Janssen Research & Development

Statistical Analysis Plan

A Randomized, Double-blind, Placebo-controlled Phase 3 Study to Assess the Efficacy and Safety of Ad26.COV2.S for the Prevention of SARS-CoV-2-mediated COVID-19 in Adults Aged 18 Years and Older

ENSEMBLE

Protocol VAC31518COV3001; Phase 3

VAC31518 (JNJ-78436735)

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

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VERSION HISTORY

Table 1 SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	23AUG2020	Not Applicable	Initial release
2	18SEP2020	Clinical Trial Protocol Amendment 1	Clinical Trial Protocol Amendment 1
3	30OCT2020	Changes to hypothesis testing strategy, adding a supportive analysis to the primary analysis based on cases that were not analysis ready at data base lock and clarifications / corrections	Including feedback received from Health Authorities
4	16 Dec 2020	Aligning analysis on any SARS-CoV-2 infection with protocol. Updates to SAP in line with protocol amendment 3, including a sample size reduction from 60,000 to approximately 40,000 participants and introduction of co-primary endpoints	Any SARS-CoV-2 infection: SAP and protocol were not aligned. Changes to protocol amendment 3.
5	14 Jan 2021	Clarifying that for not analysis-ready cases, central confirmation by the University of Washington is not needed Changed the identification of severe cases through programming and medical review. Adding CBER feedback: - Additional success criterion on the point estimate for the primary endpoint	Clarifications and feedback from FDA on severe case definition and SAP
6	22 Jan 2021	Adding - Description of viral genome sequencing analysis. - VE by variants	Not described before and planned for inclusion in the primary analysis
7	20 July 2021	Adding changes based on protocol amendment 4 and 5 - Adjudication of all endpoints - Additional analysis for the unblinding phase - Clarification on the analysis of the Asymptomatic infections - Removal of the definition of analysis ready cases and non-ready cases as this became redundant. - Additional analysis regarding the exploration of reduction in severity of covid-19 episodes, relationship with viral load, explorative analysis on PRO - Appendix with details re calculation of the frailty index	Changes to protocol amendment 4 and 5.

1. INTRODUCTION

This statistical analysis plan (SAP) describes the analysis methods for evaluation of the primary, secondary and exploratory objectives of the double blind phase of the phase 3 study designed to assess in a randomized, double-blind, placebo-controlled manner the efficacy and safety of the Ad26.COV2.S candidate vaccine.

The vaccine has been designed for the prevention of SARS-CoV-2 mediated coronavirus disease 2019 (COVID-19) in adults aged 18 years and older. The previous version of the SAP detailed the analytical plan for interim monitoring, the inferential study objectives as well as the statistical methods for the primary analysis based on all available data at the time of data base cut off (see Section 2) as well as the final analysis of the double blind phase. Sections which were applicable to the primary analysis but no longer applicable to the final analysis have been indicated in grey.

Sponsor personnel was unblinded at the time of the primary analysis. If an efficacy signal is triggered before the required 8-week follow-up after vaccination of 50% of participants is reached, an analysis will be performed (referred to as "snapshot analysis") and sponsor personnel will be unblinded at the time of the snapshot analysis. Investigator and participants remain blinded until study unblinding visit (protocol amendment 4 and 5).

This analysis plan also includes the technical details for the statistical analysis plan associated with the interim monitoring evaluation for harm, non-efficacy and efficacy to support the data and safety monitoring board (DSMB).

This SAP has been amended to incorporate the changes since protocol amendment 4 and 5. For the ease of review, some sections have been grayed out to indicate analysis that have been done prior to the primary analysis.

This randomized, placebo-controlled clinical trial is designed to enable expeditious safety, efficacy and immunogenicity evaluation of the Ad26.COV2.S candidate preventive vaccine against COVID-19 at sites with high COVID-19 attack rates, to ensure the observation of COVID-19 cases to assess the role of a vaccine in containing the pandemic. Boundaries are set up to monitor for excess harm, non-efficacy and efficacy. If a prespecified boundary is met for harm or non-efficacy or the prespecified boundaries are met for efficacy, the statistical support group (SSG) will inform the DSMB. The DSMB will provide a recommendation to the Oversight Group. The Oversight Group can trigger decision procedures to initiate health authority interactions based on the outcome of the study. The sponsor will remain blinded until the data base for the primary analysis is locked or until the time of the snapshot analysis.

The primary objective of the trial is to evaluate the vaccine's effect on the rate of virologically-confirmed moderate to severe/critical COVID-19, in adults at high risk for infection and/or disease.

The co-primary endpoints will evaluate

- the first occurrence of molecularly confirmed, moderate to severe/critical COVID 19 according to the case definition, with onset at least 14 days after double-blind vaccination

(from Day 15) with Ad26.COV2.S versus placebo, in the PP population, including all events from both age groups, with and without comorbidities.

- the first occurrence of molecularly confirmed, moderate to severe/critical COVID 19 according to the case definition, with onset at least 28 days after double-blind vaccination (from Day 29) with Ad26.COV2.S versus placebo, in the PP population, including all events from both age groups, with and without comorbidities.

The trial will enroll and randomize large numbers of adult participants in different populations. Until 1 year after the Month 6/unblinding visit, each participant will be asked at least twice a week, through the electronic clinical outcome assessment (eCOA), if they have experienced any new symptoms or health concerns that could be related to infection with SARS-CoV-2. As of 1 year after the Month 6/unblinding visit, until the end of the long-term follow-up period, the frequency of this surveillance question through the eCOA will decrease to once every 2 weeks. Vaccine efficacy to prevent mild COVID-19, to prevent COVID-19 of any severity (burden of disease), to prevent acquisition of asymptomatic SARS-CoV-2 infection, to prevent COVID-19 requiring medical intervention, to prevent acquisition of any SARS-CoV-2 infection and to investigate SARS-CoV-2 viral load for moderate to severe/critical COVID-19 cases are secondary objectives. The design has continuous monitoring of events to report results upon early evidence of vaccine efficacy, lack of efficacy, or vaccine safety concerns. The trial is powered to provide sufficient evidence of safety and vaccine efficacy to prevent COVID-19 in support of possible (potential) marketing authorizations. Note that in Protocol Amendment 3, the sample size was reduced from 60,000 to approximately 40,000 participants.

The study will have the following timepoints for efficacy analyses:

1. The evaluation of the primary objective will be performed as soon as the target number of events (TNE) has been reached in the double-blind phase for both co-primary endpoints, or earlier based on sequential monitoring of both co-primary endpoints. Sponsor unblinding will occur but investigator and participants remain blinded until implementation of CTPA4.

2. If an efficacy signal is triggered before the required 8-week follow-up after double-blind vaccination of 50% of participants is reached, an additional analysis will be performed when that follow-up timepoint is reached (8-week median follow-up timepoint). If the time between the efficacy signal and the required 8-week median follow-up is too short to make a difference in terms of preparing two analyses then a single analysis will take place at the time of the 8-week median follow-up. The analysis at the time of the 8-week median follow-up is considered the primary analysis.

3. After the primary analysis, additional analyses to support health authority interactions may be planned, if deemed appropriate.

4. A final analysis of the double-blind phase of the study, including all double-blind data will be performed when all participants have completed the Month 6/unblinding visit or

discontinued earlier. Depending on the operational implementation of the Month 6/unblinding visit, as well as the stage of the pandemic, this analysis may be conducted when a minimum of 90% of the study population has been unblinded.

5. The final analysis of the open-label phase will be performed when the last participant completes the 18 months visit which corresponds to approximately 12 months after the Month 6/unblinding visit or discontinues earlier.

6. The end-of-study analysis will be performed when all participants have completed the Year 2 visit of the study or discontinued earlier.

The cut off date is 9JUL2021 and estimated when approximately all participants have completed the unblinding visit or discontinued earlier. All available data up to the data lock point will be included in the analysis.

1.1. Objectives and Endpoints

Objectives	Endpoints
Co-Primary	
To demonstrate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed[a], moderate to severe/critical coronavirus disease-2019 (COVID-19)[b], as compared to placebo, in SARS-CoV-2 seronegative adults	• First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b], with onset at least 14 days after double-blind vaccination (Day 15) • First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b], with onset at least 28 days after double-blind vaccination (Day 29)
Secondary[e]	
Efficacy	
To demonstrate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed[a], severe/critical COVID-19[b], as compared to placebo	• First occurrence of molecularly confirmed[a], severe/critical COVID-19[b], with onset at least 14 days after double-blind vaccination (Day 15) • First occurrence of molecularly confirmed[a], severe/critical COVID-19[b], with onset at least 28 days after double-blind vaccination (Day 29)
To demonstrate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed[a], moderate to severe/critical COVID-19[b], as compared to placebo, in adults regardless of their serostatus	• First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b], with onset 1 day after double-blind vaccination • First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b], with onset at least 14 days after double-blind vaccination (Day 15) • First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b], with onset at least 28 days after double-blind vaccination (Day 29)

To evaluate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed[a] moderate to severe/critical COVID-19[b] as compared to placebo, with onset 1 day after study vaccination	First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b] with onset 1 day after study vaccination
To assess the effect of Ad26.COV2.S on COVID-19 requiring medical intervention (based on objective criteria) compared to placebo	• First occurrence of COVID-19 requiring medical intervention (such as a composite endpoint of hospitalization, intensive care unit [ICU] admission, mechanical ventilation, and extracorporeal membrane oxygenation [ECMO], linked to objective measures such as decreased oxygenation, X-ray or computed tomographic [CT] findings) and linked to any molecularly confirmed[a], COVID-19[b,c] at least 14 days after double-blind vaccination (Day 15) • First occurrence of COVID-19 requiring medical intervention and linked to any molecularly confirmed[a], COVID-19[b,c] at least 28 days after double-blind vaccination (Day 29)
To assess the effect of Ad26.COV2.S on SARS-CoV-2 viral ribonucleic acid (RNA) load compared to placebo for moderate to severe/critical COVID-19[b]	Assessment of the SARS-CoV-2 viral load by quantitative reverse-transcriptase polymerase chain reaction (RT-PCR), in participants with molecularly confirmed[a], moderate to severe/critical COVID-19[b] by serial viral load measurements during the course of a COVID-19 episode
To assess the effect of Ad26.COV2.S on molecularly confirmed[a] mild COVID-19[c]	• First occurrence of molecularly confirmed[a], mild COVID-19[b], at least 14 days after double-blind vaccination (Day 15) • First occurrence of molecularly confirmed[a], mild COVID-19[b], at least 28 days after double-blind vaccination (Day 29)
To assess the effect of Ad26.COV2.S on COVID-19 as defined by the United States (US) Food and Drug Administration (FDA) harmonized case definition[d]	• First occurrence of molecularly confirmed[a] COVID-19[b] at least 14 days after double-blind vaccination (Day 15) • First occurrence of molecularly confirmed[a] COVID-19[b] at least 28 days after double-blind vaccination (Day 29)
To assess the effect of Ad26.COV2.S on all molecularly confirmed[a] symptomatic COVID-19 [b,c], as compared to placebo	• Burden of disease (BOD) endpoint[f] derived from the first occurrence of molecularly confirmed[a] symptomatic COVID-19[b,c] (meeting the mild, moderate or severe/critical COVID-19 case definition) with onset at least 14 days after double-blind vaccination (Day 15). • BOD endpoint[f] derived from the first occurrence of molecularly confirmed[a] symptomatic COVID-19[b,c] (meeting the mild, moderate or severe/critical COVID-19 case definition) with onset at least 28 days after double-blind vaccination (Day 29).

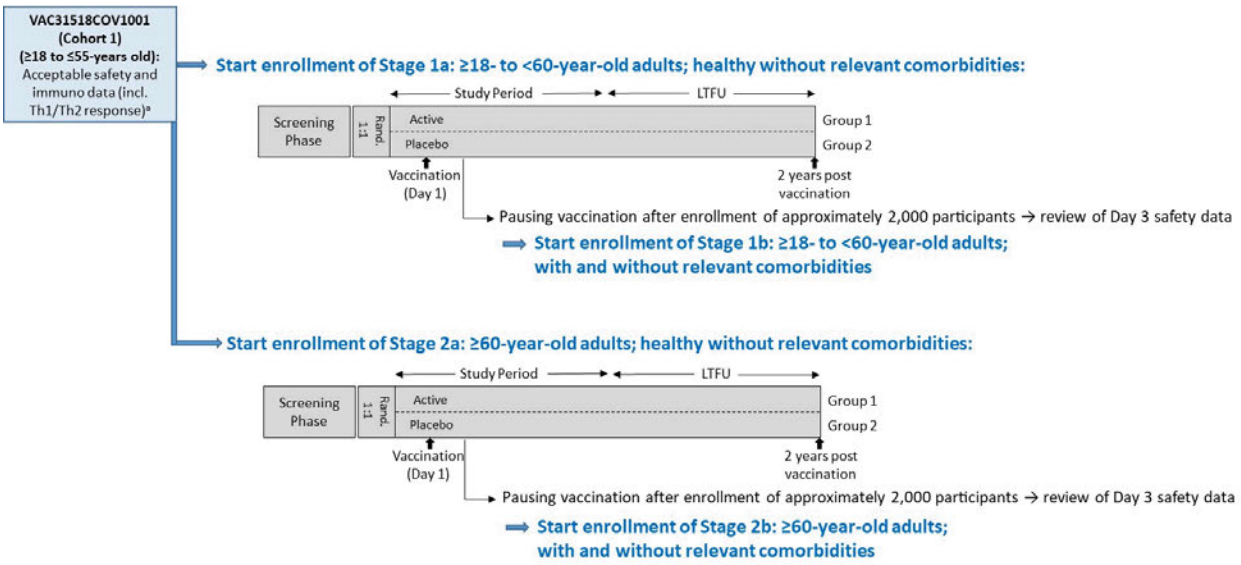
To assess the effect of Ad26.COV2.S on occurrence of confirmed asymptomatic or undetected infections with SARS-CoV-2, as compared to placebo	• Serologic conversions between baseline (Day 1; pre-vaccination) and Day 29, between Day 29 and Day 71, between Day 71 and Month 6/unblinding visit, and 18 months after double-blind vaccination (approximately 12 months after initiation of the open-label phase of the study) using an enzyme-linked immunosorbent assay (ELISA) and/or SARS-CoV-2 immunoglobulin assay that is dependent on the SARS-CoV-2 nucleocapsid (N) protein • Asymptomatic infection detected by RT-PCR at the time of the Month 6/unblinding visit
To assess the efficacy of Ad26.COV2.S in the prevention of SARS-CoV-2 infection (both symptomatic and asymptomatic infections combined, that are serologically and/or molecularly confirmed[a]), as compared to placebo	First occurrence of SARS-CoV-2 infection (serologically and/or molecularly confirmed[a]) with onset at least 28 days after double-blind vaccination (Day 29)
Safety	
To evaluate safety in terms of serious adverse events and adverse events of special interest (SAEs and AESIs; during the entire study), medically-attended adverse events (MAAEs; until 6 months after double-blind or open-label vaccination), and MAAEs leading to study discontinuation (during the entire study) for all participants	Occurrence and relationship of SAEs and AESIs (during the entire study), MAAEs (until 6 months after double-blind or open-label Ad26.COV.S), and MAAEs leading to study discontinuation (during the entire study) for all participants following vaccination
In a subset of participants, to evaluate the safety and reactogenicity in terms of solicited local and systemic adverse events (AEs) during 7 days after double-blind vaccination, and in terms of unsolicited AEs during 28 days after double-blind vaccination	Occurrence, intensity, duration, and relationship of solicited local and systemic AEs during 7 days following vaccination and of unsolicited AEs during 28 days after double-blind vaccination
Immunogenicity	
In a subset of participants, to evaluate the immunogenicity of Ad26.COV2.S, as compared to placebo	– Analysis of antibodies binding to the SARS-CoV-2 S protein by ELISA

[a] Molecularly confirmed COVID-19 is defined as a positive SARS-CoV-2 viral RNA result using a PCR-based or other molecular diagnostic test.
[b] Per case definition for moderate to severe/critical COVID-19 (see Section 8.1.3.1 in the CTP).
[c] Per case definition for mild COVID-19 (see Section 8.1.3.2 in the CTP).
[d] Per case definition for COVID-19 according to the US FDA harmonized case definition (see Section 8.1.3.3 in the CTP).
[e] All secondary endpoint analyses will occur in the per-protocol (PP) analysis set, in seronegative participants unless otherwise indicated.
[f] For more information and the definition of the BOD endpoint, refer to the Section 9.5.2 Secondary Endpoints in the CTP.

1.2. Study Design

This is a randomized, double-blind, placebo-controlled phase 3 study to assess the efficacy and safety of Ad26.COV2.S for the prevention of SARS-CoV-2-mediated COVID-19 in adults aged 18 years and older. An overview of the design is provided in Figure 1.

Figure 1 Schematic Overview of the Study



Participants will be vaccinated with one vaccination according to a 1:1 randomization:

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

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

Central randomization will be implemented in this study in the double-blind phase. Participants will be randomly assigned to 1 of 2 vaccination groups (active vaccine [Group 1] versus placebo [Group 2]). This will be based on a computer-generated randomization schedule prepared before the study under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by vaccination unit (eg, site, mobile unit), age group (≥18 to <60 years of age versus ≥60 years of age), and absence/presence of comorbidities that are or might be associated with an increased risk of progression to severe COVID-19 as described in Exclusion Criterion 15 (see CTP).

The randomization system will be used to control the age distribution of participants in the trial; in particular the age ranges of ≥18 to <40 and ≥40 to <60 years can be closed separately for further randomization in order to obtain a distribution of approximately 20% and 50% for these age ranges, respectively, and to have a minimum of approximately 30% of the population to be ≥60 years.

Blinding will be guaranteed by the preparation of the study vaccine by an unblinded pharmacist or other qualified study-site personnel with primary responsibility for study vaccine preparation and dispensing, and by the administration of vaccine in a masked syringe by a blinded study vaccine administrator.

2. STATISTICAL HYPOTHESES

The co-primary endpoints will evaluate

- the first occurrence of molecularly confirmed, moderate to severe/critical COVID-19 according to the case definition (Section 8.1.3.1 in the CTP), with onset at least 14 days post double-blind vaccination with Ad26.COV2.S or placebo, in the Per Protocol (per protocol (PP) population (see Section 4), including all events from both age groups, with and without comorbidities.

- the first occurrence of molecularly confirmed, moderate to severe/critical COVID-19 according to the case definition (Section 8.1.3.1 in the CTP), with onset at least 28 days post double-blind vaccination with Ad26.COV2.S or placebo, in the Per Protocol (per protocol (PP) population (see Section 4), including all events from both age groups, with and without comorbidities.

A successful primary efficacy conclusion will require:

1. Establishing the hypothesis H_1: VE>30% for each co-primary endpoint with a VE point estimate ≥50%). The study is designed to test the co-primary hypotheses of vaccine efficacy (VE) in the PP population. For both co-primary endpoints the following hypothesis will be tested: H_0: VE ≤30% versus H_1: VE >30% and each hypothesis will be evaluated at a 2.5% one-sided significance level.

   AND

2. A favorable split vaccine:placebo for the subset of primary endpoints meeting the severe/critical COVID-19 case definition (expressed as a VE point estimate against severe/critical COVID-19 molecularly confirmed endpoints ≥50%) and a minimum of 5 events in the placebo group. This requirement needs to be met separately for severe/critical events with start at least 14 days after double-blind vaccination and for severe/critical events with start at least 28 days after double-blind vaccination.

Both conditions 1. and 2. will simultaneously have to be met for both co-primary endpoints at the same calendar timepoint.

To evaluate the primary null hypotheses: H_0: VE ≤30% versus H_1: VE >30% for the co-primary endpoints, the truncated sequential probability ratio test will be used based on accumulating event data for each co-primary endpoint. This boundary is set up using the fully sequential design and is derived in such a way to have approximately 90% power to detect a VE=60% using a one-sided alpha=0.025 against H0:VE≤30%, with appropriate control of the type-1 error rate (alpha) for interim monitoring. The same boundary will be used for each co-primary endpoint.

For the evaluation of the favorable ratio against the severe/critical COVID-19 endpoints a sequential boundary corresponding to a VE point estimate ≥50% and a minimum of 5 events in the placebo group will be prespecified. This is further detailed in section 5.4.3.

If an efficacy signal is triggered before the required 8-week follow-up after double-blind vaccination for approximately 50% of enrolled participants is reached, an additional analysis will be performed when that follow-up timepoint is reached, to support health authority interactions. If the time between the efficacy signal and the required 8-week median follow-up is too short to make a difference in terms of preparing two analyses, then a single analysis will take place at the time of the 8-week median follow-up. The analysis at the time of the 8-week median follow-up is considered the primary analysis. The co-primary endpoints will then be re-evaluated against the null hypothesis: H_0: VE ≤30% versus H_1: VE >30% using the sequential probability ratio test with the total number of events at that time.

If the co-primary endpoint hypothesis testing reaches significance for both co-primary endpoints, with the respective data requirements met, secondary objectives will be evaluated against a null hypothesis employing a lower limit VE>0%.

For each secondary endpoint in the confirmative endpoint section 5.5.2, the hypothesis of vaccine efficacy (VE) H_0: VE ≤0% versus H_1: VE >0% will be evaluated in the PP set, including all events as defined in the vaccine evaluation window for the respective endpoint at the time of the primary analysis.

The evaluation of secondary endpoints will be adjusted for multiple testing of multiple endpoints (using a graphical approach, Bretz et al 2009) and potential stopping at an interim analysis evaluation through a Pocock boundary using Wang-Tsiatis with Delta=0.5.

The timepoint and order of evaluation of multiple endpoints will be done according to the graphical method that is detailed below in Figure 2.

