TITLE PAGE

Protocol Title:

Evaluation of the Immunogenicity, Safety, and Tolerability of a Single Dose of ABNCoV2 Vaccine in Adult Subjects Previously Vaccinated for SARS-CoV-2: a Phase 3 Trial in Two Parts—Randomized, Double-blind, Active Controlled and Open-label, Single-arm

Protocol Number:

ABNCoV2-03

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ABNCoV2-03

Sponsor Name:

Bavarian Nordic A/S

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VERSION HISTORY

This statistical analysis plan (SAP) for trial ABNCoV2-03 is based on edition 7 of the trial protocol, *Evaluation of the Immunogenicity, Safety, and Tolerability of a Single Dose of ABNCoV2 Vaccine in Adult Subjects Previously Vaccinated for SARS-CoV-2: a Phase 3 Trial in Two Parts—Randomized, Double-blind, Active Controlled and Open-label, Single-arm*, dated 15FEB2023.

SAP Version	Date	Change	Rationale
1.0	19MAY23	n/a	Original Approved Version

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
active control arm	Comirnaty (tozinameran, BNT162b2, Pfizer/BioNTech) SARS-CoV-2 vaccine
AE	adverse event
AESI	adverse event of special interest
ATC	Anatomic-Therapeutic-Chemical Class
active trial phase	The time from the trial vaccination up to and including the end of active trial phase visit at 28 to 35 days after trial vaccination
BN	Bavarian Nordic
BMI	body mass index
CDC	Centers for Disease Control
CI	confidence interval
completed primary plus boost vaccination	Completed primary plus boost vaccination with locally authorized SARS-CoV-2 vaccine(s). “Completed primary plus boost vaccination” includes full primary vaccination as described below, plus a boost vaccination administered at least 2 months after the last primary dose. The boost dose may be the same or different vaccine as received in the primary vaccination regimen.
completed primary vaccination regimen	Completed primary vaccination regimen with a locally authorized SARS-CoV-2 vaccine. “Completed primary vaccination regimen” includes full primary vaccination as described in the labeling of the initial vaccine, with no less than 3 weeks between the doses; completed primary vaccination also includes any mix/match series of 2 doses of any locally authorized SARS-CoV-2 vaccine, or a single dose of any locally authorized COVID-19 vaccine in subjects who previously had a confirmed COVID-19 infection.
CSR	clinical study report
CTS	clinical trial site
Cohort 1	adult subjects who previously completed primary vaccination for SARS-CoV-2
Cohort 2	adult subjects who have completed primary vaccination for, and received 1 booster dose, of SARS-CoV-2 vaccine
COVID-19	coronavirus disease 2019
DMC	data monitoring committee
ECG	electrocardiogram
EDC	electronic data capture
EAP	End of active trial phase. The visit (Visit 4) at the end of the active trial phase, approximately 28 to 35 days after trial vaccination. In the event of early withdrawal of a subject from the trial during the active trial phase, the EAP visit will be the visit at which the final safety endpoints for the trial are collected.
ELISpot	enzyme-linked immunospot assay

Abbreviation	Definition
ELISA	enzyme-linked immunosorbent assay
FCS	fully conditional specification
FU	follow up
FU Phase	The time after the active trial phase, up to approximately 6 months after trial vaccination.
FDA	food and drug administration
GCP	good clinical practice
GMT	geometric mean titer
GMFI	geometric mean fold increase
IAS	Immunogenicity Analysis Set
ICF	informed consent form
ICH	International Conference on Harmonization
LLOD	lower limit of detection
LLOQ	lower limit of quantitation
LS means	Least squares means
Max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
Min	minimum
mRNA	messenger ribonucleic acid
Part A	randomized, double-blind, active controlled component of the trial
Part B	open-label, single-arm component of the trial
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PI	principal investigator
PT	Preferred Term
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
index virus	Wuhan wild type isolate of SARS-CoV-2
SD	standard deviation
SDTM	Study Data Tabulation Model

