - 104.0	> 40 > 104.0
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	Hospitalization for arrhythmia[#]
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	Hospitalization for arrhythmia[#]
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	Hospitalization for malignant hypertension[#]
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	Hospitalization for malignant hypertension[#]
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	Hospitalization for hypotensive shock[#]
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Participant should be at rest for all vital sign measurements.
** For oral temperature: no recent hot or cold beverages or smoking.
*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.
[#] Revised by the sponsor.

Systemic (General)	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Vomiting[#]	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	Hospitalization; Hypotensive shock
Nausea[#]	Minimal symptoms; causes minimal or no interference with work, school, or self-care activities	Notable symptoms; Requires modification in activity or use of medications; Does NOT result in loss of work, school, or cancellation of social activities	Incapacitating symptoms; Requires bed rest and/or results in loss of work, school, or cancellation of social activities	Hospitalization; Inability to perform basic self-care functions
Diarrhea[#]	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800 gms/24 hours or oral rehydration necessary	Hospitalization; Hypotensive shock OR IV fluid replacement indicated
Headache[#]	Minimal symptoms; causes minimal or no interference with work, school, or self-care activities	Notable symptoms; Requires modification in activity or use of medications; Does NOT result in loss of work, school, or cancellation of social activities	Incapacitating symptoms; Requires bed rest and/or results in loss of work, school, or cancellation of social activities; Use of narcotic pain reliever	Hospitalization; Inability to perform basic self-care functions
Fatigue[#]	Minimal symptoms; causes minimal or no interference with work, school, or self-care activities	Notable symptoms; Requires modification in activity or use of medications; Does NOT result in loss of work, school, or cancellation of social activities	Incapacitating symptoms; Requires bed rest and/or results in loss of work, school, or cancellation of social activities; Use of narcotic pain reliever	Hospitalization; Inability to perform basic self-care functions
Myalgia[#]	Minimal symptoms; causes minimal or no interference with work, school, or self-care activities	Notable symptoms; Requires modification in activity or use of medications; Does NOT result in loss of work, school, or cancellation of social activities	Incapacitating symptoms; Requires bed rest and/or results in loss of work, school, or cancellation of social activities; Use of narcotic pain reliever	Hospitalization; Inability to perform basic self-care functions

[#] Revised by the sponsor.

Systemic Illness	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Illness or clinical adverse event (as defined according to	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Hospitalization[#]

[#] Revised by the sponsor.

B: Tables for Laboratory Abnormalities

Laboratory tests may be performed during routine medical care and assessment of AEs or other medical events based on the investigator's judgment.

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Serum *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)****
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen (BUN) mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
Creatine phosphokinase (CPK) – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN

Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as potentially life-threatening (Grade 4). For example. a low sodium value that falls within a Grade 3 parameter (125-129 mEq/L) should be recorded as a Grade 4 hyponatremia event if the participant had a new seizure associated with the low sodium value.
*** ULN is the upper limit of the normal range.

Hematology *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** ULN is the upper limit of the normal range.

Urine *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

6.11. Appendix 11: Thrombotic Events to be Reported as AESIs

At the time of protocol writing, the list of thrombotic events to be reported to the sponsor as AESIs is provided below. Further guidance may become available on thrombotic events of interest.

- MedDRA PTs for large vessel thrombosis and embolism:
    - Aortic embolus, aortic thrombosis, aseptic cavernous sinus thrombosis, brain stem embolism, brain stem thrombosis, carotid arterial embolus, carotid artery thrombosis, cavernous sinus thrombosis, cerebral artery thrombosis, cerebral venous sinus thrombosis, cerebral venous thrombosis, superior sagittal sinus thrombosis, transverse sinus thrombosis, mesenteric artery embolism, mesenteric artery thrombosis, mesenteric vein thrombosis, splenic artery thrombosis, splenic embolism, splenic thrombosis, thrombosis mesenteric vessel, visceral venous thrombosis, hepatic artery embolism, hepatic artery thrombosis, hepatic vein embolism, hepatic vein thrombosis, portal vein embolism, portal vein thrombosis, portosplenomesenteric venous thrombosis, splenic vein thrombosis, spontaneous heparin-induced thrombocytopenia syndrome, femoral artery embolism, iliac artery embolism, jugular vein embolism, jugular vein thrombosis, subclavian artery embolism, subclavian vein thrombosis, obstetrical pulmonary embolism, pulmonary artery thrombosis, pulmonary thrombosis, pulmonary venous thrombosis, renal artery thrombosis, renal embolism, renal vein embolism, renal vein thrombosis, brachiocephalic vein thrombosis, vena cava embolism, vena cava thrombosis, truncus coeliacus thrombosis
- MedDRA PTs for more common thrombotic events:
    - Axillary vein thrombosis, deep vein thrombosis, pulmonary embolism, MedDRA PTs for acute myocardial infarction*, MedDRA PTs for stroke*

Source: Shimabukuro T. CDC COVID-19 Vaccine Task Force. Thrombosis with thrombocytopenia syndrome (TTS) following Janssen COVID-19 vaccine. Advisory Committee on Immunization Practices (ACIP). April 23, 2021. https://www.cdc.gov/vaccines/acip/meetings/slides-2021-04-23.html.

*Vaccine Adverse Event Reporting System (VAERS) Standard Operating Procedures for COVID-19 (as of 29 January 2021) https://www.cdc.gov/vaccinesafety/pdf/VAERS-v2-SOP.pdf

7. REFERENCES

Agresti, A. & Min, Y. (2005). Simple improved confidence intervals for comparing matched proportions. Statistics in Medicine, 24, 729-740.
Lopez-Raton el. al (2014). OptimalCutpoints: An R Package for Selecting Optimal Cutpoints in Diagnostic Tests, Journal of Statistical Software, Volume 61, Issue 8.Reed, JF. III (2009). Closed Form Confidence Intervals for Small Sample Matched Proportions, Journal of Modern Applied Statistical Methods. 2009;8(2):511-519.
Casella, G & Berger L.R (1990). Statistical Inference. Wadsworth, INC.
Zeger SL, Liang KY. (1986) Longitudinal data analysis using generalized linear models. Biometrica. 73:13-22.