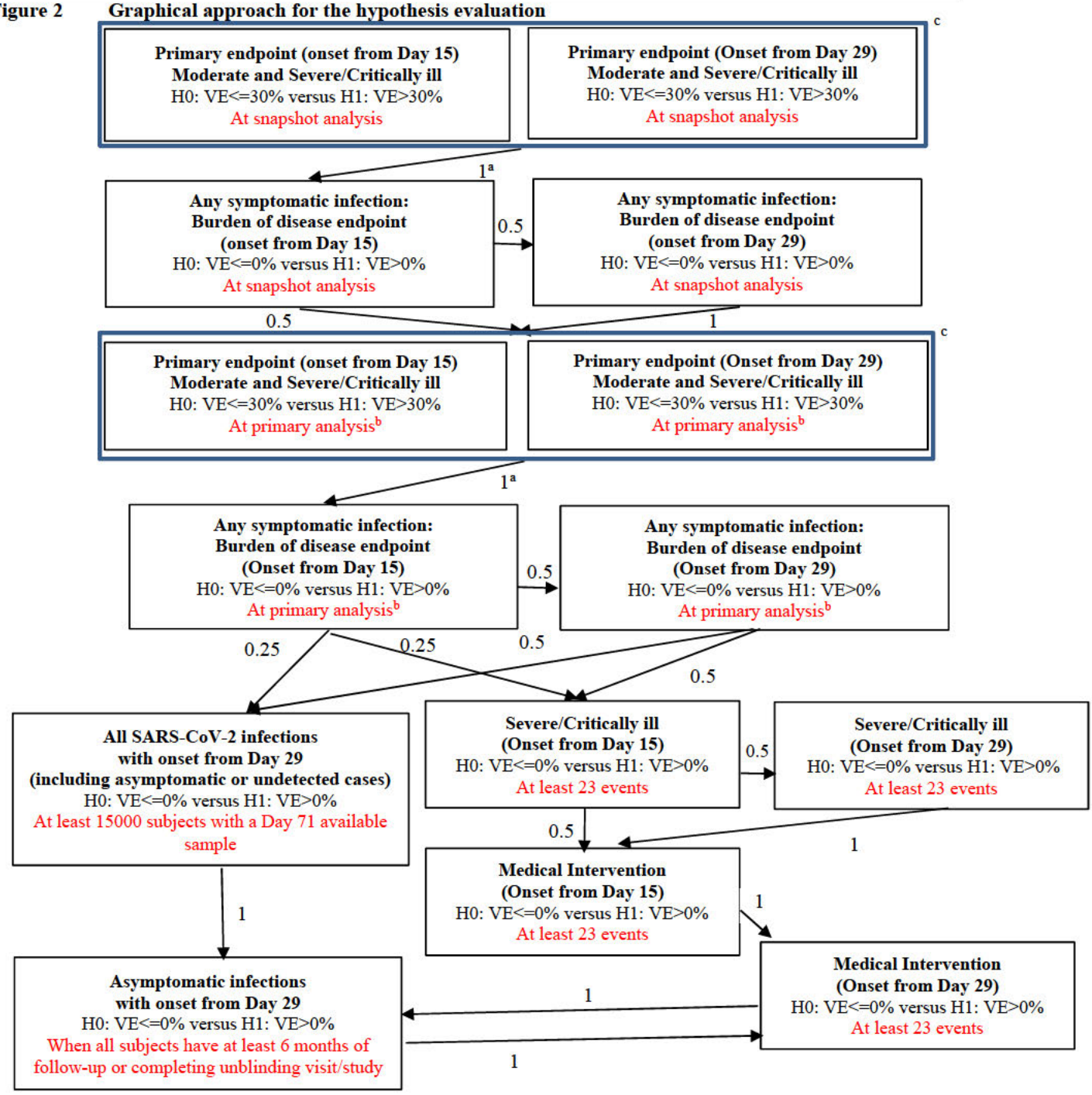
The alpha level that will be passed down to the secondary tests is based on a GSD with a single interim analysis and with information fraction determined by the primary endpoint including all events with onset at least 28 days post double-blind vaccination (i.e., number of available primary events with onset at least 28 days post double-blind vaccination at the time of data base cut off (when the respective efficacy boundary is crossed by each co-primary endpoint and the data requirements are met) divided by the TNE of 154) and corresponding alpha-level obtained from Wang-Tsiatis bounds with delta=0.5. If more than 154 primary endpoints with onset at least 28 days post double-blind vaccination are observed at the time of data base cut off (e.g. when the minimal data requirements for either co-primary endpoint are not met prior to 154), the information fraction equals 1.

With 154 or more primary endpoints with onset at least 28 days post double-blind vaccination at the time of database cutoff, the alpha-level for the secondary hypotheses is therefore 0.025 (2.5%). With, e.g., 77 primary endpoints, the information fraction equals 0.5 and the first secondary hypothesis is then evaluated at the alpha-level 0.0147. If this test is significant, the alpha will be passed on to the next hypothesis as specified in Figure 2.

Because of the change in protocol amendment 4, the evaluation of asymptomatic infections will be done at the analysis timepoint corresponding to the end of the double blind phase, which is planned when all subjects have completed the Month 6/unblinding visit or discontinued earlier.

Endpoints which were already evaluated inferentially at the primary analysis will be summarized and evaluated with a 95% confidence interval.

Figure 2 **Graphical approach for the hypothesis evaluation**



[a] alpha level passed down to the secondary tests is based on a GSD with a single interim analysis and with information fraction determined by the primary endpoint including all events with onset at least 28 days post double-blind vaccination (i.e., number of primary events with onset at least 28 days post double-blind vaccination at the time of data base cut off (when the respective efficacy boundary is crossed by each co-primary endpoint and the data requirement are met) divided by the TNE) and corresponding alpha-level obtained from a Pocock boundary.

[b] If an efficacy signal is triggered before the required 8-week follow-up after double-blind vaccination of 50% of participants is reached, an additional analysis will be performed when that follow-up timepoint is reached (8-week median follow-up timepoint), to support health authority interactions. The analysis at the time of the 8-week median follow-up is considered the primary analysis.

[c] When testing the co-primary endpoints at the time of the snapshot analysis or at the time of the primary analysis, both will have to reach significance in order to continue with the hierarchical testing.

The hypothesis VE>0% will be tested based on calculations of a $(1-2\alpha^*)\%$ two sided CI, if the lower-limit then exceeds 0%, the hypothesis is rejected.

3. SAMPLE SIZE DETERMINATION

All sample size calculations were done at the time of protocol design and in preparation for the primary analysis. No update of the sample size and/or power calculations have been done.

3.1. Efficacy (Total Sample Size)

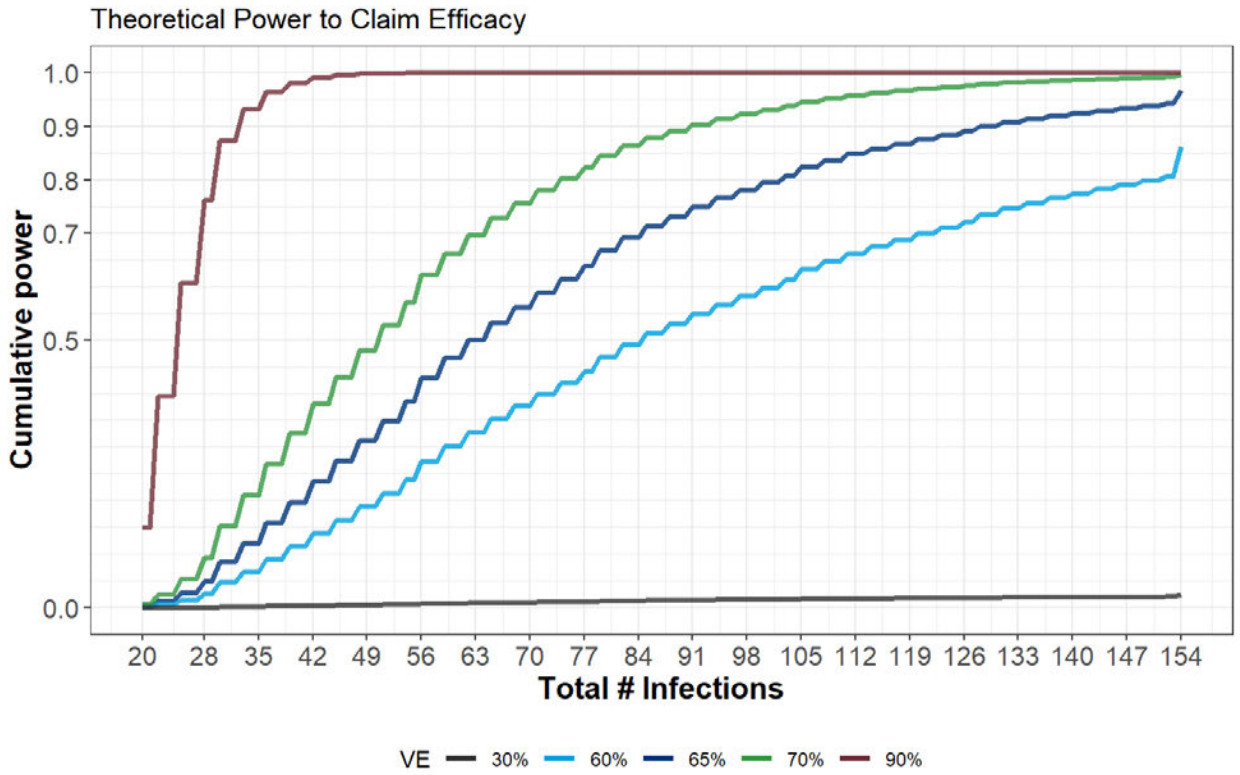
The study TNE is determined using the following assumptions:

1. a VE for molecularly confirmed, moderate to severe/critical SARS-CoV-2 infection of 60%.
2. approximately 90% power to reject a null hypothesis of H0: VE≤30%.
3. type 1 error rate α = 2.5% to evaluate VE of the vaccine regimen (employing the sequential probability ratio test [SPRT] to perform a fully sequential design analysis; detailed in Section 5.4.3.1).
4. a randomization ratio of 1:1 for active versus placebo

Events for the co-primary endpoints are defined as first occurrence of molecularly confirmed, moderate to severe/critical COVID-19 according to the case definition in Section 5.2 in the PP population at least 14 days after double-blind vaccination (Day 15) and at least 28 days after double-blind vaccination (Day 29) with study vaccine.

Under the assumptions above, the total TNE to compare the active vaccine versus placebo equals 154, based on events in the active vaccination and placebo groups, according to the primary endpoint case definition of moderate to severe/critical COVID-19 (Section 5.2). Using the SPRT until the TNE when starting from the 20th endpoint onwards will result in 86.22% power to reject H0 when VE1=60%. The overall type I error is controlled below 2.5% at 2.398% when VE0=30%. In Figure 3 the power of the testing strategy for VE1 equal to 60%, 65%, 70% and 90% is shown for a total number of endpoints from 20 to 154. From the graph, the overall study power equals 96.6% for an assumed VE=65%, and close to 100% for an assumed VE=70%.

Figure 3 **Theoretical Power based on the Exact Binomial distribution for VE1 = 60%,65%,70% and 90%; and Type I error rate under VE0 = 30%**



If the primary hypotheses testing is successful, secondary objectives will be evaluated against a null hypothesis employing a lower limit VE>0%. The method to perform hypothesis testing of primary and secondary objectives preserving the FWER is specified in section 2. The FWER will be controlled at 2.5%.

Sample Size Justification

Based on epidemiological modeling for the targeted study countries, province/states of the various site locations, the annualized incidence of moderate to severe/critical COVID-19 cases meeting the primary endpoint definitions has been predicted to be 1.4% for the October-November timeframe. The estimate incorporates that real-world-evidence data and literature data only detected and reported a fraction of SARS-CoV-2 infections.

Furthermore, it includes that, based on literature and real-world-evidence data, only a fraction of all infections meets the moderate to severe/critical COVID-19 case definition and the fraction varies by age as well (increasing with higher ages). Moreover, projections for the selected study regions indicate that incidences will decline over time. Finally, seroprevalence rates are expected to vary between 5-15%.

For the purpose of sample size evaluation, an incidence assumption of moderate to severe/critical COVID-19 cases meeting the primary endpoint definition of 1.4% during the first 3 months of the

study, with a 50% reduction in Month 4, and 62% reduction in the months thereafter is assumed in combination with a seroprevalence rate of 10%.

The epidemiological situation will remain uncertain during the course of the study: actual seroprevalence rates, degree of social distancing and use of personal protective equipment during the study, local regulations (eg, potential lockdowns, other vaccines if available) potentially becoming in effect during the course of the study and potential drop-outs from the study may impact the disease incidence rate.

To that end, the maximum sample size of approximately 60,000 participants will be selected. This sample size is selected, based on the uncertainty of the epidemiological situation in combination with the ability to provide a high probability (approximately 90%) to reach a time to signal within 8 months of the study for a vaccine with an assumed 60% VE.

Based on an estimated case-hospitalization ratio of 2.5% and estimates obtained from reported real-world-evidence data of 3-10% of all SARS-CoV-2 infections meeting the severe/critical COVID-19 definition, this will provide a reasonable likelihood of observing 5 severe cases in the placebo group within the same time frame (8 months).

Added in Protocol Amendment 3: The incidence of moderate to severe/critical COVID-19 seen in the US and reported in other COVID-19 vaccine trials is significantly higher than assumed at the time of protocol planning. Epidemiological model-predictions indicate a range of 3.8% to 6.3% for Nov 2020 and 4.1% - 6.3% for Dec 2020. Furthermore, the ratio of non-severe versus severe events has been reported approximately 5:1 to 17:1 in other COVID-19 vaccine trials (Nov 2020). Employing these assumptions, modeling indicated there is a high probability that a signal of efficacy meeting the prespecified criteria in the Protocol Amendment 3 could be reached at or prior to the time when 50% of the participants will have been followed for a 8 weeks from the time of immunization, and therefore the sample size was reduced from 60,000 to approximately 40,000 participants.

3.2. Immunogenicity Subset (double-blind Phase)

All participants included in the Immunogenicity Subset (N=400) will be added randomly at each stage of the staggered enrollment. Healthy adults (Subset 1a, n=100) will be enrolled in Stage 1a, adults with comorbidities (Subset 1b, n=100) in Stage 1b, healthy elderly (Subset 2a, n=100) in Stage 2a, and elderly with comorbidities (Subset 2b, n=100) in Stage 2b, with approximately 100 participants per group. The interactive web response system (IWRS) will be used to achieve these numbers and a 1:1 ratio between Ad26.COV2.S and placebo assignment within each Subset.

For participants in the Immunogenicity Subset (ie, participants at sites with access to appropriate processing facilities), blood will be collected for analysis of humoral immune responses on Day 1 (pre-vaccination), Day 29, Day 71, 6 months, 1 year, 18 months, and 2 years after double-blind vaccination.

A sample size of 400 participants, is estimated to be sufficient to allow robust description of immune responses to Ad26.COV2.S vaccine. These numbers are expected to provide a robust

understanding of the magnitude and kinetics of the humoral response induced by the Ad26.COV2.S vaccine.

3.3. Immunogenicity Correlates (Correlates Subset)

Correlates will be assessed based on immune responses and transcriptome modifications measured in a random subcohort of vaccine recipients and in all vaccine recipients who experience a SARS-CoV-2 event (a primary endpoint or a secondary infection endpoint). Also, placebo participants will be included in this subset (placebo infected, seropositive [based on N-protein] non-infected and seronegative non-infected), if feasible. The goal of this case–cohort study is to assess correlates of risk of the primary endpoint and of SARS-CoV-2 infection (and potential other secondary endpoints) in the vaccine group by comparing vaccine-induced immune responses and transcriptome modifications associated with COVID-19.

Controls will be matched with cases from the same stage (age, comorbidities) and other co-factors as deemed appropriate. These will be detailed in the Correlates SAP.

3.4. Safety (Safety Subset)

Solicited and unsolicited AEs will be captured only in the Safety Subset, ie, approximately 6,000 participants (~3,000 from the active group, ~3,000 from the placebo group; and including at least 2,000 from the older age group [≥60 years of age] if feasible). Solicited AEs will be followed for 7 days, unsolicited AEs will be followed for 28 days.

3.5. Power calculations for other efficacy endpoints

3.5.1. Burden of disease endpoint

The statistical power associated with the BOD endpoint was evaluated under a range of scenarios for $VEmild$ (30-50%) with $VEmod/sev=60\%$ and a relative incidence of mild events equal to 20%. The power values for the null hypothesis of $VE=0\%$ under these scenarios were all greater than 99% for the BOD endpoint (conditional on clearing the primary endpoint test and adjusted for multiplicity).

Table 2 below presents the simulation-derived Type I error rates for $H_0: VE_{BOD} = 0\%$ and $H_0: VE_{BOD} = 30\%$, (the latter included to match the null for the primary endpoint), assuming a relative incidence of mild infections of 20% and vaccine efficacy for moderate or severe/critical infections $VE_{mod/sev}$. Both controlled (using a Pocock boundary) and uncontrolled (passing down full alpha = 2.5% one-sided) values are reported.

The values of VE_{mild} in Table 2 are chosen to produce the required values of VE_{BOD} under the null hypotheses of VE equal to 30% and 0% respectively for each successive pair or rows. The large negative values of VE_{mild} required under some of the scenarios would in all likelihood be detected in the supplementary analysis planned for mild infections alone. It can be seen from Table 2 that the Type I error rate for the BOD secondary endpoint is well-controlled for both null hypotheses considered using a Pocock boundary based on a single interim analysis, but would be inflated if

an uncorrected one-sided alpha of 2.5% were used (though the inflation is relatively small, at most 1.4% for the scenarios considered).

Table 2 **Type I error rates for BOD secondary endpoint tested at the time PA is triggered referring to H_0:〖VE〗_BOD=0% and H_0:〖VE〗_BOD=30%, using a 2.5% one-sided alpha (uncorrected) and a Pocock boundary. The relative incidences of mild and severe infections are both assumed to be 20%.**

$VE_{mod/sev}$	H0:BOD	VE_{mild}	Pocock	Full alpha
30%	VE=30%	30%	0.016	0.018
	VE=0%	-150%	0.014	0.016
50%	VE=30%	-70%	**0.021**	**0.036**
	VE=0%	-250%	**0.021**	**0.039**
60%	VE=30%	-120%	**0.016**	**0.031**
	VE=0%	-300%	**0.015**	**0.028**
70%	VE=30%	-170%	0.012	0.025
	VE=0%	-350%	**0.016**	**0.031**

The simulations that produced the results in Table 2 were carried out using an event-based simulation engine. We allocate each event in a trial between the vaccine and placebo arms of the trial, and between mild, moderate and severe infections, using the categorical distribution. We compare the cumulative sums of moderate and severe events to the boundary to determine when boundary crossing occurs. We calculate the appropriate alpha level for secondary endpoint testing at the time of boundary crossing using a Pocock two-stage design, implemented using the gsDesign R package. The information fraction used is the number of moderate and severe events at the time of boundary crossing divided by the TNE. We compute the test statistic for the burden of disease endpoint using the formulas in Mehrotra et al. 2020. We simulate 10,000 trials for each scenario.

3.5.2. Medical intervention

The probability to reject the null hypothesis VE=0% for the endpoint medical intervention for a given one-sided significance level with 23 events is visualized in Table 3. This probability is approximately 85% for an assumed VE=80% and approximately 99% for an assumed VE=90%. Therefore a minimum of 23 events is deemed sufficient to ensure a reasonable power for the evaluation of the medical intervention endpoint.

Table 3 **Probability to reject the null hypothesis VE=0 for the endpoint medical intervention for a given one-sided significance level with 23 observed medical intervention endpoints**

Available alpha	Information fraction	Probability for 80%VE	Probability for 90% VE
0.0065	20/154	85%	99%
0.00665	30/154	85%	99%
0.0069	50/154	85%	99%

0.0079	100/154	85%	99%
0.0125	154/154	85%	99%

3.5.3. Asymptomatic infections and all infections (including asymptomatic)

Based on assumptions prior to unblinding the cases in the placebo group were assumed to be distributed as follows: 45% asymptomatic cases and 55% symptomatic cases of which 20% were mild infections, and 60% were moderate and 20% were severe infections, according to the case definitions. Based on a VE as detailed in Table 4, events were simulated according to a binomial distribution and the primary endpoints evaluated against the SPRT boundary.

Upon crossing the SPRT boundary, the power against asymptomatic or undetected infections as well as against the evaluation of all infections was calculated (null hypothesis VE>0). The alpha level for that evaluation was adjusted according to the procedure detailed in the statistical hypothesis evaluation.

The results are based on 1000 simulations. The powers presented are not conditional on passing the first 2 secondary hypotheses.

Table 4 Powers for Asymptomatic and All Infections for various Fractions of available N-Elisa samples at 2.5 months at the time of analysis

Fraction of available N-Elisa samples At 2.5 months	Vaccine efficacy			Power		
	Moderate/ Severe	Mild	Asympto-matic	Moderate/ Severe	Asympto-matic	All infections
100%	70%	60%	30%	99%	14%	96%
100%	70%	60%	40%	99%	28%	99%
100%	70%	60%	50%	99%	47%	>99%
50%	70%	60%	30%	99%	4%	99%
50%	70%	60%	40%	99%	7%	>99%
50%	70%	60%	50%	99%	13%	>99%

This is based on the protocol assumed incidence of 1.4% during 3 months and waning thereafter (by 50% in Month 4, by 62% in Month 5 and beyond) and a sample size of 60,000.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Vaccine assignment will be analyzed according to an as-treated principle. The analysis sets that are used for the various analyses are described in Table 5.

Table 5 Analysis Sets

Analysis Sets	Description
Enrolled	The enrolled analysis set includes all participants who signed the ICF and who were not screen failures
Randomized	The randomized analysis set includes all participants who were randomized in the study.
Full Analysis Set (FAS)	All randomized participants with a documented study vaccine administration, regardless of the occurrence of protocol deviations and serostatus at enrollment.
Per Protocol Efficacy Set (PP; primary efficacy analysis set for vaccination studies)	Participants in the FAS who received double-blind study vaccine and who were seronegative at the time of double-blind vaccination and who have no major protocol deviations that were judged to possibly impact the efficacy of the vaccine. Participants who became aware of their study vaccine allocation will cease to be part of the PP population. See below for a definition.
Per Protocol Immunogenicity Analysis Set (PPI)	All randomized and vaccinated participants, including those who are part of the Immuno Subset and for whom immunogenicity data are available, excluding participants with major protocol deviations expected to impact the immunogenicity outcomes. In addition, for participants who experience a SARS-CoV-2 event (molecularly confirmed), samples taken after the event and samples taken outside protocol windows will not be taken into account in the assessment of the immunogenicity. The PPI population is the primary immunogenicity population. For key tables, sensitivity immunogenicity analyses will also be performed on the FAS, including participants who are part of the Immuno Subset for whom immunogenicity measures are available. Excluded samples might be taken into account as well in the sensitivity analysis. Analyses of vaccine immunogenicity and immune correlates of risk will be based on PPI.

For the PP the following additional criteria will be applied:

- having received the double-blind vaccine according to the randomization schedule
- having received at least 80% of the scheduled double-blind vaccination volume (according to the administration log)
- met inclusion criteria 1 (informed consent was obtained)

Some violations will not lead to exclusion of the subject from the PP, but data from the time-point of major protocol deviation onwards will be excluded as of from that moment from the analysis (if all data after double-blind vaccination is excluded, the participant will be excluded from the PP):

- use of prohibited concomitant medications or medical conditions that were judged to probably impact the efficacy of the vaccine based on blinded medical review will be assessed on a case by case basis and documented before confirming a case for continuous monitoring or data base lock
- administration of another SARS-CoV-2 vaccine before or during the trial

The following variables are relevant for in/exclusion of analyses:

- Seropositive or seronegative at baseline. A baseline serologic test for past or current infection with SARS-CoV-2 will be performed for all participants. Samples for the baseline serologic tests will be sent to the central lab for testing. Results will be categorized as positive or negative. If a participant is seropositive at baseline, the participant will be excluded from the PP set. In case the test result is missing or unknown the participant will be considered as seronegative for analysis purposes.
- PCR positive (PCR+) or negative (PCR-) at baseline: a sample for SARS-CoV-2 infection at baseline will be collected for each participant. For participants with a positive SARS-CoV-2 infection during the study this sample will be tested. If a participant was analyzed PCR+ at baseline, the participant will be excluded from the PP set. A missing value will be considered as PCR- for analysis purposes.