Abbreviation	Definition
SFU	spot forming units
SI	Système International d'Unités
SOC	System Organ Class
SPEAC	Safety Platform for Emergency vACcines
trial phase	The active trial phase plus the follow up phase.
trial vaccination	Part A, randomized component: single dose of 100 µg ABNCoV2 or a single 30 µg dose of Comirnaty Part B, single-arm component: Single 100 µg dose of ABNCoV2
ULOQ	upper limit of quantitation
VOC	SARS-CoV-2 variants of concern
WHO	World Health Organization
WHO Drug	World Health Organization Drug Dictionary

1. INTRODUCTION

This Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing trial data and outlines the key statistical programming specifications. It describes the variables and populations, anticipated data transformations and manipulations, and other details of the analyses not provided in the trial protocol. The SAP is written based on recommendations from *ICH E3: Structure and Content of Clinical Study Reports* and *ICH E9: Statistical Principles for Clinical Trials*. Table, figure, and listing specifications are contained in a separate document.

Deviations from the current protocol are described in Section 4.8. If any unforeseen additional analyses are included in the clinical study report (CSR), they will be clearly described as additional, unplanned analyses in Section 4.8 if added prior to database lock or in the equivalent section of the CSR if ad-hoc analyses are requested post-database lock.

1.1. Objectives, Endpoints, and Estimands

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
Part A: To assess non-inferiority, or superiority, of vaccination with ABNCoV2 compared to Comirnaty in terms of neutralizing antibodies against the SARS-CoV-2 index virus (Wuhan wild type isolate), in Part A Cohort 1 (adult subjects who previously completed primary vaccination at least 3 months prior to the screening visit) and Part A Cohort 2 (adult subjects who have completed primary vaccination and have received 1 booster vaccination).	**Part A:** Geometric mean titer (GMT) of neutralizing antibodies against the SARS-CoV-2 index virus at 2 weeks after trial vaccination, in each Part A cohort.
Key Secondary	
Part A: To assess in Part A cohorts the non-inferiority, or superiority, of vaccination with ABNCoV2 compared to Comirnaty in terms of neutralizing antibodies against SARS-CoV-2 variants of concern (VOCs) circulating at time of the trial.	**Part A:** GMT of neutralizing antibodies against the SARS-CoV-2 VOCs circulating at time of the trial, at 2 weeks after trial vaccination, in the Part A cohort(s) in which the primary endpoint success criterion is met.
Other Secondary	
Part B: To assess neutralizing antibody titers against the SARS-CoV-2 index virus after vaccination with ABNCoV2 in the immunogenicity subsets of Part B Cohort 1 and Cohort 2.	**Part B:** GMTs of neutralizing antibodies against the SARS-CoV-2 index virus at 2 weeks after trial vaccination in subjects receiving ABNCoV2 in the immunogenicity subsets of Part B Cohort 1 and Cohort 2.

Objectives	Endpoints
Safety Objectives	
Part A: To assess the safety and tolerability of the ABNCoV2 vaccine compared to Comirnaty in previously vaccinated adult subjects in Part A (both cohorts). **Parts A and B:** To assess the safety and tolerability of the ABNCoV2 vaccine in previously vaccinated adult subjects (all subjects receiving ABNCoV2).	**Part A:** For all subjects receiving ABNCoV2 compared to those receiving Comirnaty, the percent who report the safety endpoints listed below. **Parts A and B:** For all subjects receiving ABNCoV2, the percent who report the safety endpoints listed below. • Serious adverse events (SAEs) or adverse events of special interest (AESIs) assessed as related to trial vaccine during the entire trial phase, which includes both the active trial phase and follow-up. • Grade 3 or higher adverse events (AEs) assessed as related to trial vaccine in the 8-day period starting with the day of vaccination. • SAEs, AESIs, or medically attended AEs (MAAEs), regardless of relationship, during the active trial phase. • SAEs, AESIs, or MAAEs, regardless of relationship, during the entire trial phase. • Grade 3 or higher AEs assessed as related to trial vaccine during the active trial phase. • Solicited local AEs in the 8-day period starting with the day of vaccination. • Solicited general AEs in the 8-day period starting with the day of vaccination.
Exploratory Objectives	
To compare total binding immunoglobulin G (IgG) antibodies against the SARS-CoV-2 index virus after vaccination with ABNCoV2 or Comirnaty in subsets of each Part A cohort.	GMT of total binding IgG antibodies against the SARS-CoV-2 index virus at 2 weeks after trial vaccination in subsets of each Part A cohort. Geometric mean fold increases, from baseline to post-baseline time points after trial vaccination, in total binding IgG antibodies

Objectives	Endpoints
	against the SARS-CoV-2 index virus in subsets of each Part A cohort.
To explore the kinetics of SARS-CoV-2-specific humoral responses in subsets of each Part A cohort.	Geometric mean fold increases, from baseline to post-baseline time points after trial vaccination, in neutralizing antibodies against the SARS-CoV-2 index virus. Geometric mean fold increases, from baseline to post-baseline time points after trial vaccination, in neutralizing antibodies against the SARS-CoV-2 VOCs circulating at time of the trial. GMT of neutralizing antibodies against the SARS-CoV-2 index virus and the SARS-CoV-2 VOCs circulating at time of the trial, at 1, 4, 13 and 26 weeks after trial vaccination in subsets of each Part A cohort.
To compare neutralizing antibodies against the SARS-CoV-2 index virus at 2 weeks after vaccination with ABNCoV2 between cohorts in Part A and Part B.	GMTs and geometric mean fold increases, from baseline to post-baseline time points after trial vaccination, in neutralizing antibodies against the SARS-CoV-2 index virus at 2 weeks after trial vaccination.
To explore SARS-CoV-2-specific cellular responses at 1 week after ABNCoV2 vaccination within the immunogenicity subsets of each Part B cohort.	Geometric means of SARS-CoV-2-specific T cells secreting interferon-g / interleukin-4 at 1 week after ABNCoV2 vaccination within the immunogenicity subsets of each Part B cohort.

AE = adverse event, AESI = adverse event of special interest, GMT = geometric mean titer, IgG = immunoglobulin G, MAAE = medically attended adverse event; SAE = serious adverse event, VOC = SARS-CoV-2 variants of concern.

Primary Estimand

The primary variable of interest is the subjects' neutralizing antibody result against the SARS-CoV-2 index virus measured at 2 weeks after trial vaccination in each Part A cohort, and the variable will be summarized as the ratio of geometric means for ABNCoV2 compared to Comirnaty in subjects meeting the Immunogenicity Analysis Set (IAS) definition.

The planned primary analysis will be conducted in each of the Part A cohorts, and the null hypothesis of inferiority will be rejected if the ratio of GMTs is within the non-inferiority margin of 0.67, i.e., the lower limit of the 2-sided 97.5% CI of the GMT ratio is ≥0.67.

The following are considered intercurrent events:

1. Development of COVID-19 symptoms and having a positive test for SARS-CoV-2 infection prior to Visit 3 (12 to 16 days after vaccination) by PCR or other testing method,

2. Administration of a booster for SARS-CoV-2 prior to Visit 3, and
3. Discontinuation from the trial due to AEs.

For the primary estimand, the third intercurrent event is not considered as having an impact on the SARS-CoV-2 neutralizing antibody levels and therefore the "treatment policy" strategy will be used. Exposure to the virus or receiving another booster vaccine can have significant effect on SARS-CoV-2 neutralizing antibody levels, and thus subjects who develop intercurrent infections will be excluded from the primary analysis. This is equivalent to the "while on treatment" strategy. Prior to database lock, a data review meeting will determine if any other intercurrent events (e.g., protocol violations) would affect the primary immunogenicity outcome. Strategies to handle these additional intercurrent events will be determined in a blinded fashion.

Secondary Estimand

The key secondary variables of interest are the subjects' neutralizing antibody titers against circulating SARS-CoV-2 VOCs measured at 2 weeks after trial vaccination in Part A, and they will be summarized as the ratios of GMTs for ABNCoV2 compared to Comirnaty.

The null hypothesis of inferiority will be rejected if the ratio of GMTs against the SARS-CoV-2 VOCs, for ABNCoV2 vaccine compared to Comirnaty vaccine, is within the non-inferiority margin of 0.67. Only Part A cohort(s) that meet the primary success criterion will be formally tested for non-inferiority of ABNCoV2 to Comirnaty for each VOC, and a Bonferroni correction will be used to control the overall type I error rate for the trial.