Timing of the infection: the onset of a symptomatic SARS-CoV-2 infection is defined in section 5.2. Based on the onset of infection, subjects will be included as

- For analysis with onset after double-blind vaccination: if onset occurred on or after Day 2 in the study (i.e. the Day after double-blind vaccination or beyond). At this stage there is however no expectation that the double-blind vaccination has achieved its full efficacy.
- For analysis with onset at least 14 days after double-blind vaccination: if onset occurred at or after Day 15. Subjects with an onset prior or at Day 14 will be excluded from the analysis.
- For analysis with onset at least 28 days after double-blind vaccination: if the onset occurred on Day 29 or beyond. Subjects with an onset prior or at Day 28 will be excluded from the analysis.

Analyses of safety will be performed on the FAS.

Analyses of efficacy will be performed on the PP population and will be repeated on the FAS.

5. STATISTICAL ANALYSES

5.1. General Considerations

Unless otherwise indicated, all analyses will pool data across ages and with/without co-morbidities for evaluation without stratification.

Analysis adjusting for randomization factors will be explicitly mentioned when done and will include the age groups and with/without co-morbidities only.

Stratification for (mobile) site unit at the time of randomization was done to ensure balance in exposure to SARS-CoV-2 between randomized groups over time because of the spatiotemporal evolution of the epidemic. However, including all stratification factors (age by comorbidity by (mobile) site) in the analysis will result in a large number of ‘empty strata’ (i.e. without cases) as the TNE of 154 is substantially lower than the anticipated number of stratification levels. Therefore no summaries will be provided by this stratification factor (mobile unit).

The final analysis planned at the end of the double blind phase, comparing vaccine versus placebo, will include efficacy and safety data collected during the 'double blind phase' of the trial, i.e. with an onset date of the event (or censor date) up to unblinding date.

To include the available data after unblinding, this analysis – comparing vaccine versus placebo - will be supplemented for primary and secondary endpoints with an analysis evaluating all available events until study discontinuation or upon administration of another authorized/approved vaccine up to the data lock point. Events that occurred after cross-over to another COVID-19 vaccine (including the Janssen Vaccine if received outside of the study) will be tabulated separately.

The analysis of the open-label phase (comparing efficacy between immediate vaccination versus delayed vaccination with the Janssen COVID-19 vaccine during the open-label phase of the study will include efficacy and safety data after unblinding and will be described in a separate SAP. Per protocol amendment 5, this analysis is planned when all subjects had at least one year of follow-up.

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 on Day 1.

The safety analysis will present all results by study phase (see Section 5.1.2). Immunogenicity results will be presented per scheduled time point as appropriate. Listings will be shown per phase and time point.

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 follows:

Table 6 Phase Definitions for Double-Blind Safety Analysis

Phase	Phase #	Period	Period #	Interval	
				From	To
Screening	1			Date and time of signing the informed consent form	One minute prior to start of post dose 1 period
Post-dose	2	Post-dose	1	Date and time of first vaccination	Minimum of: a) 23:59 at the date of last contact (for early discontinuation)

					b) 23:59 at the date of data base cut-off date in case of interim c) 23:59 on 28 days after the first vaccination (23:59 of day of vaccination + 28 days) d) One minute before date and time of treatment unblinding e) One minute before date and time of another vaccination outside the study
Follow-up (D30-M6)	3			One minute after Post-dose 1 Period end	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of data base cut-off date in case of interim c) 23:59 at date of the Month 6 (date of vaccination + 6 Months) d) One minute before date and time of treatment unblinding e) One minute before date and time of another vaccination outside the study
Follow-up (M6-W52)	4			One minute after Follow-up (D30-M6)	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of data base cut-off date in case of interim c) One minute prior to Week 52 Visit d) One minute before date and time of treatment unblinding e) One minute before date and time of another vaccination outside the study
Long term Follow-up (W52-End)	5			One minute after Follow-up (M6-W52)	Minimum of: a) 23:59 at the date of data base cut-off date in case of interim b) maximum of: 1. 23:59 at the date of last contact (for early discontinuation) 2. 23:59 at the date of last visit

					3. One minute before date and time of treatment unblinding 4. One minute before date and time of another vaccination outside the study
Open label Follow -up 1	6			Date and time of of unblinding	Minimum of a) 23:59 at the date of data base cut-off date in case of interim b) One minute prior to date and time of second/other vaccination within or outside the study c) Maximum of: 1. 23:59 at the date of last contact (for early discontinuation) 2. 23:59 at the date of last visit
Follow-up other vaccine	7			Date and time of vaccination outside the study	Minimum of a) 23:59 at the date of data base cut-off date in case of interim b) Maximum of: 1. 23:59 at the date of last contact (for early discontinuation) 2. 23:59 at the date of last visit

Table 7 Phase Definition for Pooled Open Label Safety Analysis

Phase	**Phase #**	**Period**	**Period #**	**Interval**	
				From	To
Post Dose	1	Post dose	1	Date and time of Ad26.COV.2 vaccination	Minimum of a) 23:59 at the date of data base cut-off date in case of interim b) One minute before date and time of another vaccination outside the study c) 23:59 on 28 days after the first vaccination (23:59 of day of vaccination + 28 days) d) 23:59 at the date of last contact (for early discontinuation)
Follow-up (D30-M6)	2			One minute after Post-dose 1 Period end	Minimum of:

					a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of data base cut-off date in case of interim c) 23:59 at the date of the Month 6 (date of Ad26.COV.2 vaccination + 6 Months) d) One minute before date and time of another vaccination outside the study
Follow-up (M6-W52)	3			One minute after Follow-up (D30-M6)	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of data base cut-off date in case of interim c) One minute prior to Week 52 Visit d) One minute before date and time of another vaccination outside the study
Long term Follow-up (W52-End)	4			One minute after Follow-up (M6-W52)	Minimum of: a) 23:59 at the date of data base cut-off date in case of interim b) maximum of: 1. 23:59 at the date of last contact (for early discontinuation) 2. 23:59 at the date of last visit 3. One minute before date and time of another vaccination outside the study

Under protocol amendment 3 and 4, subjects in the placebo arm may receive the active vaccine (or another authorized vaccine). For the purpose of the safety analysis, the post dose period of the double blind phases refer to the first vaccination either with placebo or active vaccine. The post dose of the open label pooled phases refer to the active vaccination, which will be the first vaccination for the active group and the second vaccination for the placebo group after unblinding. The Open-label Pooled phases, are defined only for subjects that received a Ad26.COV.2 vaccination and start from the date that they received their Ad26.COV.2 vaccination.

When the time of the first vaccination is missing and it occurred on the same day as the randomization, the time of vaccination will be imputed with the time of randomization Otherwise,

if the date is available of the first vaccination then the time will be imputed with 00:00 before applying the phase and period derivation rules.

In case the time of the second vaccination or the vaccination outside the study is missing then time will be imputed with 00:00 if the date is available. In case of a partial date and the second vaccination or the vaccination outside the study occurred after the unblinding date, then the available info will be compared to the unblinding datetime. If the month is available and it is the same as the unblinding month then the day is imputed with the day of the unblinding. If the month is after the month of unblinding then the day is imputed with the first of that month. If the month and day are missing then the year will be compared with the year of unblinding. If the year is the same then the month and day are imputed with the day and month of the unblinding date. If the second vaccination or the vaccination outside the study occurred before being unblinded then the partial date will be compared in a similar way to the first vaccination datetime. In case the time of the unblinding datetime is missing then the time is imputed with 23:59.

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

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

When unblinding, if it is determined that the participant received the Janssen vaccine (and not placebo), the participant will be informed that there are no data on the safety of receiving two different COVID-19 vaccines. Unblinded participants, both in the double-blind and open-label phase, will be asked to continue to be followed in this study in line with the schedule of activities to the extent that they permit. Safety evaluations will be identical for all participants, including participants that are unblinded to obtain another COVID-19 vaccine and who remain in the study, including participants in the safety subset, if applicable and feasible.

5.1.4. Unblinding due to cross-over for Janssen Vaccine

Section 6.4 from CTPA4 details the procedures to unblind participants at their Month6/Unblinding visit and offer participants who received placebo a single dose of Ad26.COV2.S vaccine. For all participants that are still in the study and did not have had a COVID-19 infection, nor have been censored, the Month6/Unblinding visit will mark the date of censoring for the double blind phase.

If participants decide to continue the study at the Month6/Unblinding visit, participants will be continued to be followed up and data will be collected and be analyzed separately.

5.1.5. Scope of Analysis of the double blind phase

The final analysis planned at the end of the double blind phase, comparing vaccine versus placebo, will include efficacy and safety data collected during the 'double blind phase' of the trial, i.e. with an onset date of the event (or censor date) up to unblinding.

To include the available data after unblinding, this analysis – comparing vaccine versus placebo - will be supplemented for primary and secondary endpoints with an analysis evaluating all available events up to the data lock point, until study discontinuation or upon administration of another authorized/approved vaccine up. The analysis will be censored at the date of another authorized/approved COVID-19 vaccine (if any, including the Janssen Vaccine if received outside of the study), the date of study discontinuation or the last available date (data lock point), whichever occurred first. Events that occurred after cross-over to another COVID-19 vaccine (including the Janssen Vaccine if received outside of the study) will be tabulated separately. Placebo recipients crossed-over to the Janssen COVID-19 vaccine (as part of the study) will be evaluated on placebo for the time they are exposed under placebo injection and evaluated for vaccine for the time they are exposed post Janssen COVID-19 vaccination.

The complete analysis of the open-label phase (comparing efficacy between immediate vaccination versus delayed vaccination with the Janssen COVID-19 vaccine during the open-label phase of the study will include efficacy and safety data after unblinding and will be described in a separate SAP. Per protocol amendment 5, this analysis is planned when all subjects had at least one year of follow-up.

5.2. COVID-19 case and SARS-Cov-2 infection classification

The initial COVID-19 classification will be based on a programmed algorithm (see section 5.2.2). Following the 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 charter) independently by a Clinical Severity Adjudication Committee (CSAC, see Section 5.9.8). This committee will independently evaluate the severity of the COVID-19 cases in a blinded manner, confirm the onset date as proposed by the algorithm or adapt the onset date based on clinical judgement and whether a case required medical intervention through objective findings.

Classification in terms of severity will be based on the highest degree of severity during the observation period. The assessment per CSAC is considered the final classification.

The process of adjudication is described in a separate charter, the relevant details regarding case classification are inserted in section 5.2.2.

5.2.1. Identification of COVID-19 cases for adjudication

All COVID-19 episodes and/or SARS-cov-2 infections since the start of the study will be identified using a programmed algorithm described in the section 5.2.2. All fatalities that occur within the study for which COVID-19 could be a contributory or the 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 through the use of other sources such as the Global Medical Safety database.

All cases identified by the algorithm as severe/critical (tier I)[a] or mild (tier V)[a] will be sent for adjudication for review on a case by cases basis.

Similarly, moderate cases identified by the algorithm will be sent for adjudication when they have at least one flag=Y for (tier II):

- SpO2 ≤93% from any source
- Heart rate ≥125 beats/minute
- Respiratory Rate ≥30 breaths/minute
- Medical Attended/MA-COV

In addition, a moderate case identified by the algorithm that resulted in hospitalization will be sent for adjudication.

For all other cases identified by the algorithm as moderate (tier III if 3 or more signs/symptoms, tier IV if <3 signs/symptoms)[b], adjudication may be performed for only a proportion of such cases, i.e. a sample approach. That is, the CSAC will be presented with the programmed algorithm outcomes and be asked to review a sample of such cases. Based on the results of these "sample adjudications", the CSAC will make a recommendation whether the programmed algorithm can serve as the default method of adjudication for the remainder of such cases.

Participants identified by the algorithm as asymptomatic/ undetected infections based on a PCR positive result during the course of their participation in the study and/or based on having seroconverted during their study time 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)).

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[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.

[b] 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.

The final adjudication under the previous charter version was completed on 12th April 2021. As of that date, case identification and adjudication following the current charter version (19 may 2021) will become applicable. New cases identified following the processes described in this section will be adjudicated retrospectively from study start, following the same principles described above. In addition, the following subsets of cases may be re-adjudicated following the methods stipulated in the charter:

- Cases previously adjudicated as not severe/critical where the programmed algorithm now demonstrates a change in severity classification.
- Cases where a critical data point has changed due to subsequent data cleaning.
- Cases previously adjudicated that were subsequently hospitalized (without additional data that changed the tiered classification detailed above). These cases will not be re-adjudicated on the severity classification, rather, the CSAC will be asked to adjudicate the onset date and to judge whether hospitalization/emergency room care for the COVID-19 episode was linked to objective measures

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 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 following preferred terms are included in this analysis: "COVID-19", "ASYMPTOMATIC COVID-19", "SUSPECTED COVID-19", "COVID-19 PNEUMONIA" and "SARS-COV-2 TEST POSITIVE"). [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 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.] A sensitivity analysis will be done to evaluate the change in onset date based on the 7 day window compared to the algorithm implemented at the primary analysis, where a day without symptoms interrupted the 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 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 University of Washington central testing facility.

- **A suspected COVID-19 case** is a case which meets any of the symptomatic COVID-19 definitions according to the CSAC without a document PCR positive results (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 8.1.2. This section provides guidance on how these will be applied.

- Information on symptoms is to be collected from the eCOA (see Appendix 6 of the CTP) and from the eCRF entered by the site (including AEs linked to COVID-19). In case the sources are inconsistent (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.
- The 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 has to 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”).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 method (oral, armpit, ear, or rectal).

- The definitions of *mild*, *moderate*, and *severe/critical* are mutually exclusive, where the most severe category takes priority.
- At the time of resolution of the COVID-19 episode, the collected information will be applied against the clinical case definition. For the purpose of continuous monitoring, the clinical case definition will be included as soon as analysis-ready independent of resolution (see above). In case symptoms worsen afterwards, increasing the classification of severity, the next continuous monitoring analysis will analyze the case according to the highest degree of severity at that time (see Section 5.9).

As there can be specific unforeseen situations where definitions as detailed in the SAP did not cover the specific situation, the Sponsor will at that time define additional data handling guidelines based on an assessment (blinded to treatment assignment) as close as possible to the intent of the rules as specified above. The Study Statistics and Programming team at the Sponsor will provide their additional data handling guideline to the SSG, which will be documented in the Data Presentation Specification document (DPS).

5.2.4. Symptomatic COVID-19 Case Derivation

Some symptoms lead to suspicion of a COVID-19 and are used as triggers to proceed with home-collection of the nasal swabs for SARS-CoV-2 testing as based on interaction of the participant with the site. 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, where the case may fail to reach the mild case definition (or worse) at any time during the episode. These cases are not considered as symptomatic. In other words, symptomatic COVID-19 cases are those that are at least of mild severity as defined below.

For any case to be considered a case at least one sample needs to have a SARS-CoV-2 positive RT-PCR from the central laboratory (University of Washington). 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 Vital signs 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 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:

- SpO2 ≤ 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, meaning that each subject with a case of molecularly confirmed COVID-19 is considered as an FDA harmonized case (yes/no), and considered as either a case of mild, moderate, or severe/critical case.

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 (eg, nasal swab sample, sputum sample, throat swab sample, saliva sample) or other sample

OR

develops a positive serology (non-S protein) test

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

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

5.2.5.2. Classification

As for symptomatic COVID-19 case classification, a similar approach will be taken to identify asymptomatic infections or undetected cases via an algorithmic approach. Cases will then be reviewed and classified as being an "Asymptomatic SARS-CoV-2 infection" by the Clinical Severity Adjudication Committee.

Relevant definitions for programmed algorithm:

Identification of potential asymptomatic SARS-CoV-2 infections via PCR: in the event of a positive PCR, the cases will be reviewed for the presence of signs and/or symptoms of COVID-19 since baseline 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 with onset Day >28** is based on the available data from Day 71, Month 6 and/or unblinding visit. If positive at any timepoint while the subject was seronegative at baseline (and at Day 29 for the PP analysis after day 28), a subject is considered seroconverted. If Day 29 is missing or not available, then the subject is considered negative on that Day.

- **SARS-CoV-2 seroconversion from Day 1 to Day 29**, is based on the available data on day 29. If positive at day 29 while the subject was seronegative at baseline or missing, a subject is considered seroconverted between day 1 and day 29.

- A **seroconverted participant** is a subject with serological conversion without an earlier molecularly confirmed (SARS-CoV-2 positive RT-PCR or molecular test result from any available respiratory tract sample)

Upon algorithmic identification, 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 since 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 infections .

- If at least one sign or symptom present, those cases will be sent to the CSAC for review for a possible undetected symptomatic COVID-19.

    - If reviewed by the CSAC as asymptomatic sars-cov-2 infections, cases will be classified as asymptomatic infections.

    - Seroconverted cases reviewed by the CSAC as symptomatic will be classified as **serologically confirmed COVID-19** and evaluated according to the accepted/reviewed severity and onset date.

    - PCR+ 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 (eg, nasal swab sample, sputum sample, throat swab sample, saliva sample) that is 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 positive 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.

A sensitivity analysis will be done based upon the algorithmic classification from the primary analysis.

5.3. Participant Dispositions

Participant information will be shown for the full analysis set.

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

- participants screened
- participants screen failed (and main reason for screen failure)
- participants in the FAS
- participants in the PP
- participants in the FAS but not in the PP (and reasons for not being in the PP)
- participants vaccinated and not randomized
- participants randomized and not vaccinated
- participants vaccinated with incorrect treatment
- participants who discontinued study (and reasons for termination)
- participants unblinded
- participants crossed over
- participants having another COVID-19 vaccine

Also, the number of participants and percentage per phase will be tabulated.

Graphical displays will be created for the follow-up time in the double blind phase for all subjects, by country, age, co-morbidities as well as by age crossed with co-morbidities will be visualized.

5.4. Primary Endpoint(s) Analysis

5.4.1. Timepoint of primary analysis

The interim monitoring for the primary analysis can start as soon as the following conditions are met:

1. A minimum of 6 COVID-19 primary endpoint cases for the ≥60 years age group with onset at least 28 days after double-blind vaccination

2. At least 42 cases meeting the primary endpoint definition of moderate to severe/critical COVID-19 with onset at least 28 days after double-blind vaccination
3. A subset of at least 5 cases meeting the definition of severe/critical COVID-19 with onset at least 28 days after double-blind vaccination

No interim evaluation will be done, until those conditions are fulfilled. Monitoring for efficacy will not start before the above conditions 1-3 are met.

The efficacy analysis will be triggered by either:

a) An interim evaluation if all prespecified efficacy boundaries have been met simultaneously at the same calendar timepoint OR if at least 154 cases meeting the primary endpoint definition of moderate to severe/critical COVID-19 are observed for events with onset at least 28 days after double-blind vaccination

AND

b) The above 3 conditions are met.

OR, alternatively,

If the prespecified non-efficacy has been met (evaluating events with start 14 days after vaccination) or when the harm boundary has been crossed. The decision rules for harm and non-efficacy are detailed in Section 5.9

If an efficacy signal is triggered before the required 8-week follow-up after vaccination of 50% of the enrolled participants is reached, an additional analysis will be performed when that follow-up timepoint is reached. If the time between the efficacy signal and the required 8-week median follow-up is too short to make a difference in terms of preparing two analyses, then a single analysis will take place at the time of the 8-week median follow-up. The analysis at the time of the 8-week median follow-up is considered the primary analysis.

If more than 154 primary endpoints are observed for events with onset at least 28 days after double-blind vaccination before the 3 conditions above are met, a single analysis will take place as soon as the conditions are met, using the full 2.5% one-sided significance level.

5.4.2. Definition of Endpoint and Estimand

The co-primary endpoints are defined as a COVID-19 case meeting either the moderate or severe/critical case definition with onset at least 14 days post double-blind vaccination and with onset at least 28 days post double-blind vaccination as defined in Sections 5.2.4.2 and 5.2.4.3.

The other estimand attributes therefore are:

Population: Prior SARS-CoV-2-uninfected, adults ≥18 years with or without comorbidities for COVID-19

Endpoints:

- Confirmed symptomatic moderate to severe/critical COVID-19 infections with onset ≥14 days after study double blind vaccination, as defined in section 8.1.3.1 of the protocol.

- Confirmed symptomatic moderate to severe/critical COVID-19 infections with onset ≥28 days after study double-blind vaccination, as defined in section 8.1.3.1 of the protocol.

Interventions: Ad26.COV2.S 5×10^{10} vp and placebo

Summary Measure: Vaccine Efficacy: 100 x (1-ratio of incidence vaccine/placebo)%

Intercurrent Events: None

Data handling for estimators: Subjects with major protocol deviations potentially impacting efficacy will be excluded from the analysis. Subjects with a positive serology test at baseline will be excluded from the analysis. Cases will be counted from Day 15 and Day 29 (depending on the co-primary endpoint) until unblinding (for the double blind phase analysis). Subjects with an event before Day 15 or Day 29 (depending on the co-primary endpoint) will be excluded from the analysis.

5.4.3. Analysis Methods for double blind phase

Vaccine efficacy and evaluation of the primary hypotheses will be done based on the truncated sequential probability ratio test (Section 5.4.3.1) in the per-protocol analysis set including seronegative subjects.

The pre-specified boundary to declare a significant result for each of the co-primary endpoints is based on a one-sided truncated SPRT, assuming approximately 90% power to detect a VE=60%, at a 2.5% one-sided significance, starting from the 20th COVID-19 case in the PP population that meets the primary endpoint definition, up and until the 154th case (value at which the testing is curtailed). The boundary is visualized in Figure 6 .

In case interim monitoring has started (i.e. because minimal data requirements 1-3 were met) and the total number of events at the time of the primary analysis exceeds the TNE, e.g. due to rapid accrual of events in the last week, the SPRT boundary will be extended until the observed total number of events, keeping the overall alpha below 2.5% one-sided. This is achieved by avoiding the truncation of the SPRT boundary at the TNE, distributing the remaining alpha across the overrun events, in such a way as to maximize the boundary at the observed total number of events.

The operational evaluation of this boundary is detailed later in this section. As soon as this prespecified boundary has been crossed for both co-primary endpoints together with the second efficacy criterion related to the severe infections (simultaneously at the same calendar timepoint) and the other data requirements have been met, the primary hypotheses of vaccine efficacy (VE) against moderate to severe infections in the PP set: H_0: VE ≤30% versus H_1: VE >30% will be established.

To evaluate whether the second efficacy criterion has been met, the VE against severe infections will be calculated, as soon as the primary endpoints contain a subset of 5 severe events for each of the co-primary endpoints. If the point estimate VE >= 50% AND a minimum of 5 cases observed in the placebo group for both co-primary endpoints, this criterion is considered to be met.

The analysis of the primary endpoint will evaluate vaccine efficacy and the associated 100% (1-2α*) - confidence interval with α * as indicated in section 2 will be estimated as referenced in Appendix 8.

The primary analysis will be supplemented with subgroup analyses for age group (18 to <60 years, ≥60 years) and presence of comorbidities (yes/no) employing a descriptive summary including (unadjusted) 95% confidence intervals to describe the VE in each subpopulation using the same methods. Depending on the recruited study population, the ≥60 years subgroup may be further subcategorized (≥70 years, ≥80 years). No hypothesis testing will be performed in these subgroups.