The intercurrent events for the secondary analyses are the same as for the primary analysis and will be handled in a similar fashion.

1.2. Trial Design

Details of the trial design are listed in Table 2.

Table 2: Details of Trial Design

Design Element	Description
Study phase and study population	Phase 3, healthy adult subjects previously vaccinated for SARS-CoV-2
Design type	Part A: Parallel Part B: Single arm
Control Method	Part A: Active controlled, Comirnaty Part B: None
Blind level	Part A: Double blind Part B: Open label
Method of Assignment	Part A: Randomized 1:1 to a single dose of ABNCoV2 or Comirnaty, stratified by age group (<65 years vs. ≥65 years) and prior vaccination regimens, within each cohort. Part B: Non-randomized, all assigned to a single dose of ABNCoV2

Design Element	Description
Duration of Trial Participation	Screening: 2 Weeks Active Trial Phase: 4 Weeks Follow-up: 22 Weeks
Dose Adjustment Rules	Not applicable, single dose given on Day 1
Planned Interim Analyses	No interim analysis of immunogenicity is planned; however, a data monitoring committee will review cumulative safety data throughout the trial. No immunogenicity data will be reviewed prior to the primary analysis.
Timing of Primary Analysis	The primary analyses of immunogenicity and analyses of safety will be performed once all subjects within a trial part have completed the 8-week Follow-up 1 visit. Data will be cleaned through the 8-week timepoint. A data review meeting will be conducted to review the key trial data and determine if strategies to handle other intercurrent events are needed in addition to the strategies to handle the planned intercurrent events in a blinded manner. Treatment assignment will not be unblinded for the primary analyses until the data are locked and analysis populations and strategies to handle intercurrent events are set.
Timing of Subsequent Analyses	Follow-up analyses will be performed once all subjects have completed the 3 month and the 6 month follow-up visits, respectively. The final analysis for the trial will occur once all subjects have completed all follow-up or have withdrawn early from the trial and the database has been locked.

2. STATISTICAL HYPOTHESIS

In Part A of the trial, the non-inferiority of ABNCoV2 will be assessed in comparison with Comirnaty in terms of neutralizing antibodies against the SARS-CoV-2 index virus and circulating VOCs. The hypothesis will be tested in the randomized, double-blind component, in Cohort 1 (adult subjects who previously completed primary vaccination only) and Cohort 2 (adult subjects who have received 1 booster vaccination after a primary regimen) simultaneously. If the non-inferiority margin is met, superiority comparison will be carried out in the same cohort with the same type I error level.

No hypothesis testing is planned for the open-label, single-arm Part B of the trial.

2.1. Multiplicity Adjustment

The hypothesis test of non-inferiority of ABNCoV2 to Comirnaty in terms of neutralizing antibody titers for SARS-CoV-2 will be performed in Part A in up to 2 cohorts. A Bonferroni correction will be used to control the trial-wide type I error of $\alpha = 0.025$, one-sided. In the event a cohort does not meet the requirement of 400 evaluable subjects for the primary endpoint analysis, summaries for the under-enrolled cohort will be considered purely descriptive.

The key secondary endpoints, ratios of GMTs for the VOCs at 2 weeks after trial vaccination, will be formally tested in Part A for non-inferiority of ABNCoV2 to Comirnaty only in the cohort(s) in which the primary success criterion is met. If the primary success criterion is met in only one cohort, VOCs will be formally tested in that cohort only. A Bonferroni adjustment will be used such that each VOC non-inferiority hypothesis will be tested at the $\alpha = \frac{0.025}{number\ of\ VOCs\ tested}$ level. For example, if 3 VOCs are tested, each test will be performed at the $\alpha = 0.0083$ level such that success would require the lower bound of a 98.3% CI to be at least 0.67. In the event that success criteria are met for both Cohort 1 and Cohort 2, the number of tests will multiply, and thus non-inferiority hypothesis will be tested at the $\alpha = \frac{0.0125}{number\ of\ VOCs\ tested}$ level so that the overall type I error rate will be no more than 5%.