To assess potential time-effects of VE, the primary analysis will be further supplemented with Vaccine efficacy summarized for the following time intervals with VE and associated 95% confidence intervals: Day 1-14, Day 15-28, Day 29-56, Day 57-end DB phase. The interval Day 57-end of double blind may be further separated into Day 57-112 and Day 113-End of double blind phase, whereby Day 56 and Day 112 correspond to approximately median F/U times of the primary and final analysis of the double blind phase respectively.

5.4.3.1. Sequential Probability Ratio Test

Using a similar notation of Dragalin et al. (2002) and Dragalin and Fedorov (2006) consider, X_1 and X_2 the number of events in the placebo group and the vaccine group, respectively. The distribution of X_1 and X_2 can be approximated by a Poisson distribution with the following parameters: $\lambda_i = n_i p_i$ $(with\ i = 1{,}2)$. Thus, the conditional distribution of X_2 given $T = X_1 + X_2 = \mathrm{t}$ approximately follows a binomial distribution with parameters (t, π), where $\pi = \frac{\lambda_2}{(\lambda_1+\lambda_2)} = \frac{n_2 p_2}{n_1 p_1 + n_2 p_2} = \frac{1-VE}{2-VE}$, with VE=1-RR, $RR = \frac{p_2}{p_1}$, assuming a vaccine group allocation ratio of 1:1. Consequently, testing the null hypothesis $H0: VE = VE_0$ against $H1: VE = VE^*$ is equivalent to testing $H0: \pi = \pi_0$ against $H1: \pi = \pi^*$ using the conditional binomial test.

Consider $\alpha = P(reject\ H0 | VE = VE_0)$ and $\beta = P(accept\ H0 | VE = VE^*)$. Rejecting H0 occurs when $X_2 <= C_\alpha$ with $C_\alpha = C_\alpha(T)$ calculated to preserve α over all the sequential looks such that $P(X_2 <= C_\alpha | \pi = \pi_0) = B(C_\alpha;\ T, \pi_0) \leq \alpha$. With $B(.;T,\pi)$ the cumulative binomial distribution function with parameter T and π. The solution to the above equation, the TNE T^*, is the smallest T such that $B(B^{-1}(\alpha;\ T, \pi_0); T, \pi^*) \geq 1 - \beta$, with $B^{-1}(\alpha;\ T; \pi)$ the α-quantile of the cumulative binomial distribution function with parameters T and π. Under the assumptions stated in Section 3.1, this formula suggests a TNE of T^*=154.

The implemented critical boundaries for success (Section 5.9.5) are based on the truncated SPRT (cfr. Jennison and Turnbull, 2000, chapter 12) for which success boundaries are set based on observing X_2 events on the vertical axis out of total T events on the horizontal axis. These boundaries are created by comparing the Likelihood Ratio of observing X_2 out of T endpoints under $H1$ vs. $H0$, using the above-mentioned exact binomial distribution. If the log-likelihood ratio is larger or equal to $ln(1-\beta)/\alpha$ then H1 is concluded.

5.4.4. Operational implementation of SPRT and analysis in case of overrun

Based on modeling and simulation to minimize the risk of inconsistency and operationally to increase consistency in case evaluation, the evaluation whether or not the efficacy boundary has been crossed will be done on at least a weekly basis.

The boundary will be evaluated based on the available cases i.e., a COVID-19 episode that has been molecularly confirmed and analysis-ready according to the severity scale. The COVID-19 may still be ongoing.

1. At least every week, the available analysis-ready cases for efficacy monitoring will be evaluated against the primary endpoint definition and analysis population.

2. Based on the total number of analysis-ready cases and the vaccine:placebo ratio, the SSG will evaluate against the prespecified boundary whether the primary hypothesis has been rejected.

3. In case of rejection, the DSMB will provide the recommendation to proceed to the primary analysis to the Governance Committee upon which a decision can be implemented.

When the required 8-week follow-up after vaccination of 50% of participants is reached and when the decision is reached to proceed to analysis, the database cut-off date will be set to the date of the analysis when both boundaries are crossed and data requirements have been met. If an efficacy signal is triggered before the required 8-week follow-up after vaccination of 50% of enrolled participants is reached, an additional analysis will be performed when that follow-up timepoint is reached. If the time between the efficacy signal and the required 8-week median follow-up is too short to make a difference in terms of preparing two analyses, a single analysis will take place at the time of the 8-week median follow-up. The analysis at the time of the 8-week median follow-up is considered the primary analysis.

The primary analysis will be based on the cases of COVID-19 that were analysis-ready at this database cut-off date. The analysis of the secondary endpoints will include all analysis ready and resolved cases at the time of database lock.

This analysis will be supplemented with an analysis including cases that were not analysis-ready at the time of database lock, so irrespective of whether a confirmed positive central reading was available for any sample taken before the time of the database lock. Those cases will be classified using the most severe classification during the episode available at the time of the locked database.

The alpha level for the confidence interval and associated p-value will be based on the corresponding alpha level when the boundary was crossed.

For the operating characteristics of the SPRT and the statistical considerations justifying the practical implementation, the reader is referred to the modeling and simulation report.

5.4.5. Supportive analyses

The primary analysis will be supplemented with the following analyses.

For subjects with molecularly confirmed COVID-19, the follow-up time is defined as the time between double-blind vaccination and the time of onset of the case. For all subjects without COVID-19, follow-up time is defined as the time since vaccination until the date of unblinding or study discontinuation.

Time to first occurrence of molecularly confirmed moderate or severe/critically ill COVID-19 is defined as the time between double-blind vaccination until onset of the case for the PP set. Subjects without moderate and severe/critically ill COVID-19 are censored at their follow-up time as defined above.

In a supportive analysis of the primary efficacy endpoint, vaccine efficacy will be estimated with an associated two-sided confidence interval (Wald test) based on the hazard ratio obtained from a Cox proportional hazards regression model. The analysis will be stratified for age (>=60 yrs, <60 yrs) and comorbidities (with or without comorbidities). The strata will be based on the values in the database (which may differ to the strata as recorded in IWRS). The alpha-level at the time of crossing the boundary will be used to calculate the confidence interval.

As a supplementary analysis, a Negative Binomial model (using an asymptotic model including estimation of a dispersion parameter) will also be fitted.

The primary and supportive analysis as described for moderate and severe/critically ill COVID-19 cases in the per-protocol population in seronegative subjects will be repeated using the following analysis populations and endpoints:

- FAS, SN (seronegative) with onset of molecularly confirmed, moderate and severe/critically ill COVID-19 one day after double-blind vaccination
- PP, SN subjects with onset of molecularly confirmed, moderate and severe/critically ill COVID-19, at least 28 days after double-blind vaccination, thereby excluding subjects who were seropositive at or before Day 29 based on PCR or serological testing of Day 29 (subjects with missing data will be included)
- PP, SN subjects with onset of molecularly confirmed, moderate and severe/critically ill COVID-19, at least 14 and at least 28 days after double-blind vaccination, thereby excluding subjects with a missing result for the baseline serology sample

The primary efficacy and supportive analyses will be repeated by serostatus (seronegative, seropositive and overall) if > 6 moderate and severe/critically ill COVID-19 cases were observed in seropositive subjects.

5.4.6. Sensitivity analyses

In case of potential waning VE over time the cumulative incidence vaccine efficacy against moderate or severe/critical COVID-19 with onset at least 14 days post double-blind vaccination and with onset at least 28 days post double-blind vaccination will be evaluated in the PP set, where all participants were seronegative at the time of the double-blind vaccination. The method of Zeng (2004) will be used to estimate the cumulative incidence functions within each intervention arm, and pointwise two-sided Wald-based 95% confidence intervals for a log-transformed cumulative incidence ratio estimate will be provided over time. These intervals will be transformed to yield intervals for the cumulative incidence VE.

The method of Lin et al. (2021) may be used to estimate the instantaneous hazard based VE whereby time is defined as on calendar time since study start, and, using an average VE over time periods, to characterize VE over time intervals.

To evaluate the sensitivity to potential differential exclusion of major per-protocol deviations in the primary estimand, the following causal inference methods may be used. The efficacy will be estimated marginally among all participants who were seronegative at the time of vaccination in the full analysis set (FAS-SN). Longitudinal causal inference methods will be used to formally define this efficacy estimand. In particular, having major protocol deviations will be treated as a time-varying intervention and the estimand is defined as efficacy in the counterfactual world where no participants have a major protocol deviation and no participants are lost to follow-up (Robins, 1986). Methods for estimating this quantity make use of data from all participants in the FAS-SN cohort, including those who, in fact, do not belong to the PP set. For the causal estimand to be learnable from the data available, these methods require that time-varying covariates are available such that, at any given time, whether or not a person has yet had a major protocol deviation or has been lost to follow-up is independent of whether or not the person would have subsequently experienced moderate to severe COVID-19 in the scenario where, possibly contrary to fact, that person had not yet had a major protocol deviation or been lost to follow-up. Covariates to be considered include demographics, clinical participant characteristics, and clinic-level information.

A sequentially doubly robust targeted minimum loss-based estimator (TMLE) will be used to estimate the aforementioned causal efficacy estimand (see Algorithm 1 in Luedtke, 2017; see also van der Laan and Gruber, 2012). This TMLE has been shown to be more robust than alternative methods for estimating longitudinal causal effects (e.g., Bang and Robins, 2005 and van der Laan and Gruber, 2012). The TMLE that we will use is designed for a setting where time is discrete, and its performance guarantees rely on the number of time points not being too large relative to the sample size. Therefore, to properly account for the fact that moderate to severe COVID-19 is measured on a daily scale, the TMLE will be run with time discretized into two-week windows,

and then the fact that events are measured on a finer scale will be accounted for by incorporating inverse probability of censoring weights into the estimation procedure.

The resulting TMLE requires an estimate of the probability of experiencing moderate and or severe COVID-19 by the start of each two-week period considered, conditionally on time-varying covariates and intervention arm. Similarly, the TMLE also requires the probability experiencing a composite censoring event by the start of each of these two-week periods, conditionally on these same variables, where this composite censoring event is defined as either having a major protocol deviation or being lost to follow-up. Both of these estimates will be obtained using the ensemble method superlearner (van der Laan, Polley, and Hubbard 2007) with logistic regression, using the cross-entropy loss function and 5-fold cross-validation. Superlearner selects an optimal weighted combination of the predictions from a collection of candidate regression algorithms, such as those based on generalized linear models or random forests. Each superlearner will be supplied with the following library of learners: SL.mean, SL.step, SL.bayesglm, SL.glm, SL.glm.interaction, SL.glmnet, SL.earth, SL.xgboost, SL.ranger. Inverse probability of censoring weights will be obtained using a Kaplan-Meier estimator for the time to the composite censoring event, conditionally on being at risk at the beginning of the given two-week window. A 95%-level Wald-type confidence interval will be developed for the log-transformed cumulative incidence ratio, and will then be transformed to yield a confidence interval for the vaccine efficacy (VE).

5.4.7. Tabulations and Graphical displays

The time to onset of the first occurrence of molecularly confirmed COVID-19 (definition in section 5.2.4) will be graphically summarized using Kaplan-Meier methods for the following subgroups:

For moderate or severe/critical COVID-19,

- PP, seronegative subjects only with onset at least 14 days and at least 28 days after double-blind vaccination (co-primary endpoints)
- PP, seronegative subjects only with onset 1 day after double-blind vaccination
- PP, seronegative and seropositive subjects with onset 1 day after double-blind vaccination
- FAS, seronegative subjects only with onset 1 day after double-blind vaccination
- FAS, seronegative and seropositive subjects with onset 1 day after double-blind vaccination

*Note that in the PP there are no baseline-seropositive subjects – this population is defined as subjects who are baseline-seropositive and otherwise comply with the PP analysis set definition (e.g. no major protocol deviations).

These graphs will be summarized combined as well as for each type of infection separately (moderate or severe/critically ill COVID-19).

Furthermore, the number of events and incidence for each endpoint and population (#of events/#person-years of follow-up) will be tabulated by randomized group. For the tabulations regardless of serostatus, cases will be additionally summarized by serostatus at baseline and combined.

To assess potential time-effects of VE, two additional graphical explorations will be conducted. First, the Kaplan-Meier method will be used to plot the estimated cumulative incidence rates over time for the vaccine and placebo groups. This method will be used to estimate cumulative VE over time, defined as [(1 minus ratio (vaccine/placebo) of cumulative incidence by time t) ×100%] with the method of Parzen, Wei and Ying applied to estimate pointwise and simultaneous $(1-\alpha)\times 100\%$ CIs. Secondly, the method of Gilbert et al. (2002) will be used to evaluate VE over time based on the ratio of the smoothed instantaneous hazard in the vaccine and the placebo arm. More specifically, graphs will be created with [(1 minus ratio (vaccine/placebo) of smoothed instantaneous hazard by time t) ×100%] and accompanying pointwise and simultaneous $(1-\alpha)\times 100\%$ CIs over time since vaccination.

Any subgroup analysis for VE will also be visualized with forest plots.

5.4.8. Analysis of VE versus placebo on primary endpoint including data after unblinding

The following analysis will use data available before and after unblinding. The goal of this analysis is to use all available relevant data to analyze efficacy over time.

For the analysis of efficacy including data after unblinding, follow-up time will be expressed on a calendar time scale, and defined as time since study start (21 Sep 2020) to adjust for changing incidence over time. Follow-up time will begin on the date of administration of Janssen COVID-19 vaccine or placebo, expressed on a calendar time scale as time since study start, although follow-up time and events occurring within 14/28 days post vaccination with Janssen COVID-19 vaccine (including after cross-over) will be ignored.

The follow-up time is the time to first occurrence of moderate to severe disease, with an onset at any time after vaccination with placebo and before crossover to Janssen COVID-19 vaccine as part of the study, if such crossover occurs, or at any time at least 14/28 days post vaccination with Janssen COVID-19 vaccine, including after cross-over. 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, iii) the date of occurrence of moderate to severe disease before 14/28 days post vaccination with Janssen COVID-19 vaccine, including after cross-over, iv) the date of receipt of prohibited concomitant medications or development of a medical condition as described in Section 4 or v) the last available date, whichever occurred first. The analysis will be repeated with time to first occurrence of severe disease only.

Placebo recipients crossed-over to the Janssen COVID-19 vaccine (as part of the study) will be evaluated on placebo for the time they are exposed under placebo injection and evaluated for vaccine for the time they are exposed post Janssen COVID-19 vaccination, excluding follow-up time 14/28 days post Janssen COVID-19 vaccination.

Vaccine efficacy will be summarized using time-dependent Cox Proportional hazards models to account for i) changing incidence over calendar time, ii) potential confounding by country (or alternatively region), age (<60 years, >= 60 years), co-morbidities (Y/N) and unblinding status (all

of which will be accounted for via stratification rather than adjustment), and iii) time-dependent vaccine efficacy.

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

To evaluate possible time-dependent vaccine efficacy, the following two models may be explored:

- A model allowing for a log-linear change in vaccine efficacy over time since vaccination.
- A flexible splines model (Fintzi et al., 2021) whereby vaccine efficacy is a smooth function of time since vaccination. Following Fintzi et al., 2021, a penalized spline with 8 terms and 3 degrees of freedom will be used.

Models that do not converge will be omitted, and reported as non-convergent although in the event of non-convergence adjustment rather than stratification for covariates will be explored.

This analysis will be done on the per-protocol set including only baseline seronegative subjects. Models employing the assumption of constant vaccine efficacy or log-linear change in vaccine efficacy will also be fit for each country separately and, if there are sufficient cases, for each variant of interest separately.

These methods will be implemented as well during the open-label phase, and described in a SAP that will be prepared to analyze the open-label phase of the study, [planned after 1 year follow-up for all subjects that cross over].

5.5. Secondary Endpoint(s) Analysis

5.5.1. Tabulations and graphical displays

The time to onset of the first occurrence of molecularly confirmed COVID-19 will be graphically summarized using Kaplan-Meier methods for the following analysis populations following subgroups:

- PP, seronegative subjects only with onset at least 14 days and at least 28 days after double-blind vaccination
- PP, seronegative subjects only with onset 1 day after double-blind vaccination
- PP, seronegative and seropositive subjects with onset 1 day after double-blind vaccination
- FAS, seronegative subjects only with onset 1 day after double-blind vaccination
-

*Note that in the PP there are no baseline-seropositive subjects – this population is defined as subjects who are baseline-seropositive and otherwise comply with the PP analysis set definition (e.g. no major protocol deviations).

These graphs will be prepared regardless of severity according to the case definitions mild, moderate and severe and for the US FDA harmonized case definition. Furthermore, the graph will be prepared by severity (for mild COVID-19 only, COVID-19 requiring medical intervention).

The number of events and event rate for each endpoint and population (#of events/#person-years of follow-up) will be tabulated by randomized group.

Unless otherwise indicated, follow-up time for each subject is defined as time since double-blind vaccination until onset of a COVID-19 episode or the date of unblinding (For subjects without a COVID-19 episode in the double blind phase).

To assess potential time-effects of VE for secondary endpoints the following graphical explorations will be conducted. First, the Kaplan-Meier method will be used to plot the estimated cumulative incidence rates over time for the vaccine and placebo groups. This method will be used to estimate cumulative VE over time, defined as [(1 minus ratio (vaccine/placebo) of cumulative incidence by time t) ×100%] with the method of Parzen, Wei and Ying applied to estimate pointwise and simultaneous $(1-\alpha)\times 100\%$ CIs. Secondly, the method of Gilbert et al. (2002) will be used to evaluate VE over time based on the ratio of the smoothed instantaneous hazard in the vaccine and the placebo arm. More specifically, graphs will be created with [(1 minus ratio (vaccine/placebo) of smoothed instantaneous hazard by time t) ×100%] and accompanying pointwise and simultaneous $(1-\alpha)\times 100\%$ CIs over time since vaccination.

Any subgroup analysis for VE will be visualized as well with forest plots.

5.5.2. Key Confirmatory Secondary Endpoint(s) and Estimand(s)

5.5.2.1. Definition of Endpoint(s)

Endpoint Label	Endpoint definition
Any symptomatic infection (BOD)	For all subjects with a symptomatic, molecularly confirmed COVID-19 episode, classification based on any severity will be included. Weight-adjusted analysis for severe disease will be done as follows. Any case of mild or moderate COVID-19 will be given a score of 1, severe/critical COVID-19 cases will be given a score of 2. Subjects without a symptomatic, molecularly confirmed COVID-19 episode are implicitly categorized as 0.
Asymptomatic infection	Asymptomatic infection with an onset at least 28 days after vaccination is considered as a subject with either serologic conversion (day 71 or month 6) or with a SARS-CoV-2 positive RT-PCR or molecular test result from any available respiratory tract sample (eg, nasal swab sample, sputum sample, throat swab sample, saliva sample) or other sample but both without a previous suspected, symptomatic COVID-19 episode according to the adjudication committee (asymptomatic as defined in section 5.2.5). Additionally, both types of asymptomatic infections will be analyzed separately as well (based on PCR versus based on serology).

	Supportive endpoints: 1. Seroconverted participants will be defined as participants with a serologic conversion (day 71 or Month 6 and/or unblinding visit) and without a previous SARS-CoV-2 positive RT-PCR or molecular test result from any available respiratory tract sample (eg, nasal swab sample, sputum sample, throat swab sample, saliva sample) or other sample regardless of prior symptoms 2. Subset of asymptomatic infections based on PCR results from the Month 6 and/or unblinding visit 3. Asymptomatic infections between Day 1 and Day 29 will also be analyzed as a supportive endpoint. If positive at Day 29, while the subject was seronegative at baseline, a subject is considered seroconverted.
All infections (Any SARS-CoV-2 Infection)	First occurrence of SARS-CoV-2 infection (serologically, including serologically symptomatic confirmed, and/or molecularly confirmed[a]) with onset at least 28 days after double-blind vaccination with study vaccine.
Severe/critical infection	A subject is considered as an event when the first occurrence of molecularly confirmed COVID-19 case meeting severe/critical definition with onset at least 14 days and at least 28 days post double-blind vaccination.
COVID-19 requiring Medical intervention	COVID-19 events requiring medical intervention including hospitalization based on objective findings such as ICU admission, mechanical ventilation, ECMO, decreased oxygenation, X-ray, CT findings, use of supportive medications or clinical course following adjudication by the CSAC with onset at least 14 days and at least 28 days post double-blind vaccination The evaluation whether the endpoint is linked to objective measures will be done through the adjudication committee using all available information. In addition, an algorithmic interpretation will be done, based on the MRU questionnaire only for consistency with the primary analysis.

The confirmatory estimands therefore are

Population: Prior SARS-CoV-2-uninfected, adults ≥18 years with or without comorbidities for COVID-19

Endpoint: as defined above.

Interventions: Ad26.COV2.S $5x10^{10}$ virus particles and placebo

Summary Measure: Vaccine Efficacy: 100x(1-ratio of endpoint mean vaccine/placebo)%

Intercurrent Events: /

Data handling for estimator: Subjects with major protocol deviations potentially impacting efficacy will be excluded from the analysis. Subjects with a positive serology test at baseline will be excluded from the analysis.

For the secondary endpoints all available cases at the time of data base cut off will be included in the analysis according to the pre-specified analysis population and time window for endpoint calculation.

The populations for analysis for the secondary endpoints are presented in Table 8.

Table 8 Key confirmatory secondary endpoints and analysis set evaluations

	Key analysis population for evaluation of the statistical hypothesis	Supportive analysis set
Any symptomatic infection (BOD)	Per-Protocol analysis set baseline-Sero-Negative subjects with onset of infection at least 14 days and at least 28 days post double-blind vaccination	PP, SN/SP, Day 28* FAS, SN, Day 1 FAS, SN/SP, Day 1*
Any SARS-CoV-2 infection	Per-Protocol analysis set Sero-Negative subjects with onset of infection at least 28 day post double-blind vaccination	FAS, SN, Day 1 FAS, SN/SP, Day 1* PP, SN/SP, Day 28
Severe infection	Per-Protocol analysis set Sero-Negative subjects with onset of infection at least 14 and at least 28 days post double-blind vaccination	PP, SN/SP, Day 28* FAS, SN, Day 1 FAS, SN/SP, Day 1*
Medical intervention	Per-Protocol analysis set Sero-Negative subjects with onset of infection at least 14 and at least28 days post double-blind vaccination	PP, SN/SP, Day 28* FAS, SN, Day 1 FAS, SN/SP, Day 1*
Asymptomatic or undetected infection	Per-Protocol analysis set Sero-Negative subjects with onset at least 28 days post double-blind vaccination	FAS, SN Day 1
Asymptomatic or undetected infection from Day 1 to Day 29	FAS, SN Day 1	
PP=per-protocol, SN=sero-negative subjects, Day 1/28=including infections with onset 1 day/28 days post double-blind vaccination, SP=seropositive subjects, FAS=full analysis set		

(*)Any analysis regardless of serostatus will be done only if 7 or more events observed in the group of subjects who were seropositive at baseline.

5.5.3. Supportive Secondary Endpoint(s)

To understand and characterize the vaccine efficacy against any symptomatic infection, as well as under any infection, the following supportive endpoints will be supplemented with the confirmatory secondary endpoints.

The evaluation of secondary endpoints will be done in the per-protocol analysis set in seronegative subjects, with onset at least 14 and at least 28 days after double-blind vaccination. All analyses will be repeated regardless of serostatus.

	Endpoint definition
Mild infection	A subject is considered as an event when the first occurrence of molecularly confirmed COVID-19 case meeting mild definition with onset at least 14 and at least 28 days post double-blind vaccination.
Moderate infection	A subject is considered as an event when the first occurrence of molecularly confirmed COVID-19 case meeting moderate definition with onset at least 14 and at least 28 days post double-blind vaccination.
US FDA Harmonized COVID-19 cases	A subject is considered as an event when the first occurrence of molecularly confirmed COVID-19 case meeting the US FDA harmonized case definition with onset at least 14 and at least 28 days post double-blind vaccination
Viral Load AUC (VL-AUC)	Area under the viral load-time curve (VL-AUC in $\log_{10}$ copies/ml) of SARS-CoV-2 viral RNA load as determined by quantitative RT-PCR assay of nasal available samples during the COVID-19 episode. Nasal swab samples are taken at the start of the COVID-19 episode and every 2 days thereafter for the next 14 days or until 2 consecutive negative swabs, whichever occurs later. VL-AUC is calculated based on the viral load values until resolution of the COVID-19 episode. In the calculation of the AUC, all available information (date, timing in hours, and minutes as captured in the data base will be used, but the AUC result will be reported in hours), of the assessment, is taken into account. Data handling regarding the following will be added to the Data Presentation Specifications (DPS): • PCR local lab versus central lab data • saliva • handling of values below LLOQ/LLOD

	$$\text{AUC VL} = \sum_{i=2}^{T} \frac{[VL_{t_i} + VL_{t_{(i-1)}}]}{2}[t_i - t_{(i-1)}]$$ where $\mathbf{t_i}$ **= (actual) timepoint i** $\mathbf{t_{i-1}}$ **= (actual) timepoint (i − 1)** $\boldsymbol{T}$ ***= last timepoint*** $\mathbf{t_1}$ **= first timepoint** $\mathbf{VL_{t_i}}$ **= $\log_{10}$ viral load at (actual) timepoint i** $\mathbf{VL_{t_{(i-1)}}}$ **= $\log_{10}$ viral load at (actual) timepoint (i − 1)** This will be calculated for all subjects with a molecularly confirmed infection.

5.5.4. Analysis Methods for double blind phase

5.5.4.1. VE against severe/critical infection with onset at least 14 and at least 28 days after double-blind vaccination

The VE will be estimated with an associated two-sided (1- 2α*) confidence interval (methodology described in Appendix 8). The alpha-level α* is derived as detailed in section 2. To evaluate the hypothesis H0: VE<=0%, the lower-limit of the adjusted confidence interval will be compared to 0, the hypothesis of moderate to severe infection with onset at least 14 and at least 28 days after double-blind vaccination will be rejected if the lower limit of the confidence interval is > 0%.

A descriptive summary of the reason for severe disease, as indicated by the adjudicators will be provided.

To assess potential time-effects of VE, two additional graphical explorations will be conducted. First, the Kaplan-Meier method will be used to plot the estimated cumulative incidence rates over time for the vaccine and placebo groups. This method will be used to estimate cumulative VE over time, defined as [(1 minus ratio (vaccine/placebo) of cumulative incidence by time t) ×100%] with the method of Parzen, Wei and Ying applied to estimate pointwise and simultaneous $(1-\alpha) \times 100\%$ CIs. Secondly, the method of Gilbert et al. (2002) will be used to evaluate VE over time based on the ratio of the smoothed instantaneous hazard in the vaccine and the placebo arm. More specifically, graphs will be created with [(1 minus ratio (vaccine/placebo) of smoothed instantaneous hazard by time t) ×100%] and accompanying pointwise and simultaneous $(1-\alpha) \times 100\%$ CIs over time since vaccination.

Vaccine efficacy will be summarized for the following time intervals, Day 1-14, Day 15-28, Day 29-56, Day 57-end DB phase. The interval Day 56-end of double blind may be further separated into Day 56-112 and Day 112-End of double blind phase, whereby Day 56 and Day 112 correspond to approximately median F/U times of the primary and final analysis of the double blind phase respectively.

5.5.4.2. VE against any symptomatic infection – burden of disease

To evaluate the vaccine efficacy against any symptomatic infection, the severity-adjusted vaccine efficacy VE_{BOD} will be calculated based on BOD as follows. This vaccine efficacy measure is equal to the percent reduction in mean BOD score in the vaccine arm relative to that in the placebo arm.

Letting p_1 and p_2 denote, respectively the relative incidence of mild and moderate infections among symptomatic infections, and VE_1, VE_2, VE_3 represent, respectively, the vaccine efficacy for mild, moderate and severe/critical infections, the vaccine efficacy for BOD, under 1:1 allocation for vaccine and placebo, can be expressed as

$$VE_{BOD} = 1 - \left[(1 - VE_1)p_1 + (1 - VE_2)p_2 + 2(1 - VE_3)\left(1 - (p_1 + p_2)\right)\right] / \left(2 - (p_1 + p_2)\right)$$

Letting $BOD_V(n)$ and $BOD_P(n)$ represent the sums of the BOD scores for (symptomatic) infections in the vaccinated and placebo arms, respectively, then the estimated vaccine efficacy for the BOD endpoint after n infections (under equal allocation to vaccine and placebo) is $\widehat{VE}_{BOD}(n) = 1 - BOD_V(n)/BOD_P(n)$. An expression for an (asymptotic) lower confidence bound for VE_{BOD} based on $\widehat{VE}_{BOD}(n)$ is provided in (supplementary appendix, Mehrotra et al, 2020). The alpha* - level of the confidence interval will be compared against 0.

This lower bound will be compared against 0% to evaluate the study hypothesis against any symptomatic infection according to the statistical testing strategy specified in section 2.

In addition, the vaccine efficacy will be estimated with an associated unadjusted confidence interval for each severity separately (mild, moderate, severe/critical) according to the case definition.

Estimators for VE1, VE2 and VE3 in the PP-SN, together with their 95% CIs, are presented in Appendix 8.

In addition, to assess potential time-effects of VE, the Kaplan-Meier method will be used to plot the estimated cumulative incidence rates over time for the vaccine and placebo groups. This method will be used to estimate cumulative VE over time, defined as [(1 minus ratio (vaccine/placebo) of cumulative incidence by time t) ×100%] with the method of Parzen, Wei and Ying applied to estimate pointwise and simultaneous $(1 - \alpha) \times 100\%$ CIs.

Vaccine efficacy for any symptomatic COVID-19 will be summarized for the following time intervals, Day 1-14, Day 15-28, Day 28-56, Day 56-end DB phase. The interval Day 56-end of double blind may be further separated into Day 56-112 and Day 112-End of double blind phase, whereby Day 56 and Day 112 correspond to approximately median F/U times of the primary and final analysis of the double blind phase respectively.

5.5.4.3. Any SARS-CoV-2 infections and asymptomatic infections

The proportion of subjects (out of subjects with available measurements) who serologically converted will be graphically visualized and tabulated at every available timepoint by randomized group, together with the number of subjects with an available measurement.

Additional tabulation will summarize the number of subjects with and without a SARS-CoV-2 infection as having

1. Not infected
2. Asymptomatic infections
    - Based on serological conversion
    - Based on positive RT-PCR
3. Symptomatic molecularly confirmed, with mild COVID-19
4. Symptomatic molecularly confirmed, with moderate COVID-19
5. Symptomatic molecularly confirmed, with severe COVID-19
6. Symptomatic serologically confirmed, with mild COVID-19
7. Symptomatic serologically confirmed, with moderate COVID-19
8. Symptomatic serologically confirmed, with severe COVID-19

A subject will be classified based on their worst occurrence and in one category only.

All subjects with multiple SARS-CoV-2 molecularly confirmed infections during the study will be tabulated by severity and double-blind vaccination group in the FAS-SN as well as SP set.

To assess the effect of Ad26.COV2.S on occurrence of any infection with SARS-CoV-2 as compared to placebo, VE will be estimated with an associated 95% confidence interval. If the timepoint of hypothesis testing is reached (when at least 15,000 subjects with a Day 71 available sample), adjusted two-sided (1- 2α*) confidence interval (methodology described in Appendix 8). The alpha-level α* is derived as detailed in section 2. To evaluate the hypothesis H0: VE<=0, the

lower-limit of the adjusted confidence interval will be compared to 0, the hypothesis of protection against infection will be rejected.

To understand the vaccine efficacy of Ad26.COV2.S on occurrence of asymptomatic infections with SARS-CoV-2 alone, as compared to placebo, the VE will be estimated with a 95% confidence interval. If the timepoint of confirmatory testing is reached (when all participants have at least 6 months of follow-up), an associated adjusted two-sided (1- 2α*) confidence interval (methodology described in Appendix 8). The alpha-level α* is derived as detailed in section 2. To evaluate the hypothesis H0: VE<=0, the lower-limit of the adjusted confidence interval will be compared to 0, the hypothesis of protection against infection will be rejected.

For cases, the follow-up time is defined as the time between double-blind vaccination and the time of onset of infection (timepoint of a positive N-protein Elisa for asymptomatic subjects).

For supportive endpoints, Vaccine efficacy will be estimated with a 95% confidence intervals (as described in appendix 8).

5.5.4.4. Medical intervention

Vaccine efficacy will be summarized with a 95% confidence interval (methods in Appendix 8)

When sufficient number of events are observed, an adjusted confidence interval will be calculated with the alpha-level α* derived as detailed in section 2. To evaluate the hypothesis H0: VE<=0%, the lower-limit of the adjusted confidence interval will be compared to 0%, the hypothesis of protection on medical intervention endpoints will be rejected if the lower limit of the confidence interval is > 0%.

For cases, the follow-up time is defined as the time between double-blind vaccination and the onset of the first event (according to the considered event linked to the medical intervention). For non-cases, it is the time between double-blind vaccination and data base cut off date (for subjects ongoing) or study discontinuation.

The reason linked to medical intervention will be tabulated.

5.5.4.5. AUC viral load

To compare VL-AUC after infection between the active and placebo groups, the exact Wilcoxon Rank Sum test will be performed.

Values below the LLOQ will be imputed with 1 when detected and with 0 when not detected.

These imputations will be used when calculating the AUC based on equation (1). In addition, in case some observations are missing at the first timepoint after infection and/ or the last timepoint after challenge, missing values should be imputed with 0. No other missing values will be imputed.

AUC-VL values will be descriptively summarized (mean, median, SD, SE, range) by randomized group and COVID-19 severity (all symptomatic infections, mild, moderate to severe/critical).

Individual profiles of viral load over time and log10[viral load] over time since onset of a COVID-19 episode will be summarized by randomized group and severity of COVID-19.

The vaccine efficacy against AUC-VL will be estimated through the geometric mean ratio of AUC-VL with associated 95% confidence interval.

As the comparison of the AUC VL after infection between the active and placebo groups is based on post-randomization groups, this analysis may not assess the causal effect of the vaccine on viral load. A sensitivity analysis as described by Gilbert et al. (2003) will be carried out. In this sensitivity analysis, a logistic selection bias model is employed to define a causal estimator for the vaccine effect on viral load. The unknow slope (b) of this logistic model determines the amount of selection bias; b is varied over a plausible range of values. For each value of b, a non-parametric estimate of the causal vaccine effect is calculated. A confidence interval and p-values for the appropriate hypothesis of interest are obtained by bootstrap. If $b<0$, there is a selection bias towards a lower viral load in the vaccine group as compared to the placebo group. When $b=0$, no selection bias is assumed. The hypothesis of interest is the one-sided hypothesis of a reduction of the viral load. Therefore, values of $b \leq 0$ will be considered (from -5 to 0 in steps of 0.01). The estimate of the causal vaccine effect with its 100*(1-2*alpha) % confidence interval and the p-value for the one-sided hypothesis of a viral load reduction in the vaccine group will be plotted against the assumed value of b.

The analysis will be carried using R-code developed by P.N. Gilbert and R.J. Bosch. Number of bootstrap samples will be set to 10000 to achieve adequate precision for the derived p-values. The seed will be fixed to allow reproducibility of the result.

5.5.4.6. US FDA Harmonized definition

Estimating the Vaccine Efficacy (*VE*) and the associated 95% confidence interval for the US FDA harmonized definition will be done according to the methodology as explained in Appendix 8.

5.5.4.7. Mild Cases

Estimating the Vaccine Efficacy (*VE*) and the associated 95% confidence interval for participants with an infection that is at most of mild severity will be done according to the methodology as explained in Appendix 8.

5.5.5. Analysis of VE versus placebo for secondary endpoints using data after unblinding

The analysis as described in section 5.4.8 for the primary endpoint will be repeated for the endpoints severe events and FDA definition.

5.6. Tertiary/Exploratory Endpoint(s) Analysis

The potential association between vaccine efficacy and baseline or other potential influential factors (including but not limited to region, age group, comorbidities, Ad26 VNA seropositivity, SARS-CoV-2 seropositivity, profession, smoking status, seropositivity against other coronaviruses and coinfection with any other respiratory pathogens and other risk factors) will be explored by multivariate, covariate-adjusted analyses or subgroup summaries, including 95% confidence intervals.

All exploratory endpoints analysis will occur in the PP analysis set, in seronegative subjects unless otherwise indicated.

Other ad hoc analyses may be performed if deemed appropriate to characterize the safety, immunogenicity and efficacy profile of the vaccine. Post-hoc analyses (analyses performed that are different from this SAP) that are included in the final CSR will be documented in the Changes to Planned Analyses section of the CSR.

5.6.1.1. Definition of Endpoint(s)

Endpoint	Endpoint definition
Time to SARS-CoV-2 virus no longer detectable	A subject is considered as having an infection if the case is classified as mild, moderate or severe. For each subject the time to "SARS-CoV-2 virus no longer detectable" is the time between the onset of the COVID-19 episode and the first sample that is negative and after which no positive sample was observed. For this assessment only centrally confirmed assessments will be taken into account. The precision of this difference will be in Days, defined as the Day of the episode where this criterion is met (e.g., if the first sample that was negative was on Day 12 of the episode, the time to no longer detectable will be set at 12 Days.
Peak viral load	A subject is considered as having an infection if the case is classified as mild, moderate or severe. The peak viral load is defined as the highest viral load that was observed during a COVID-19 episode. For this assessment only centrally confirmed assessments will be taken into account.
Viral load over time	A subject is considered as having an infection if the case is classified as mild, moderate or severe. For this assessment only centrally confirmed assessments will be taken into account. For each assessment the viral load will be categorized to the two day schedule, where the first value will define the series. If a viral load is available before and after a scheduled day, the average on the $\log_{10}$ scale will be used. If only one value is available in an adjacent day this value will be used.
ok	A subject is considered as having an infection if the case is classified as mild, moderate or severe. The first viral load is defined as the first viral load that was observed within a COVID-19 episode. For this assessment only centrally confirmed assessments will be taken into account.

The additional endpoints on viral load by quantitative RT-PCR are defined above and will be analyzed descriptively for all symptomatic cases separately by severity (all symptomatic infections, mild, moderate to severe/critical) as well as asymptomatic cases collected via PCR on the baseline and unblinding visits.

Assessment of the efficacy of Ad26.COV2.S in the prevention of SARS-CoV-2 infection (both symptomatic and asymptomatic infections combined, that are serologically and/or molecularly confirmed), as compared to placebo by first occurrence of SARS-CoV-2 infection (serologically and/or molecularly confirmed) from Day 1 to Day 29.

First occurrence of any health care utilization linked to any molecularly confirmed COVID-19. Health care utilization is defined as any event such as hospitalization, ICU admission, ventilator use linked to any molecularly confirmed COVID-19 at least 14 days and 28 days after double-blind vaccination.

Assessment of the efficacy of Ad26.COV2.S in the prevention of SARS-CoV-2 infection in participants with comorbidities associated with increased risk of progression to severe COVID-19, as compared to placebo defined as first occurrence of SARS-CoV-2 infection (serologically and/or molecularly confirmed) in participants with comorbidities associated with increased risk of progression to severe COVID-19 with onset at least 28 days after double-blind vaccination with study vaccine.

To explore the effect of Ad26.COV2.S on other potential complications of COVID-19 (linked to any respiratory disease and linked to any molecularly confirmed COVID-19) not previously described, as compared to placebo by first occurrence of potential complications of COVID-19 linked to any respiratory disease and linked to any molecularly confirmed COVID-19, with onset at least 14 days and at least 28 days after double-blind vaccination with study vaccine.

To explore the effect of Ad26.COV2.S on all-cause mortality, as compared to placebo by deaths occurring at least 14 days and at least 28 days after double-blind vaccination with study vaccine.

To evaluate the immune response in participants with COVID-19 in relation to risk of development of COVID-19, protection induced by Ad26.COV2.S, and risk of accelerated disease by assessment of the correlation of humoral immune responses with emphasis on neutralizing, binding and functional antibodies, as well as gene transcript profiling (RNA sequencing), with the risk of COVID-19 and protection induced by the study vaccine.

In a subset of participants to further assess the humoral immune response to Ad26.COV2.S, as compared to placebo for functional and molecular antibody characterization including, but not limited to avidity, Fc-mediated viral clearance, Fc characteristics, Ig subclass, IgG isotype, antibody glycosylation, and assessment of antibody repertoire, adenovirus neutralization as measured by VNA, analysis of antibodies to S and the receptor-binding domain (RBD) of the SARS-CoV-2 S protein and SARS-CoV-2 neutralization as measured by virus neutralization assay (VNA; wild-type virus and/or pseudovirion expressing SARS CoV-2 S protein).

To explore changes in the SARS-CoV-2 genome by development of SARS-CoV-2 variants

To evaluate patient-reported outcomes (PROs) in relation to the presence of SARS-CoV-2 infection and the presence, severity and duration of COVID-19 signs and symptoms in participants who received Ad26.COV2.S, as compared to placebo by presence, severity and duration of COVID-19 signs and symptoms and confirmation of SARS-CoV-2 infection by molecular testing.

To assess the difference in severity of cases in participants who received Ad26.COV2.S as compared to placebo by reduction in severity of COVID-19 signs and Symptoms

To assess the impact of pre-existing humoral immunity against coronaviruses other than SARS-CoV-2 at baseline on Ad26.COV2.S vaccine immunogenicity.

To assess the incidence of co-infection of COVID-19 and other respiratory pathogens and to assess the effect of the vaccine during such co-infections as well as to estimate the incidence of other respiratory pathogens during the study period.

To assess the frailty index in participants who received Ad26.COV2.S as compared to placebo.

5.6.1.2. Analysis Methods

For the assessment of the SARS-CoV-2 viral load by quantitative RT-PCR, in participants with molecularly confirmed, mild COVID-19 by serial viral load measurements during the course of a COVID-19 episode the analysis method as described in section 5.5.4.5 will be repeated limited to the molecularly confirmed, mild COVID-19 cases. To compare viral load of the asymptomatic cases at the unblinding visit between the active and placebo groups, with the exact Wilcoxon test. Descriptive statistics of the viral load will be calculated and box plots will be created for the active and the placebo group.

The number of days with detectable levels of viral load will be compared between vaccination groups and descriptively summarized. A non-parametric test may be employed to compare a shift in distribution.

For the first occurrence of any health care utilization linked to any molecularly confirmed COVID-19 defined as any event such as hospitalization, ICU admission, ventilator use linked to any molecularly confirmed COVID-19 at least 14 days and 28 days after double-blind vaccination, the proportion of participants will be tabulated and and the VE as described in appendix 8 will be computed with the 95% exact CIs. If possible the impact of age group and comorbidities (as defined by the CDC, section 6.7) will be investigated. If enough cases per event type are available (more than 6) a separate model can be performed per event type.

For the assessment of the efficacy of Ad26.COV2.S in the prevention of SARS-CoV-2 infection (both symptomatic and asymptomatic infections combined, that are serologically and/or molecularly confirmed), as compared to placebo by first occurrence of SARS-CoV-2 infection (serologically and/or molecularly confirmed) with onset at least 28 days after double-blind vaccination with study vaccine the analysis method as described in section 5.3 will be repeated using all SARS-CoV-2 infections. This analysis will be done using the PP and will be repeated in

the FAS for participants with comorbidities associated with increased risk of progression to severe COVID-19 (as defined by the CDC, section 6.7).

For the assessment of the effect of Ad26.COV2.S on other potential complications of COVID-19 (linked to any respiratory disease and linked to any molecularly confirmed COVID-19) not previously described, as compared to placebo by first occurrence of potential complications of COVID-19 linked to any respiratory disease and linked to any molecularly confirmed COVID-19, with onset at least 14 days and at least 28 days after double-blind vaccination with study vaccine the proportion of participants will be tabulated and the VE as described in appendix 8 will be computed for the vaccine versus placebo with an associated 95% CI. If possible the impact of age group and comorbidities (as defined by the CDC, section 6.7) will be investigated.

For the assessment of the effect of Ad26.COV2.S on all-cause mortality, as compared to placebo by deaths occurring at least 14 days and at least 28 days after double-blind vaccination with study vaccine, the proportion of participants will be tabulated and the VE as described in appendix 8 will be computed for the vaccine versus placebo with an associated 95% confidence interval. If possible the impact of age group and comorbidities (as defined by the CDC, section 6.7) and age group will be explored. All-cause deaths occurring will be summarized by Kaplan-Meier method, and KM plot will be provided. In addition, summary will be provided for COVID-19 related deaths versus other reasons.

For the evaluation of the immune response in participants with COVID-19 in relation to risk of development of COVID-19, protection induced by Ad26.COV2.S, and risk of accelerated disease by assessment of the correlation of humoral immune responses with emphasis on neutralizing, binding and functional antibodies, as well as gene transcript profiling (RNA sequencing), with the risk of COVID-19 and protection induced by the study vaccine participants with a COVID-19 episode immunogenicity data will be tabulated by vaccine regimen at baseline, 28 days post double-blind vaccination, on COVID-19 Day 3-5 and on COVID-19 Day 29 for the standard immunogenicity assays (S-ELISA and VNA) and on COVID-19 Day 3-5 and on COVID-19 Day 29 for all other assays that are available (Table 9). Immunogenicity data will be graphically displayed by vaccine regimen where actual values are shown as dot plots with dots for participant values, and the corresponding geometric mean and 95% CI per time point for each assay. Correlates will be assessed in a subset where immune responses and transcriptome modifications are measured in all vaccine recipients who experience a SARS-CoV-2 event, and in random samples of vaccine recipients who have not been infected. These analyses will be described in a separate correlates SAP for this purpose.

For the assessment of the humoral immune response to Ad26.COV2.S, as compared to placebo for functional and molecular antibody characterization including, but not limited to avidity, Fc-mediated viral clearance, Fc characteristics, Ig subclass, IgG isotype, antibody glycosylation, and assessment of antibody repertoire, adenovirus neutralization as measured by VNA and analysis of antibodies to the receptor-binding domain (RBD) of the SARS-CoV-2 S protein refer to section 5.8.1.