Due to the challenges of finding non-boosted potential trial subjects during enrollment, Cohort 1 was under-enrolled for the primary analysis, even with extension of the enrollment period. Therefore, only Cohort 2 will be formally tested.

3. ANALYSIS SETS

Data for all subjects will be assessed to determine if subjects meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database.

Table 3: Populations for Analyses

Analysis Set	Definition
Enrolled	All subjects who have signed informed consent.
Randomized	All subjects who are assigned a randomization number in the randomization system.
Safety Analysis Set	All subjects who received a trial vaccination with either ABNCoV2 or Comirnaty.
Immunogenicity Analysis Set (IAS) [a]	All subjects who are in the Safety Analysis Set, have at least a baseline and 1 post-vaccination neutralizing antibody result, and have neither intercurrent events indicative of SARS-CoV-2 infection nor received a booster for SARS-CoV-2 outside of the trial within 2 weeks of vaccination. If further protocol deviations are found that would have a significant impact on a subject's humoral responses to trial vaccination, decisions on removing these subjects from the IAS will be made prior to locking the database and unblinding for the primary analysis.
Kinetics Analysis Set – 3 Months [a]	Subset of Part A subjects in the IAS who have neutralizing antibody results for the SARS-CoV-2 index virus at the Week 13 visit (91-105 days after vaccination) and have neither had a SARS-CoV-2 infection by Week 13 nor received a booster for SARS-CoV-2 outside of the trial by Week 13.
Kinetics Analysis Set – 6 Months [a]	Subset of Part A subjects in the IAS who have neutralizing antibody results for the SARS-CoV-2 index virus at the Week 26 visit (182-196 days after vaccination) and have neither had a SARS-CoV-2 infection by Week 26 nor received a booster for SARS-CoV-2 outside of the trial by Week 26.

[a]SARS-CoV-2 infection for IAS and the kinetics analysis sets will be determined by subject-reported adverse events of SARS-CoV-2 infection, positive PCR testing, or an increase in nucleocapsid protein indicating COVID-19 infection.

In general, immunogenicity analyses will be performed using the IAS according to the vaccine to which the subject was assigned (ABNCoV2 or Comirnaty by randomization for Part A, ABNCoV2 for Part B). In Part A, subgroup analyses performed within randomization strata will be analyzed according to the randomization stratum the subject reported at the time of randomization, even if upon further review it is determined to be different than the actual grouping to which the subject should have been assigned. This is most likely the case for prior vaccination stratum in Part A. In case the difference between the derived randomization stratum and as-randomized stratum is different for >5% of subjects in Part A, an analysis will be performed using the stratum "as-derived" from the prior COVID-19 vaccination history data.

Because SARS-CoV-2 infection or receipt of an additional SARS-CoV-2 boost vaccine outside of the trial would affect immunogenicity results, kinetic analyses of immunogenicity at Week 13/Month 3 and Week 26/Month 6 will be based on a subset of subjects who have not been naturally infected or received additional boost vaccinations prior to the time point of interest. In addition, to ensure the same population is followed over time, only subjects who have results for

Week 13 or Week 26, respectively, will be included in these analyses. If the number of subjects eligible for the Kinetics Analysis Sets is more than the pre-specified sample size, subjects will be selected randomly.

All safety analyses will be performed on the Safety Analysis Set, and subjects will be summarized based on the vaccine actually received.

4. STATISTICAL ANALYSES

4.1. General Considerations

All individual data entered in the electronic case report form (eCRF) will be listed as recorded in subject-level data listings. Listings will be sorted by trial part (A or B), Cohort (1 or 2), vaccination arm (for Part A), subject, time point, and parameter (if applicable), based on the domain presented. Tables and figures for Part A will be created separately from Part B tables.

Descriptive statistics presented for categorical variables will include frequencies and percentages (i.e., n (%)), with the denominator for the percentage calculation defined in the table. Unless otherwise stated, descriptive statistics presented for continuous variables will be n, mean, median, standard deviation, minimum, and maximum.