Changes in the SARS-CoV-2 genome are focused at analyses of the S protein sequence. The presence of predefined viral variants will be tabulated. Further detail on vaccine efficacy by viral variant is described in section 5.8.2.6. Sequence analyses will be reported in a separate report.Time to resolution of COVID-19 episodes will be described for participants in the Ad26.COV2.S and placebo groups, using the Kaplan-Meier methodology, and if applicable compared with a logrank test.

For the medical intervention endpoint, a descriptive summary will be provided by type of intervention (as indicated by the adjudicators). A severity adjusted analysis will be done on the medical intervention endpoint (mechanical ventilation and ECMO, ICU, hospitalization).

A frailty index will be calculated at baseline and during the study at certain timepoints. The frailty index will be assessed in participants who received Ad26.COV2.S as compared to placebo.

The concordance between PCR results at an individual level as well as case level from various labs will be compared. For subjects with a PCR+ test result, a comparison will be done versus the subsequent serological result and the time to detect antibody levels since the positive PCR.

5.6.1.3. Vaccine efficacy on symptoms and reduction of severity

The analysis on whether the vaccine will reduce the severity of COVID-19 once participants are infected compared to placebo will be examined in 3 parts: reduction of severity based on case definitions, reduction of severity of any symptoms and reduction of lingering of symptoms. In a separate section the relation between viral load and symptom reduction and pattern will characterized.

Based on case definitions

To assess whether there is a shift in severity of cases between the vaccine group and the placebo group a proportional odds model will be applied with associated p-value and confidence interval. The different severities of cases going from asymptomatic, mild, moderate to severe (further subcategories can be defined) are the ordinal categories used in the analysis. Barchat plots are used to present the shift in severity of cases between vaccinations groups

Additionally to the BOD model described above, a Burden of infection model (BOI) may be explored. In this analysis, asymptomatic cases, mild, moderate and severe cases are considered. A weighted-adjusted analysis for more severe cases will be implemented as 0 for asymptomatic, 1 for mild, 2 for moderate and 3 for severe cases.

Furthermore, analyses will be done that evaluates how many signs/symptoms as part of the definition were met during the episode. This will be graphically compared between randomized groups by severity (mild, moderate, severe). To investigate if vaccinated subjects experience less symptoms as part of the definition of a severe case and separately of a moderate case compared to placebo, VEs will be calculated by number of symptoms met as part of that definition. Further exploration of the moderate cases will be done to possibly identify subcategories (less severe moderate cases versus more severe moderate cases) using the number of symptoms reported as

part of the definition, the severity grade of the symptoms reported and the tier definitions as used for the adjudications (see Charter). This further exploration will be done to characterize the distribution of symptoms and severity among all moderate cases, and will be compared between vaccination groups.

Based on any symptoms

To evaluate if the vaccine induces a reduction of severity, the patient-reported outcomes (PROs) in relation to the presence of SARS-CoV-2 infection across case definitions are investigated. The presence, severity and duration of COVID-19 signs and symptoms are captured in multiple scores and statistics as described in section 5.8.4 and are compared for subjects with a SARS-CoV-2 infection between the vaccine group and the placebo group. Mean differences of scores and statistics are tabulated as well as graphically presented. Additionally, examination of the severity of symptoms over time will be done graphically by presenting symptom scores over time and will be used to explore differences in severity profiles over time between vaccination groups. A Markov multistate chain analysis on the severity changes over time may be applied to compare between vaccinated and placebo group with an associated p-value and confidence intervals .

Furthermore an analysis of the composite scores of the PROs will be done to possibly depict stronger reduction of severity of certain specific domains of symptoms for vaccinated subjects versus placebo subjects.

Lingering of symptoms

Time to resolution of symptoms will be presented by a Kaplan-Meier curve for participants in the Ad26-CoV-2 and placebo groups and will be compared with a log rank test with associated p-value and confidence interval if applicable. This analysis will be supplemented by time to resolution of domain specific symptoms using the composite scores as described in section 5.8.4

Relation between viral load and symptom reduction and pattern

Furthermore the association between viral load and symptoms may be explored graphically as well as via longitudinal modeling, at an individual level and a population level

5.6.1.4. Vaccine efficacy by variant

Upon availability of viral genome sequencing data for molecularly confirmed COVID-19 cases and upon the condition that the proportion of sequenced cases is comparable between the active group and the placebo group, vaccine efficacy for the efficacy endpoints defined in section 5.4 and section 0 above will be evaluated by variant (as defined in section 5.8.2.6.) as well as those with no variant of interest.

For each efficacy endpoint and each variant the following analysis will be done:

Endpoints identified with a specific variant will be included in the analysis. Subjects with an endpoint for which the variant is missing or identified to be different, are not included as a case. Their follow-up time is included up to the onset of the case with the missing or other variant.

The time to onset of the first occurrence of molecularly confirmed COVID-19 for a given variant will be graphically summarized using Kaplan-Meier methods for each group by variant, by variant within a country. Vaccine Efficacy (*VE*) and the associated confidence interval will be calculating according to the methodology as explained in Appendix 8. If less than 6 cases observed for a given variant, or for a given variant within a country, no VE calculation will be done and the numbers only tabulated.

The above analysis will be repeated by country. The analysis will be done based on cases with onset after Day 14 after double-blind vaccination (PP-set, seronegative subjects), on cases with onset after Day 28 after double-blind vaccination (PP-set, seronegative subjects) and cases with onset after Day 1 double-blind vaccination (full-analysis set).

The analysis will be repeated regardless of serostatus.

5.7. (Other) Safety Analyses

Following information will be collected for:

Participants in the Safety Subset:

- Solicited local and systemic adverse events (AEs) for 7 days after double-blind vaccination
- Unsolicited AEs for 28 days after double-blind vaccination

All participants in the FAS during the entire study:

- Serious adverse events (SAEs) and MAAEs leading to study discontinuation after vaccination
- AESI (AE of Special Interest)

All participants in the FAS during the first 6 months:

- Medically-attended adverse events (MAAEs) after vaccination

Safety analyses will be performed on the FAS. No formal statistical testing of safety data is planned. Safety data by double-blind vaccination group will be analyzed descriptively. Specific safety analyses will be performed on the Safety Subset. All safety analyses will be tabulated by treatment group (active vaccine, placebo) according to the as-treated principle. All safety analyses will be presented overall and by age and comorbidity (with/without) strata. The main age strata for reporting purposes are ≥18 to <60 years of age and ≥60 years of age. In addition, safety data will be analyzed by treatment group and participant seropositivity status at screening.

For the double-blind phase, the safety data up to the unblinding date will be presented separately for the Ad26.Cov 2 double-blind group and the placebo double-blind group (Analysis I). Safety data after the unblinding date but before the open label vaccination date are listed separately.

Additionally, safety data will be pooled for all subjects that received Ad26.Cov 2 (in the double blind phase or in the open label phase) from the start of their Ad26.Cov 2 vaccination to the end of the trial (Analysis II): unsolicited AEs up to day 28, SAEs and MAAEs leading to discontinuation during the entire study, MAAEs until 6 months after last vaccination, AEs of special interest and AEs of interest during the entire study. All tables will be presented by phase.

The safety data from subjects that were unblinded and who received a vaccine outside the study will be tabulated separately.

Subjects that took another COVID-19 vaccine before being unblinded are excluded from the safety tables from the moment they received the other vaccine. The safety data from those subjects after they received the other vaccine are listed separately.

Denominator for the percentages is the number of participants in the considered population and phase for a certain regimen (incidence per 100 participants/phase).

Continuous variables will be summarized using the following statistics, as appropriate: number of observations, arithmetic mean (mean), 95% CI for the mean, standard deviation (SD), median, quartiles (Q1 and Q3), minimum and maximum. Frequencies and percentages (one decimal place) will be generated for categorical variables. No formal comparisons between groups will be provided.

Other exploratory or sensitivity analyses may be performed in addition to the analyses described below on an ad-hoc basis.

5.7.1. Adverse Events

5.7.1.1. Definitions

Solicited AEs are used to assess the reactogenicity of the study vaccine and are predefined local (at the injection site) and systemic events for which the participant is specifically questioned, and which are noted by participants in their diary. Unsolicited AEs are all AEs for which the participant is not specifically questioned.

Solicited AEs shown in the tables are extracted from the investigator assessment pages (CE) of the CRF (Safety Subset). For unsolicited AEs, only the AEs within the 28-day period following the double-blind vaccination will be presented in the safety tables (Safety Subset), except for SAEs, MAAEs leading to study discontinuation and AESIs, which will be captured and tabulated in the outputs covering the whole study period and for all subjects in the FAS, and MAAEs (including new onset of chronic diseases) which will be captured and tabulated in the outputs covering the 6 month post double-blind vaccination period (Phases: Post-dose, Follow-up (D30-M6), and Follow-up (M6-W52)) and for all subjects in the FAS.

Solicited administration site symptoms will be by definition considered as related to the study vaccine.

The severity of the AEs will be classified as grade 1 to 4. Solicited events that are graded less than grade 1, are not considered as AE. In case no grades are available, the grading of the solicited events will occur according to the grading list in Appendix 6.

5.7.1.2. Analysis of Adverse Events

Number and percentage of participants with at least one particular AE (unsolicited/solicited) will be tabulated with exact 95% CI, when appropriate. Unsolicited AEs will be summarized by System Organ Class and Preferred Term. Solicited AEs will be summarized by class (administration site, systemic) and preferred term.

For solicited AEs 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 (>5%) 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 double-blind vaccination period.

For unsolicited AEs following tables will be provided: summary table (including SAE, MAAEs, MAAEs leading to study discontinuation, fatal outcome, and discontinuation), all events, most frequent (>5%), at least grade 3, related and SAE. The proportion of AEs resulting in a medically attended visit (other than routine health maintenance visits) will also be tabulated.

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

5.7.1.3. 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 data base 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:

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.

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 data base 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.

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 data base 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.

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.

In case the completely missing end date is imputed (for period allocation), this date is also considered as a complete date.

Time is not considered when determining overlap of events.

5.7.1.4. Missing Data

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

5.7.2. Vital Signs

No ECG are measured in this study. For HIV Viral Load and CD4 counts only abnormalities emerging after double-blind vaccination will be tabulated by worst abnormality grade using the following gradings (absolute CD4+ Count: 300 – 400/mm3 (grade 1); 200 – 299/mm3 (grade 2)

100 – 199/mm3 (grade 3) and < 100/mm3 (grade 4) and for viral load when a subject goes from undetectable to detectable HIV RNA copies/mL.

For all participants, weight and height (and BMI) at baseline will be summarized using descriptive statistics. Vital sign abnormalities emerging after double-blind vaccination may be tabulated/listed by worst abnormality grade using the FDA grading table in Appendix 6.

Temperature will be measured at each scheduled time point and summarized using descriptive statistics. A listing of participants with fever will be provided. Other vital signs may be measured at the discretion of the investigator. For those, vital signs abnormalities of at least grade 3 will be listed.

For COVID-19 cases, temperature will be summarized over time from start of symptoms, using descriptive statistics and/or graphically. Temperature and oxygen saturation will be summarized separately for the measures by the participants as well as by the site. For temperature, systolic and diastolic blood pressure, heart rate, respiratory rate, oxygen saturation, and pulse oximetry, values and the percentage of participants with values beyond clinically relevant limits will be summarized at each scheduled time point. Descriptive statistics will be calculated for changes between COVID-19 Day 29 and COVID-19 Day 3-5 for vital signs that were captured by the site. The schedule for COVID-19 cases will start for each participant on Day 1 of a COVID-19 Episode, will be on a daily basis and take the maximum of the values recorded for each subject per day.

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. In case a laboratory test result is censored (no numeric value is available, but only a verbatim term) then 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).

Note: as the grading scale for some parameters in the grading table has some gaps (zones where no toxicity grade definition exists), results falling in these zones will be allocated to the adjacent worst-case grade (cf Appendix 9 of the CTP).

5.8. Other Analyses

5.8.1. Reactogenicity

For all participants in the safety subset the diary data will be summarized descriptively by treatment group. Temperature will be summarized using the maximum of the recorded temperature per subject by study day, and summarizing incidences of fever using the highest grade of fever observed for each subject using the grading system in Appendix 6. The same approach will be taken for the maximum size of any swelling. All symptoms will be summarized taking the worst grading as captured by the investigator at the Day 28 visit. For all symptoms also incidences of worst gradings will be summarized by Day comparing treatment groups.

5.8.2. Immunogenicity

Blood will be collected from all non-Immuno Subset participants for humoral immunogenicity assessments before double-blind vaccination, 28 days after double-blind vaccination and at D71, W24 and W782 after double-blind vaccination. For a total of approximately 400 participants in the Immuno Subset, blood will be collected for analysis of humoral immune responses before double-blind vaccination, 28 days after double-blind vaccination, 70 days after double-blind vaccination, and 24, 52, 78, and 104 weeks after double-blind vaccination.

During a COVID-19 episode, blood will be collected on COVID-19 Day 3-5 and on COVID-19 Day 29 for immunogenicity assessments, including the assays summarized in Table 9.

Table 9 Immunogenicity and Transcriptomic Assessments

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

Ad26 = adenovirus type 26; ELISA = enzyme-linked immunosorbent assay; Fc = crystallizable fragment; Ig(G) = immunoglobulin (G); MSD = Meso Scale Discovery; N = nucleocapsid; RBD = receptor-binding domain; RNA = ribonucleic acid; S = spike; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; VNA = virus neutralization assay.

The analysis of immunogenicity will use the PPI set.

For the non-immuno subset, humoral immunogenicity data will be analyzed according to the as-treated principle by vaccine regimen (active vaccine, placebo), by vaccine regimen and participant seropositivity status at screening and by vaccine regimen and COVID-19 (no infection, asymptomatic infection, mild, at least mild, at least moderate, at least severe) and by vaccine regimen and age and

comorbidity (with/without) strata, by vaccine regimen and country/region, by vaccine regimen and emerging CD4 count abnormality (at least grade 1 at any time after double-blind vaccination) and viral load (treatment emergent detectable viral load). Specific immunogenicity analyses will be performed on the Immuno Subset. All immunogenicity analyses for the immuno subset will be analyzed by vaccine regimen and by vaccine regimen and age and comorbidity (with/without) strata.

At the time of primary analysis, partially available immunogenicity data are summarized. Analysis will be updated when complete data available.

For participants with a COVID-19 episode immunogenicity data will be analyzed by vaccine regimen at baseline, 28 days post double-blind vaccination, on COVID-19 Day 3-5 and on COVID-19 Day 29 for the standard immunogenicity assays (S-ELISA and VNA) and on COVID-19 Day 3-5 and on COVID-19 Day 29 for all other assays that are available (Table 6).

Correlates will be assessed in a subset where immune responses and transcriptome modifications are measured in all vaccine recipients who experience a SARS-CoV-2 event, and in random samples of vaccine recipients who have not been infected. These analyses will be described in a separate correlates SAP.

In addition to viral neutralization, humoral vaccine-elicited responses correlating with protection may further include functional mechanisms mediated by the fragment crystallizable (Fc)-domain of the antibody. Those include antibody-mediated cellular phagocytosis or killing, complement deposition or cellular activation mediated by Fc-receptors. Based on the available samples, these antigen-specific functionalities may be investigated by biophysical characterization using a multiplexed array and a series of functional assays commonly referred to as a systems serology approach. Further, the contribution of innate or inflammatory responses may be investigated through transcriptional profiling by RNA sequencing. Details of these analyses will be described in a separate SAP.

5.8.2.1. Parameters

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

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

Missing immune response data will not be imputed.

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

Data above the ULOQ will be imputed with the ULOQ.

5.8.2.3. Immune Response Analysis

No formal hypothesis on immunogenicity will be tested.

5.8.2.4. Immunogenicity Against the Insert:

5.8.2.4.1. Humoral assays

For **VNA (**both wild-type virus and pseudovirion expressing S protein, as available) and **S-ELISA** assays following results will be calculated: N, geometric mean[a]and corresponding 95% CI of the actual values and fold increases from baseline will be tabulated and graphically presented.

For the calculation of the geometric mean and its corresponding 95% CI, the arithmetic mean and its corresponding 95% CI are calculated on the log10 transformed values. These values are back transformed to provide the geometric mean and its corresponding 95% CI.

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

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

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

- The baseline sample value is less than or equal to the LLOQ (≤LLOQ) and the post-baseline sample is strictly greater than the LLOQ (>LLOQ)

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

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

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

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

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

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

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

Further details may be provided in the DPS.

For the **N-ELISA** the proportion of participants that are positive will be tabulated.

5.8.2.5. Immunogenicity Against the Vector

For immunogenicity against the Ad26 vector backbone (Adenovirus neutralization by neutralization assay) 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.

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

5.8.2.6. 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.

Parameters to Analyze

The following parameters will be analyzed:

Number (%) of participants with a SARS-CoV-2 variant with a specific substitution ("amino acid level", see below).

Number (%) of participants with a SARS-CoV-2 variant with a specific substitution profile ("variants", see below)

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):

- B.1.1.7 – Alpha - H69del,V70del,Y144del,N501Y,A570D,D614G,P681H,T716I,S982A,D1118H·
- B.1.351 – Beta – K417N,E484K,N501Y,D614G, A701V
- B.1.617.2/AY.1/AY.2 – Delta – L452R,T478K,D614G,P681R·
- B.1.427/429 – Epsilon – W152C,L452R,D614G·
- B.1.525 - Eta - A67V,H69del,V70del,Y144del,E484K,D614G,Q677H,F888L·
- P.1 – Gamma - K417T,E484K,N501Y,D614G,H655Y·
- B.1.526 – Iota - L5F,T95I,D253G,D614G,E484K, A701V·
- B.1.617.1 – Kappa - G142D,E154K,L452R,E484Q,D614G,P681R·
- C.37 – Lambda - R246del,S247del,Y248del,L249del,T250del,P251del,G252del,D253N,L452Q,F490S,D614G,T859N·
- P.3 – Theta - L141del,G142del,V143del,A243del,L244del,E484K,N501Y,D614G,P681H,E1092K,H1101Y,V1176F
- P.2 – Zeta - E484K,D614G,V1176F (and not P.1, not P.3)·
- B.1.621 - T95I,Y144T,Y145S,ins145N,R346K,E484K,N501Y,D614G,P681H,D950N·
- C.36.3 - W152R,R346S,L452R,D614G,Q677H,A899S·
- R.1 - W152L,E484K,D614G,G769V·
- B.1.1.519 - T478K, D614G,P681H,T732A
- B.1/B.1.2/B.1.1/B.1.1.214 - D614G (not any other variant)

Additional variants may be added depending upon the epidemiology of SARS-CoV-2 infection.

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. Summaries will be provided by subgroup and intervention arm.

5.8.3. Definition of Subgroups

Selected safety and efficacy analyses will be summarized by treatment group for the following subgroups:

- sex
- race
- ethnicity
- age categories 1 (18-≤59, ≥60years)
- age categories 2 (18-<40, 40-≤59, ≥60 years)
- age categories 3 (18-<40, 40-≤59, 60-≤69, 70-≤79, ≥80 years)
- age categories 4 (18-≤64, ≥65years)
- age categories 5 (≥75years)
- country
- region (South-Africa, US, Latin-America, Europe (if applicable), Asia (if applicable)). Regions may be modified/pooled based on participation.
- presence of baseline comorbidity
- baseline seropositivity status (positive vs. negative)
- frailty index (frail, pre-frail, non-frail, unknown, see appendix 6.9)
- in subjects with a baseline PCR+ test result (Day 1)
- in subject with a baseline PCR+ test result (Day 1) OR are baseline seropositive
- baseline VNA Ad26. Status (responder/nonresponder)

If necessary, for country approval/submission, an analysis by country or country*subgroup interactions may be added.

5.8.4. Patient-Reported Outcomes

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

The SIC is a disease-specific patient-reported outcome (PRO) instrument that is completed by the participant, self-administered. The SIC has a total of 30 items assessing signs and symptoms of COVID-19. The first 25 items, the participant indicates “yes” or “no” if they have a symptom and if “yes” report a severity from 0 (none) to 10 (worst possible). The second part has the participant enter their temperature, and the third part has the participant record “yes” or “no” (absence or presence of additional signs and symptoms). The analyses are conducted in two ways, by part 1, part 2 and part 3, scored separately, and also grouped into related categories for composite scoring :

SIC Analysis Approach One:

- Part 1 (25 symptoms): Each symptom is present or absent (0), and if present rated on a 10 point scale 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 AUC** is the area under the curve for the complete COVID-19 episode.

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

- Part 2: Fever/ temperature.

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

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

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

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

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

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

SIC Analysis Approach Two: Composite Scoring

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

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

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

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

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

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

Musculoskeletal = average of (M1, M2, M3)

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

Neurological = average of (N1, N2, N3)

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

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

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

= 10 if YES to both items

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

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

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

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

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

For each composite the following analysis will be conducted:

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

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

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

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

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

5.8.4.2. Analysis Methods

SIC scores will be analyzed for participants with any COVID-19 episode based on the PP set.

For continuous variables, number of observations, mean, standard deviation, median, first and third interquartile will be tabulated and means with standard errors will be graphically presented per vaccine regimen and means with standard errors per group and time point (starts since onset of COVID-19 episode). Counts will be tabulated.

These analyses will also be summarized by COVID-19 for each classification (mild, moderate, severe-critical cases) and additionally in a cumulative fashion (at least mild, at least moderate, and all symptomatic cases).

Subgroup analysis may be explored.

5.9. Interim Analyses

Interim analyses are performed in the form of continuous monitoring and are provided in Table 10. No other interim analyses are planned.

Table 10 Specification of Sequential Statistical Analyses

Parameter	Population	Hypothesis	Statistical Method	Criterion	Monitoring Plan
Potential Harm[a] of Symptomatic Cases	FAS	H_0: VE ≥0% vs. H_1: VE < 0%	Exact 1-sided binomial test of the fraction of infections assigned to receive the vaccine.	Constant p-value cut-off controlling α at 5%	After every event starting from the 12th event[b]
Potential Harm[a] of Severe Cases	FAS	H_0: VE ≥0% vs. H_1: VE <0%	Exact 1-sided binomial test of the fraction of infections assigned to receive the vaccine.	one-sided p-value compared to α at 5%, no multiplicity adjustment	After every event starting from the 5th event
Non-efficacy	PP	H_0: VE ≥40% vs. H_1: VE <40%	Exact 95% CI	Upper limit of the 95%CI <40%	Every week, starting from the 20th event after 14 days post dose 1 (Day 15)[b]
Efficacy[c]	PP	H_0: VE ≤30% vs. H_1: VE >30%	Sequential probability ratio test	Controlling the family- wise error rate α at 2.5%	Starting from the 42nd event 14 days post dose 1 are observed, **then at least weekly thereafter**[c]
Efficacy[c]	PP	H_0: VE ≤30% vs. H_1: VE >30%	Sequential probability ratio test	Controlling the family- wise error rate α at 2.5%	Starting from the 42nd event 28 days post dose 1 are observed, **then at least weekly thereafter**[c]

CI = confidence interval; FAS = full analysis set; PP = per protocol; VE = vaccine efficacy.

[a] Harm in the form of an increased rate of symptomatic COVID-19 events due to vaccination.

[b] Monitoring stops when the primary efficacy analysis is triggered.

[c] The monitoring can only start as soon as the conditions outlined in Section 5.4.1 are met.

All boundaries will be monitored by the Statistical Support Group (SSG). If a boundary has been crossed, then the SSG immediately informs the Chair of the DSMB through secure communication procedures. At this point the DSMB will convene, evaluate the totality of the data and provide a recommendation to the Sponsor.

The study team is responsible for providing the blinded information to the SSG. For relevant definitions regarding a case assignment, see Section 5.2.

5.9.1. Assigning cases for continuous monitoring

Definitions and general case assignment rules are described in Section 5.2.

For continuous monitoring the order of cases will be based on the *onset of symptoms*. An episode of COVID-19 may however start with mild symptoms and may deteriorate to a degree that it satisfies a more severe classification. To avoid situations that an event occurs that already should have been analyzed as based on the onset of symptoms, the approach chosen here is that each case will be analysis-ready at the latest at **Day 15** (see also CTP Section 8.1).

For this approach it is of concern if an event is not resolved at Day 15, AND if that event worsens in severity after analysis-ready status. In the rare case that this happens AND affects one of the 4 monitoring processes, the case will be added to the first upcoming monitoring analysis based on the moment it is established that it satisfies a more severe definition.

Continuous monitoring will be performed on analysis-ready cases known up to that and including that calendar Day; if multiple cases are analysis-ready on a Day, the boundary will be verified for the total number of cases.

For the monitoring of potential severe harm, the event will be entered in the monitoring as soon as the events becomes confirmed as satisfying the severe/critical case definition (from Amendment 5 of the SAP, only severe/critical cases as adjudicated by the Clinical Severity Adjudication Committee will be used in the severe harm monitoring).

The period to define analysis ready- for an episode of COVID-19 to take its course is chosen as it is expected to have limited impact on case classification, and it also allows to assess critical information that is required to determine if the case is part of a continuous monitoring process (and how it should be entered):

- Was the participant included in the FAS? (Note that this means that the participant was randomized and treated.)
- Was the participant treated with the assigned treatment? (Note that if not, the participant would be analyzed *as treated* in the FAS and excluded from the PP population.)
- Was the volume of the injection sufficient (≥80%) according to the drug administration log?
- Was the participant seronegative at baseline?
- Was the participant part of the PP population (see Section 4)?
- Was the onset of symptoms after double-blind vaccination (Day 2 or later)?
- Was the onset of symptoms after Day 14 (Day 15 or later) or Day 28 (Day 29 or later)?

5.9.2. Harm monitoring for excess symptomatic COVID-19 cases

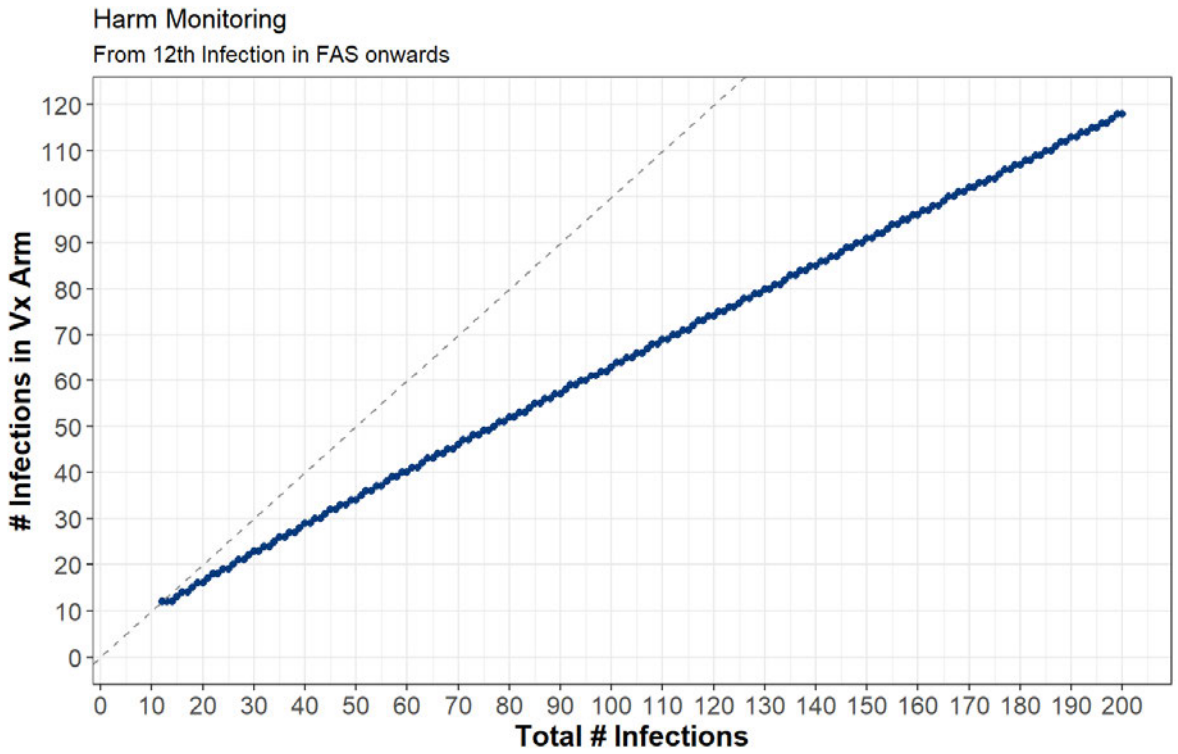
Continuous monitoring for vaccine-associated *enhanced* COVID-19 will be performed based on *symptomatic* COVID-19 events in the FAS population. Only cases where the onset of symptoms is on Day 2 or later will be included. Monitoring for harm will be performed on a daily basis on analysis-ready cases only.

The monitoring starts when there are in total 12 analysis-ready symptomatic cases observed and will continue to be monitored on each calendar day until the primary analysis is triggered. In order to calculate the boundaries for this monitoring while controlling overall alpha level as specified (i.e. 5% overall alpha) an assumption must be made on maximum number of looks that will have to be made. For this purpose, it is assumed that there will be a maximum of 200 symptomatic cases in the FAS before the primary analysis is triggered. This leads to the following boundaries on the number of events in the placebo treatment group for each total number of events. Starting at 12 analysis-ready cases, the boundary is crossed if there are 0 or 1 analysis-ready cases on placebo and all other cases are on active treatment. If there are 2 analysis-ready cases on placebo, the boundary is crossed if the total is 14 cases (i.e., 12 on active), etcetera (Table 11). The boundary is illustrated graphically in Figure 4.

Table 11 The number of Symptomatic Cases on Placebo and Total number of Symptomatic Cases at which Point the Boundary is Crossed (FAS)

Placebo	Total	Placebo	Total	Placebo	Total	Placebo	Total
≤1	12	22	65	43	113	64	160
2	14	23	67	44	115	65	162
3	17	24	69	45	118	66	164
4	20	25	72	46	120	67	167
5	23	26	74	47	122	68	169
6	25	27	76	48	124	69	171
7	28	28	79	49	127	70	173
8	31	29	81	50	129	71	175
9	33	30	83	51	131	72	178
10	36	31	86	52	133	73	180
11	38	32	88	53	136	74	182
12	41	33	90	54	138	75	184
13	43	34	93	55	140	76	186
14	46	35	95	56	142	77	189
15	48	36	97	57	144	78	191
16	50	37	99	58	147	79	193
17	53	38	102	59	149	80	195
18	55	39	104	60	151	81	197
19	58	40	106	61	153	82	200
20	60	41	109	62	156		
21	62	42	111	63	158		

Figure 4 Harm Monitoring Boundary - Active versus Total Number of Symptomatic Cases (FAS)



5.9.3. Harm monitoring for excess severe COVID-19 cases

Vaccine harm monitoring is intended to monitor for vaccine-induced enhanced disease and will be performed for severe/critical COVID-19 cases based on the FAS each calendar day. Specifically, monitoring for a higher rate of severe/critical disease or death starts at the 5th event, until the harm boundary is reached, or until the primary efficacy analysis is triggered. Monitoring for harm of severe/critical COVID-19 cases will be performed on a daily basis on all available severe cases, irrespective of their analysis ready status. (from Amendment 5 of the SAP, only severe/critical cases as adjudicated by the Clinical Severity Adjudication Committee will be used in the severe harm monitoring).

The monitoring excess severe is done using an exact one-sided binomial test of the null hypothesis $H_0: p \leq 1/2$ versus the alternative hypothesis $H_1: p > 1/2$, where p is the probability that an -infected participant was assigned to the vaccine arm (as opposed to being assigned to the placebo arm). The testing for harm starts at the 5th total severe cases in the FAS and is performed continuously through the primary analysis. Each test is performed at an uncorrected one-sided significance level of $\alpha = 0.05$.

5.9.4. Non-efficacy monitoring

The non-efficacy monitoring is based on analysis-ready moderate/severe cases in the FAS, where a participant must be seronegative at baseline to be included in this boundary monitoring. Every effort will be made to establish seronegativity in time. In the unlikely case seronegativity is not

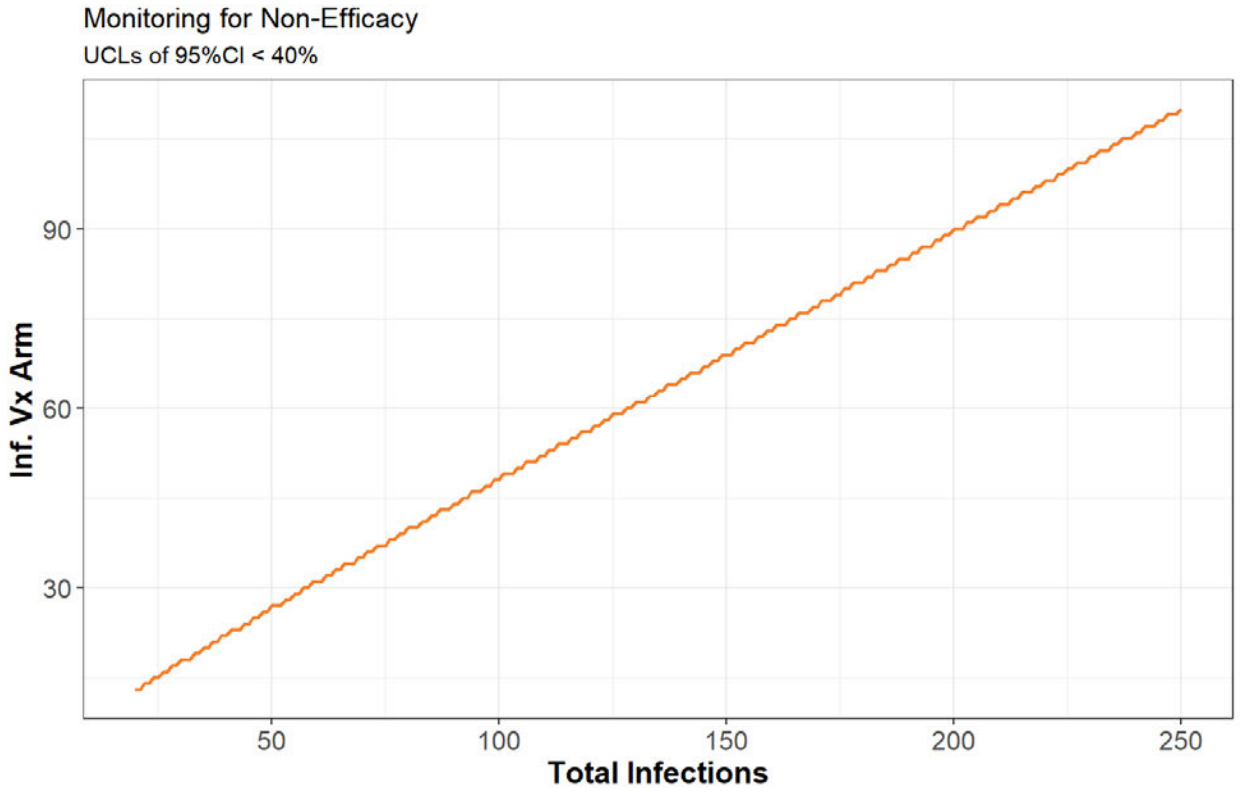
established in time for a case that is to be included in a monitoring calculation otherwise (ie, on Day 14 of an episode), the case will only be included for non-efficacy monitoring at the time seronegativity is established; monitoring calculations will not be repeated at that time.

This boundary will be verified starting once 20 analysis-ready moderate/severe cases in the FAS (seropositive) are observed. From that point onwards, after at least weekly, the boundary will be checked on analysis-ready cases. Monitoring for non-efficacy stops when the primary analysis is triggered. The boundary to be used for non-efficacy is provided in Table 12 and illustrated in Figure 5 , and is based on the case splits that trigger the rules as defined in Table 10 using the methods laid out in Appendix 8 with the exact binomial based confidence intervals.

Table 12 The Number of Confirmed Moderate/Severe Cases on Placebo and Total Number of Confirmed Moderate/Severe Cases at which Point the Non-efficacy Boundary has been Crossed (FAS – seronegative)

Placebo	Total	Placebo	Total	Placebo	Total	Placebo	Total
≤7	20	27	56	47	91	67	126
8	21	28	58	48	93	68	127
9	23	29	60	49	95	69	129
10	25	30	61	50	96	70	131
11	27	31	63	51	98	71	132
12	29	32	65	52	100	72	134
13	31	33	67	53	102	73	136
14	32	34	68	54	103	74	138
15	34	35	70	55	105	75	139
16	36	36	72	56	107	76	141
17	38	37	74	57	108	77	143
18	40	38	75	58	110	78	144
19	42	39	77	59	112	79	146
20	43	40	79	60	114	80	148
21	45	41	81	61	115	81	150
22	47	42	82	62	117	82	151
23	49	43	84	63	119	83	153
24	51	44	86	64	120	84	155
25	52	45	88	65	122	85	156
26	54	46	89	66	124	86	158

Figure 5 Boundary for Non-Efficacy (FAS, seronegative)



5.9.5. Efficacy monitoring

As the efficacy monitoring is linked to the co-primary endpoints, the statistical details on efficacy monitoring are already described in the corresponding section, section 5.4.

Table 13 describes the number of analysis-ready co-primary endpoints required as a fraction of the total number of cases in order to stop and reject the primary study hypotheses, and is illustrated in Figure 6.

If the prespecified boundary is met for both co-primary endpoints in the situation that the constraints have also been met (a minimum of 42 molecularly confirmed, moderate to severe/critical COVID-19 cases including 6 in the population of participants aged 60 years or older with onset at least 28 days after double-blind vaccination, a minimum of 5 of molecularly confirmed severe/critical COVID-19 cases in the placebo group with onset at least 28 days after double-blind vaccination with a favorable split for both co-primary endpoints), the SSG will inform the DSMB and, if deemed appropriate by the DSMB, a meeting with the DSMB and the Sponsor Committee will be set up to discuss the efficacy signal. Upon this meeting the Sponsor Committee can trigger internal decision procedures to initiate health authority interactions based on the outcome of the study. If deemed appropriate based on the data, the Sponsor Committee will send the reviewed data package to a designated unblinded team independent of the study team (including a clinician, a statistician, a statistical programmer, and a regulatory person) through a secured medium, who will ensure the complete package meets the requirements for a regulatory interaction and is subsequently transmitted securely to the appropriate regulatory agency. The

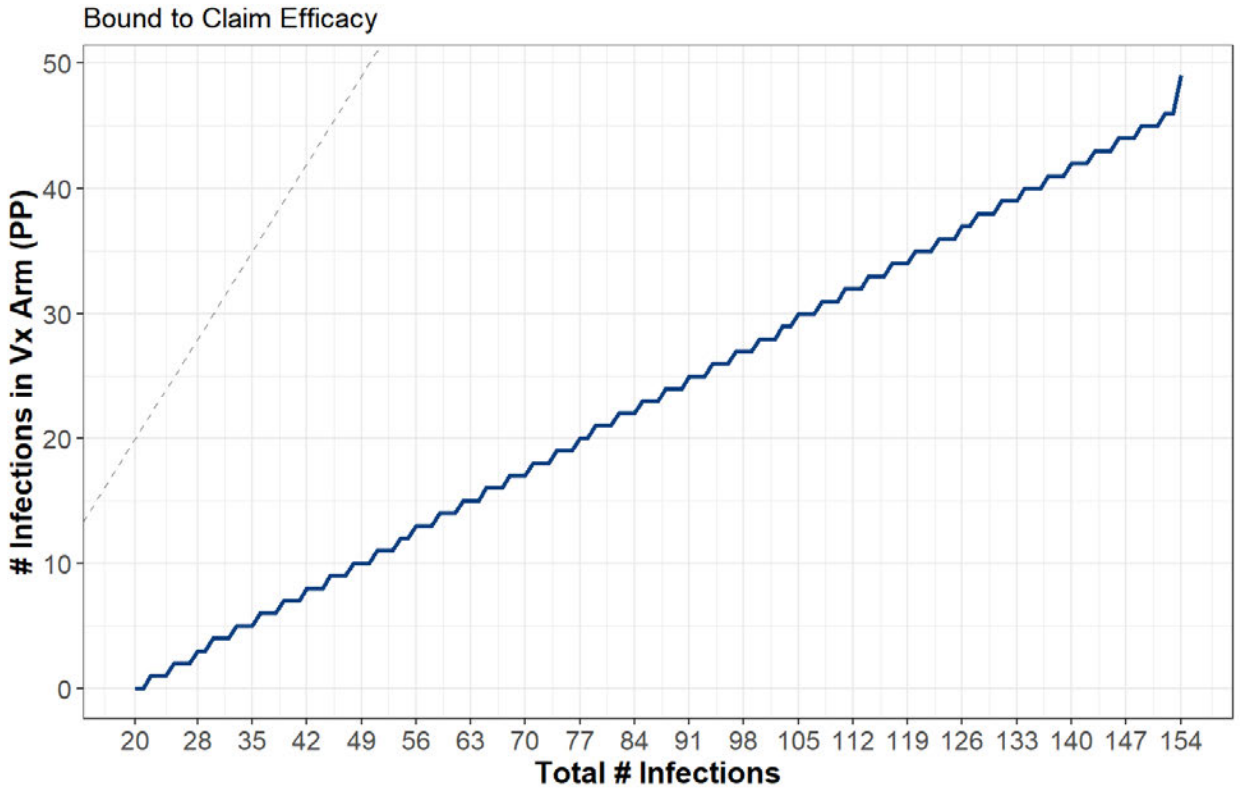
sponsor will remain blinded until the data base for the primary analysis is locked or until the time of the snapshot analysis.

Table 13 The Number of Confirmed Moderate/severe Cases on Active and Total Number of Confirmed Moderate/severe Cases at which Point the Efficacy Boundary has been Crossed (PP)

Active	Total	Active	Total	Active	Total
0	20	16	65	32	111
1	22	17	68	33	114
2	25	18	71	34	117
3	28	19	74	35	120
4	30	20	77	36	123
5	33	21	79	37	126
6	36	22	82	38	128
7	39	23	85	39	131
8	42	24	88	40	134
9	45	25	91	41	137
10	48	26	94	42	140
11	51	27	97	43	143
12	54	28	100	44	146
13	56	29	103	45	149
14	59	30	105	46	152
15	62	31	108	49	154

The blinded total number of infections in the FAS with onset of infection after study double-blind vaccination may be monitored to track progress and ensure timely cleaning to facilitate operationalization of data base lock.

Figure 6 Boundary for Efficacy (PP)



5.9.6. Sample size monitoring

The incidence of moderate to severe COVID-19 seen in the US and reported in other COVID-19 vaccine trials is significantly higher than assumed at the time of protocol planning. Furthermore, based on that incidence and modeling there is a high degree of probability that a signal of efficacy meeting the prespecified criteria in the protocol amendment 3 will be reached at or prior to the time when 50% of participants will have been followed for 8 weeks from the time of immunization, therefore the sample size was reduced from 60,000 to approximately 40,000.

5.9.7. Data and Safety Monitoring Board (DSMB)

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

The DSMB will also review Day 3 safety data (ie, from Day 1 to Day 3; including safety data from the ongoing clinical studies) from participants enrolled in Stage 1a and Stage 2a, before enrollment of participants in Stage 1b and Stage 2b is initiated, respectively. Vaccination of participants in the respective age groups will be paused during these safety reviews.

Continuous monitoring of safety and (non-) efficacy is described in detail in Section 5. If a boundary is met, the SSG immediately informs the DSMB through secure communication procedures. At this point a quorum of the DSMB will be convened as soon as possible and provide a recommendation to the Oversight Group. See also Section 9.8 of the CTP.

5.9.8. 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 SAP, as well as those requiring medical intervention (such as a composite endpoint of hospitalization, ICU admission, mechanical ventilation, and ECMO, linked to objective measures such as decreased oxygenation, X-ray or CT findings), including onset of cases, taking into account all available relevant information at the time of adjudication. More details will be provided in the revised charter of the Clinical Severity Adjudication Committee. Depending on an algorithmic selection the cases will be send to for adjudication on a case by cases basis or on a sample approach, as explained in section 5.2.1. Re-adjudication 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

ADaM	Analysis Data Model
AE	adverse event
AESI	adverse event of special interest
ATC	anatomic and therapeutic class
BMI	body mass index
CD4	cluster of differentiation 4
CD8	cluster of differentiation 8
CI	confidence interval
CRF	case report form
CTP	clinical trial protocol
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunospot
FAS	full analysis set
FDA	Food and Drug Administration
GMC	geometric mean antibody concentration
GMT	geometric mean titer
GSD	group sequential design
HR	hazard ratio
ICF	informed consent form
IDMC	Independent Data Monitoring Committee
IFNg	interferon gamma
IL2	interleukin 2
IRR	incidence rate ratio
ITT	intent-to-treat
LLOQ	lower limit of quantification
NA	not applicable
PBMC	peripheral blood mononuclear cells
PP	per protocol efficacy analysis set
PPI	per protocol immunogenicity analysis set
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDTM	Study Data Tabulation Model
SE	standard error
SFU	spot forming units
SN	seronegative
SP	seropositive
TNE	target number of events
SPRT	sequential probability ratio test
TNFa	tumor necrosis factor alpha
ULOQ	upper limit of quantification
VE	vaccine efficacy
VNA	virus neutralizing antibody
vp	virus particle
WHO	World Health Organization

6.2. Appendix 2 Changes to Protocol-Planned Analyses

SAP according to EDMS-RIM-50860, Amendment 5

History:

SAP Version	**CTP Version**
1	Initial release
2	SAP according to EDMS-RIM-50860, Amendment 1
3	SAP according to EDMS-RIM-50860, Amendment 2
4	SAP according to EDMS-RIM-50860, Amendment 3
5	SAP according to EDMS-RIM-50860, Amendment 4 and 5

6.3. Appendix 3 Demographics and Baseline Characteristics

The following demographic and baseline characteristics will be summarized.

Table 14 presents a list of the demographic variables that will be summarized by vaccine regimen and overall for the FAS. Demographics will also be summarized by region using the FAS.

Table 14 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	
Age group 1 (18-≤59, ≥60 years)	Frequency distribution with the number and percentage of participants in each category.
Age group 2 (18-<40, 40-≤59, ≥60 years)	
Age group3 (18-<40, 40-≤59, 60-≤69, 70-≤79, ≥80 years)	
Age group 4 (18-64, ≥65years)	
Age group 5 (,≥75years)	
Sex (male, female, unknown, intersex)	
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)	
BMI ([underweight <18.5 kg/m^2, normal 18.5-<25 kg/m^2, overweight 25-<30 kg/m^2, obese ≥30 kg/m^2])	
Working Status	
Profession	
Breastfeeding (yes, no)	
Frailty index (frail, pre-frail, non-frail, unknown)	

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

6.4. Appendix 4 Protocol Deviations

Major protocol deviations and major protocol deviations potentially impacting immunogenicity or efficacy (see section 4) will be summarized.

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 data base lock and the participants with major protocol deviations will be summarized by category.

[Developed withdrawal criteria but not withdrawn]

[Entered but did not satisfy criteria]

[Received a disallowed concomitant treatment]

[Received wrong treatment or incorrect dose]

[Other]

6.5. Appendix 5 Prior and Concomitant Medications

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

For all participants, concomitant therapies associated with an SAE will be collected and recorded in the eCRF from the moment of vaccination through the end of the study. Concomitant therapies associated with MAAEs will be collected and recorded in the eCRF from the moment of double-blind vaccination until 6 months after double-blind vaccination. Concomitant therapies associated with MAAEs leading to study discontinuation will be recorded in the eCRF during the entire study. The proportion of participants with concomitant medication associated with these SAEs and MAAEs will be tabulated with exact 95% CI.

For all participants, concomitant therapies associated with COVID-19 will be captured in the electronic eCRF for the duration of the study. The proportion of participants with new concomitant medication associated with these cases will be tabulated with exact 95% CI. New concomitant medications are defined as medications not available at baseline or medication with an increased dosage (See below, New Concomitant Medications, for details), compared to baseline. Baseline medications are all medications reported prior to and at the day of double-blind vaccination. In case a baseline medication is reported multiple times then only the last available record reported prior to or at the day of double-blind vaccination will be used.

For participants in the Safety Subset, concomitant therapies associated with unsolicited AEs will be collected, recorded in the eCRF from the time of double-blind vaccination through 28 days after double-blind vaccination and the proportion of participants with concomitant medication will be tabulated with exact 95% CI. Concomitant therapies associated with solicited AEs will be collected by the participants, recorded in the eCRF from the time of double-blind vaccination through 7 days after double-blind vaccination and the proportion of participants with concomitant medication will be tabulated with exact 95% CI.

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

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

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

There will be special attention to any systemic use of analgesics/antipyretics, started during 8 days following each 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.

Additionally, safety data will be presented for subjects that uses corticosteroids.

New Concomitant Medications – Increase in dosage Calculation

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

This rule applies for the following medication frequencies:

- Once weekly (1 time per week)
- Twice weekly (2 times per week)
- Three Times weekly (3 times per week)
- Four Times weekly (4 times per week)
- Twice Daily (BID)
- Twice per Month (BIM)
- Every two weeks (Every 2 weeks)
- Every four weeks (Every 4 weeks)
- Weekly (Every week)
- Once
- Per Year
- Every three months (Q3M)
- Daily (QD)
- Four times daily (Q1D)
- Monthly (QM)
- Every Other Day (QOD)
- Three times daily (TID)

For frequencies equal to ‘other’at baseline, any change to one of the above frequencies will beconsidered an increase, given that the form remains the same. For frequencies equal to ‘as necessary’ (PNR) or ‘occasional’, any change to another frequency or dose will be considered as

an increase. A change from 'as necessary' (PNR) to 'occasional' or 'other' will not be considered as an increase.

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

6.6. Appendix 6 FDA Toxicity Grading Scale for Vaccine Trials

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

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 judgement 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 applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Hospitalization[#]

[#] Revised by the sponsor.

6.7. Appendix 7 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. * Smoking and controlled grade 1 hypertension are allowed per protocol and are not exclusion criteria.

6.8. Appendix 8 Statistical Methodology for Poisson Regression

Vaccine efficacy is defined as 1 minus the ratio of the expected incidence rate of cases of COVID-19 in the active group compared to the expected incidence rate in the placebo group.

Vaccine efficacy can be estimated by:

$$\widehat{VE} = 1 - \frac{n_2/N_2}{n_1/N_1} = 1 - \frac{r * n_2}{n_1}$$

Where:

n_2 = number of cases in the vaccinated group
N_2 = follow-up time in the vaccinated group
n_1 = number of cases in the control group
N_1 = follow-up time in the control group
r = $\frac{N_1}{N_2}$.

Let $n = n_1 + n_2$ denote the total number of cases. Suppose that $n_i|N_1, N_2 \sim Poisson(N_i p_i)$, $i = 1,2$, so that $VE = 1 - p_2/p_1$. In this case, conditionally on n and r, n_2 is binomially distributed as $B(n, \pi)$, where $\pi = N_2 p_2/(N_1 p_1 + N_2 p_2) = (1 - VE)/(r + 1 - VE)$.

Let $q = n_2/n$ denote the proportion of cases in the vaccine group. Then, the vaccine efficacy estimator can be rewritten as:

$$\widehat{VE} = 1 - \frac{n_2}{n} * \frac{r * n}{(n - n_2)} = 1 - \frac{r * q}{(1 - q)}$$

Therefore, there is a monotonically decreasing link between the estimated VE and $q = n_2/n$, the observed proportion of cases in the vaccine group among the total cases, and so rejecting a hypothesis for extreme values of q is equivalent to rejecting that same hypothesis for inversely extreme values of $\widehat{VE}$.

Given the sequential testing strategy, the confidence interval for the vaccine efficacy will be adjusted accounting for repeated testing. At the primary analysis when the boundary is crossed or at 154 events, the vaccine efficacy estimate will be reported using the estimated VE (as detailed above) at the time of analysis, accompanied with $(1 - 2\alpha^*)\%$ two sided CI, where alpha* is the type I error at that time. Using the exact binomial CI for p an (adjusted) exact Poisson regression CI can be constructed (Dragalin et al, 2002; Nauta, 2011). In section X1 the R code to generate the SPRT bounds and to derive the relevant $(1 - 2\alpha^*)\%$ levels is given. The results of the code are presented in Table 15.

1. Section X1: R code SPRT

```
# Code to generate the curtailed SPRT boundaries
# required libraries: gsDesign -- version 3.1.1
# setting the parameters
V0 <- 0.3
V1 <- 0.60
a <- 0.025
b <- 0.1
h <- 1
pi1 <- (1 - V1) / (1 + h - V1)
pi0 <- (1 - V0) / (1 + h - V0)
# Single-stage UMP binomial test
UMP <- gsDesign::nBinomial1Sample(p0 = pi1, p1 = pi0, alpha = b, beta = a, n = 10:200,
outtype = 2)
UMP
# Setup of the curtailed SPRT bounds
# need 154 events
maxn <- UMP$n
# and have for 1-stage test upper bound of 52
upper <- UMP$b
# start the SPRT at 20 events
minn <- 20
# set the last test so that alpha remains under 0.025; higher values of upper
# will result in inflation, lower values in loss of power
cb <- upper - 3
# generate the bounds from minn to maxn
x <- gsDesign::binomialSPRT(p0 = pi1, p1 = pi0, alpha = b, beta = a, minn = minn, maxn
= maxn)
Vx_bounds <- x$lower$bound
k <- length(Vx_bounds)
# set the bound of the last test at cb
Vx_bounds[k] <- cb
# no testing for futility
bb <- rep(maxn+1, length = k)
# assess the operating characteristics under pi1 and pi0
y <- gsDesign::gsBinomialExact(k = k, theta = c(pi1, pi0), n.I = minn:(minn + k - 1),
a = Vx_bounds, b = bb)
# power and type I
colSums(y$lower$prob)
# output object
out <- data.frame(Total_Infections = y$n.I,
       Vx_Arm = Vx_bounds,
       Obs_VE = 1-(Vx_bounds/y$n.I)/((y$n.I-Vx_bounds)/y$n.I),
       Cum_alpha = cumsum(y$lower$prob[,2]),
       alpha_per_test=y$lower$prob[,2],
       Nominal_alpha = pbinom(Vx_bounds, y$n.I, prob=pi0),
       Power_VE_60= cumsum(y$lower$prob[,1]))
out
```

Table 15 Results of the SPRT code

	Total Infections	Vx Arm	Observed VE	Cumulative α	α per test	Nominal α	Power (VE 60%)
Analysis 1	20	0	1.000000	0.000025	0.000025	0.000025	0.001195
Analysis 2	21	0	1.000000	0.000025	0.000000	0.000014	0.001195
Analysis 3	22	1	0.952381	0.000144	0.000119	0.000140	0.006074
Analysis 4	23	1	0.954545	0.000144	0.000000	0.000086	0.006074
Analysis 5	24	1	0.956522	0.000144	0.000000	0.000052	0.006074
Analysis 6	25	2	0.913043	0.000339	0.000195	0.000287	0.014252
Analysis 7	26	2	0.916667	0.000339	0.000000	0.000182	0.014252
Analysis 8	27	2	0.920000	0.000339	0.000000	0.000115	0.014252
Analysis 9	28	3	0.880000	0.000609	0.000270	0.000469	0.025810
Analysis 10	29	3	0.884615	0.000609	0.000000	0.000306	0.025810
Analysis 11	30	4	0.846154	0.001175	0.000566	0.001002	0.046241
Analysis 12	31	4	0.851852	0.001175	0.000000	0.000671	0.046241
Analysis 13	32	4	0.857143	0.001175	0.000000	0.000448	0.046241
Analysis 14	33	5	0.821429	0.001744	0.000569	0.001289	0.067262
Analysis 15	34	5	0.827586	0.001744	0.000000	0.000880	0.067262
Analysis 16	35	5	0.833333	0.001744	0.000000	0.000599	0.067262
Analysis 17	36	6	0.800000	0.002339	0.000595	0.001565	0.089746
Analysis 18	37	6	0.806452	0.002339	0.000000	0.001088	0.089746
Analysis 19	38	6	0.812500	0.002339	0.000000	0.000753	0.089746
Analysis 20	39	7	0.781250	0.002951	0.000612	0.001822	0.113398
Analysis 21	40	7	0.787879	0.002951	0.000000	0.001285	0.113398
Analysis 22	41	7	0.794118	0.002951	0.000000	0.000903	0.113398
Analysis 23	42	8	0.764706	0.003569	0.000618	0.002057	0.137842
Analysis 24	43	8	0.771429	0.003569	0.000000	0.001470	0.137842
Analysis 25	44	8	0.777778	0.003569	0.000000	0.001045	0.137842
Analysis 26	45	9	0.750000	0.004184	0.000615	0.002265	0.162739
Analysis 27	46	9	0.756757	0.004184	0.000000	0.001637	0.162739
Analysis 28	47	9	0.763158	0.004184	0.000000	0.001178	0.162739
Analysis 29	48	10	0.736842	0.004790	0.000605	0.002448	0.187805
Analysis 30	49	10	0.743590	0.004790	0.000000	0.001787	0.187805
Analysis 31	50	10	0.750000	0.004790	0.000000	0.001299	0.187805
Analysis 32	51	11	0.725000	0.005380	0.000590	0.002604	0.212815
Analysis 33	52	11	0.731707	0.005380	0.000000	0.001919	0.212815
Analysis 34	53	11	0.738095	0.005380	0.000000	0.001408	0.212815
Analysis 35	54	12	0.714286	0.005952	0.000572	0.002736	0.237591
Analysis 36	55	12	0.720930	0.005952	0.000000	0.002033	0.237591
Analysis 37	56	13	0.697674	0.006887	0.000936	0.003782	0.271760
Analysis 38	57	13	0.704545	0.006887	0.000000	0.002844	0.271760
Analysis 39	58	13	0.711111	0.006887	0.000000	0.002129	0.271760
Analysis 40	59	14	0.688889	0.007651	0.000764	0.003871	0.300287
Analysis 41	60	14	0.695652	0.007651	0.000000	0.002931	0.300287

Analysis 42	61	14	0.702128	0.007651	0.000000	0.002209	0.300287
Analysis 43	62	15	0.680851	0.008342	0.000691	0.003935	0.326691
Analysis 44	63	15	0.687500	0.008342	0.000000	0.002998	0.326691
Analysis 45	64	15	0.693878	0.008342	0.000000	0.002274	0.326691
Analysis 46	65	16	0.673469	0.008980	0.000638	0.003977	0.351653
Analysis 47	66	16	0.680000	0.008980	0.000000	0.003047	0.351653
Analysis 48	67	16	0.686275	0.008980	0.000000	0.002325	0.351653
Analysis 49	68	17	0.666667	0.009574	0.000594	0.003999	0.375428
Analysis 50	69	17	0.673077	0.009574	0.000000	0.003080	0.375428
Analysis 51	70	17	0.679245	0.009574	0.000000	0.002362	0.375428
Analysis 52	71	18	0.660377	0.010129	0.000555	0.004004	0.398148
Analysis 53	72	18	0.666667	0.010129	0.000000	0.003098	0.398148
Analysis 54	73	18	0.672727	0.010129	0.000000	0.002388	0.398148
Analysis 55	74	19	0.654545	0.010649	0.000519	0.003993	0.419895
Analysis 56	75	19	0.660714	0.010649	0.000000	0.003104	0.419895
Analysis 57	76	19	0.666667	0.010649	0.000000	0.002403	0.419895
Analysis 58	77	20	0.649123	0.011135	0.000486	0.003969	0.440729
Analysis 59	78	20	0.655172	0.011135	0.000000	0.003098	0.440729
Analysis 60	79	21	0.637931	0.011909	0.000774	0.005002	0.468684
Analysis 61	80	21	0.644068	0.011909	0.000000	0.003934	0.468684
Analysis 62	81	21	0.650000	0.011909	0.000000	0.003083	0.468684
Analysis 63	82	22	0.633333	0.012524	0.000615	0.004927	0.491412
Analysis 64	83	22	0.639344	0.012524	0.000000	0.003889	0.491412
Analysis 65	84	22	0.645161	0.012524	0.000000	0.003058	0.491412
Analysis 66	85	23	0.629032	0.013070	0.000545	0.004843	0.512020
Analysis 67	86	23	0.634921	0.013070	0.000000	0.003835	0.512020
Analysis 68	87	23	0.640625	0.013070	0.000000	0.003027	0.512020
Analysis 69	88	24	0.625000	0.013565	0.000496	0.004751	0.531182
Analysis 70	89	24	0.630769	0.013565	0.000000	0.003775	0.531182
Analysis 71	90	24	0.636364	0.013565	0.000000	0.002988	0.531182
Analysis 72	91	25	0.621212	0.014020	0.000455	0.004654	0.549186
Analysis 73	92	25	0.626866	0.014020	0.000000	0.003708	0.549186
Analysis 74	93	25	0.632353	0.014020	0.000000	0.002945	0.549186
Analysis 75	94	26	0.617647	0.014441	0.000420	0.004552	0.566200
Analysis 76	95	26	0.623188	0.014441	0.000000	0.003637	0.566200
Analysis 77	96	26	0.628571	0.014441	0.000000	0.002896	0.566200
Analysis 78	97	27	0.614286	0.014830	0.000390	0.004445	0.582333
Analysis 79	98	27	0.619718	0.014830	0.000000	0.003561	0.582333
Analysis 80	99	27	0.625000	0.014830	0.000000	0.002844	0.582333
Analysis 81	100	28	0.611111	0.015192	0.000362	0.004337	0.597669
Analysis 82	101	28	0.616438	0.015192	0.000000	0.003483	0.597669
Analysis 83	102	28	0.621622	0.015192	0.000000	0.002788	0.597669
Analysis 84	103	29	0.608108	0.015529	0.000337	0.004225	0.612271

Analysis 85	104	29	0.613333	0.015529	0.000000	0.003401	0.612271
Analysis 86	105	30	0.600000	0.016063	0.000534	0.005082	0.631765
Analysis 87	106	30	0.605263	0.016063	0.000000	0.004113	0.631765
Analysis 88	107	30	0.610390	0.016063	0.000000	0.003318	0.631765
Analysis 89	108	31	0.597403	0.016485	0.000422	0.004932	0.647532
Analysis 90	109	31	0.602564	0.016485	0.000000	0.004000	0.647532
Analysis 91	110	31	0.607595	0.016485	0.000000	0.003234	0.647532
Analysis 92	111	32	0.594937	0.016857	0.000372	0.004783	0.661771
Analysis 93	112	32	0.600000	0.016857	0.000000	0.003887	0.661771
Analysis 94	113	32	0.604938	0.016857	0.000000	0.003149	0.661771
Analysis 95	114	33	0.592593	0.017195	0.000337	0.004635	0.674967
Analysis 96	115	33	0.597561	0.017195	0.000000	0.003774	0.674967
Analysis 97	116	33	0.602410	0.017195	0.000000	0.003063	0.674967
Analysis 98	117	34	0.590361	0.017504	0.000309	0.004490	0.687334
Analysis 99	118	34	0.595238	0.017504	0.000000	0.003662	0.687334
Analysis 100	119	34	0.600000	0.017504	0.000000	0.002978	0.687334
Analysis 101	120	35	0.588235	0.017789	0.000285	0.004346	0.698997
Analysis 102	121	35	0.593023	0.017789	0.000000	0.003550	0.698997
Analysis 103	122	35	0.597701	0.017789	0.000000	0.002892	0.698997
Analysis 104	123	36	0.586207	0.018052	0.000264	0.004204	0.710038
Analysis 105	124	36	0.590909	0.018052	0.000000	0.003440	0.710038
Analysis 106	125	36	0.595506	0.018052	0.000000	0.002807	0.710038
Analysis 107	126	37	0.584270	0.018297	0.000245	0.004066	0.720520
Analysis 108	127	37	0.588889	0.018297	0.000000	0.003332	0.720520
Analysis 109	128	38	0.577778	0.018684	0.000387	0.004774	0.734481
Analysis 110	129	38	0.582418	0.018684	0.000000	0.003930	0.734481
Analysis 111	130	38	0.586957	0.018684	0.000000	0.003225	0.734481
Analysis 112	131	39	0.576087	0.018989	0.000305	0.004606	0.745749
Analysis 113	132	39	0.580645	0.018989	0.000000	0.003797	0.745749
Analysis 114	133	39	0.585106	0.018989	0.000000	0.003121	0.745749
Analysis 115	134	40	0.574468	0.019257	0.000269	0.004443	0.755911
Analysis 116	135	40	0.578947	0.019257	0.000000	0.003667	0.755911
Analysis 117	136	40	0.583333	0.019257	0.000000	0.003018	0.755911
Analysis 118	137	41	0.572917	0.019501	0.000243	0.004284	0.765319
Analysis 119	138	41	0.577320	0.019501	0.000000	0.003540	0.765319
Analysis 120	139	41	0.581633	0.019501	0.000000	0.002918	0.765319
Analysis 121	140	42	0.571429	0.019723	0.000223	0.004129	0.774129
Analysis 122	141	42	0.575758	0.019723	0.000000	0.003416	0.774129
Analysis 123	142	42	0.580000	0.019723	0.000000	0.002819	0.774129
Analysis 124	143	43	0.570000	0.019928	0.000205	0.003979	0.782433
Analysis 125	144	43	0.574257	0.019928	0.000000	0.003296	0.782433
Analysis 126	145	43	0.578431	0.019928	0.000000	0.002723	0.782433
Analysis 127	146	44	0.568627	0.020118	0.000190	0.003834	0.790292

Analysis 128	147	44	0.572816	0.020118	0.000000	0.003179	0.790292
Analysis 129	148	44	0.576923	0.020118	0.000000	0.002630	0.790292
Analysis 130	149	45	0.567308	0.020294	0.000176	0.003693	0.797753
Analysis 131	150	45	0.571429	0.020294	0.000000	0.003066	0.797753
Analysis 132	151	45	0.575472	0.020294	0.000000	0.002539	0.797753
Analysis 133	152	46	0.566038	0.020458	0.000164	0.003556	0.804851
Analysis 134	153	46	0.570093	0.020458	0.000000	0.002956	0.804851
Analysis 135	154	49	0.533333	0.023976	0.003518	0.010603	0.862198

6.9. Appendix 10: Frailty Index

Frailty status is measured using the accumulation of deficits approach. Deficits were coded as 0 = absent to 1 = present. Each participant deficits were summed to generate a total deficit score (max score 46). The FI is calculated by dividing by the number of possible deficits as follows: FI = (Sum of all deficits)/ (Total no. of deficits).

The different aspects of frailty composing the frailty index (FI) were assessed through the following 5 strata captured at baseline:

1. Medical history (max 17 deficits): The total number of deficits for confirmed medical terms. The following medical terms are considered in the study:
    a. Diabetes
    b. Myocardial Infarction/Ischemic Heart Disease
    c. Congestive Heart Failure
    d. Hypertension
    e. Stroke (=cerebrovascular accident)
    f. Chronic lung disease (COPD, Asthma, ILD)
    g. GI/peptic ulcer disease
    h. Arthritis
    i. Cancer
    j. Hearing problems
    k. Cataract
    l. Glaucoma
    m. Migraine
    n. Kidney disease
    o. Liver disease/hepatitis
    p. Immunocompromize including HIV
    q. Neurological condition
2. Medications (max 1 deficit): Deficit if >=5x medications before vaccination.
3. Vitals (max 2 deficits): Deficit if out of range of BP and HR.
   Normal range considered as,
    - Systolic BP: 90-140 mmHg
    - Diastolic BP: 60-90 mmHg
    - HR: 60-99 bpm
4. Body mass index (BMI) (max 1 deficit): BMI: <20 kg/m^2 = 1; 20 kg/m^2 – 24.9 kg/m^2 = 0; 25 kg/m^2 -29.9 kg/m^2 = 0.5; >=30 kg/m^2 = 1.
5. Symptoms of Infection with Coronavirus-19 (SIC) Questionnaires (max 25 deficits): Deficit if a SIC items is answered as “Yes”. The following SIC items are considered in the study:

SIC Items
Feeling generally unwell (run down)
Fatigue
Physical weakness
Cough
Shortness of breath
Sore throat
Nasal congestion
Wheezing
Runny nose

Sneezing
Chest congestion
Chest pain/pressure/tightness
Muscle aches/pains
Joint aches/pains
Headache
Feeling faint
Problems thinking clearly/brain fog
Chills
Skin rash
Eye irritation/discharge
Diarrhea
Vomiting
Nausea
Abdominal/stomach pain
Loss of appetite

Note: For each of the SIC item, at least 1% of participants required to have symptoms to consider under summary.

Each study participant is assigned to one of three subgroup categories are based on the total FI scores as follows:

- FI ≤0.08 is classified as non-frail;
- FI >0.08 to ≤0.25 is classified as pre-frail;
- FI >0.25 is classified as frail.
- Participants with a missing FI were classified as unknown.

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