In general, all tables and figures will be presented by cohort (Cohort 1, Cohort 2, Cohort 1+2). For Part A, tables will also be presented by vaccination arm (ABNCoV2 versus Comirnaty) within each cohort. For subject population summaries including disposition and demographics, an "Overall" column will be presented for the combined Cohort 1+2 grouping.

Unsolicited AEs will be summarized at both the event and subject level, with percentages based on subject counts. As solicited AEs can only be experienced once per event type per subject, only subject level counts and percentages will be presented.

All statistical summaries and analyses will be performed using SAS® version 9.4 or higher (SAS Institute, Cary, NC, USA).

4.1.1. Handling of Immunogenicity Data

Immunogenicity data are log-normally distributed and will be presented using n, geometric means and corresponding 95% confidence intervals (CI), median, minimum, and maximum. Figures for immunogenicity data will be scaled using a logarithmic y-axis.

Neutralizing antibody results for the index virus and any VOCs with World Health Organization (WHO) normalized units at the time of analysis will be scaled to WHO standard units (IU/mL). Neutralizing antibody results for the VOCs without WHO normalized units will be summarized as titer values. For all neutralizing antibody results, values below the lower limit of detection (LLOD) will be given a value of half of the LLOD. Values that are below the LLOQ but at or above the LLOD will be analyzed as half of the value of the LLOQ.

Total antibody results measured by ELISA will also be scaled to WHO standard units (BAU/mL). Values below the LLOQ will be given a value of half of the LLOQ.

ELISpot results will be presented in spot forming units (SFUs)/10^6 PBMCs. Interferon-γ and interleukin-4 results will be summarized separately within individual stimulant pools. Values below the LLOD will be given a value of half of the LLOD. Values that are below the LLOQ but at or above the LLOD will be analyzed as half of the value of the LLOQ. Values above the upper limit of quantitation (ULOQ) will be given a value of twice the ULOQ.

4.1.2. Handling of Missing Data

All data will be listed and summarized as captured in the eCRF or transferred from external sources (e.g., central lab results, immunogenicity results, protocol deviations).

It may be necessary to impute incomplete AE and medication start and end dates to assign these events to the correct trial phase. For prior and concomitant medications, as well as AEs, imputation of partial start and end dates will be done for analysis purposes according to the following rules:

Table 4: Adverse Event and Concomitant Medication Date Imputation Rules

Missing	Rule for Start Date[a]	Rule for End Date[b]	Flag for Imputation[c]
Day	First of month	Last of month	D
Month	1 January	31 December	M
Year	No imputation	Last visit date	Y

[a] If the imputed start date is before the trial vaccination date, the trial vaccination date is used to be conservative.
[b] If the imputed end date is after last visit date, the last visit date available is used to be conservative.
[c] It is assumed that a missing month implies a missing day as well, and that a missing year implies a missing month and day.

If the imputation of a partial start date of an AE leads to a start date prior to the date of trial vaccination, it will be set to the date of trial vaccination and assigned to be on treatment and in the Active Trial Phase, to be conservative. Original date values as collected will be presented in listings.

For AEs and medications with partial or missing start and/or stop dates, the "worst case" should be applied to be conservative. Therefore, the following rules will apply:

AEs

- If start date is partial and any portion (i.e., year or month and year) would confirm the AE was prior to trial vaccination, the AE will be considered a Baseline Sign or Symptom.
- If the start date is completely missing and the end date, or any portion of a partial end date, confirms the AE ended prior to trial vaccination, the AE will be considered a Baseline Sign or Symptom.
- Otherwise, the AE will be considered as belonging to the Active Trial Phase.

Medications

- If the end date is partial, and any portion confirms the medication was ended prior to trial vaccination, the medication will be considered a Prior Medication.
- Otherwise, the medication will be considered a Concomitant Medication.

Missing data imputation for immunogenicity data as a sensitivity analysis of the primary endpoint is described in Section 4.2.3.1.

4.1.3. Unblinding

Unblinding for Part A reporting will happen after the lock for the primary analysis (see Section 4.7). After unblinding for the primary analyses, the operational team will remain blinded on individual subject level until the follow-up phase of Part A of the trial is completed. Bavarian

Nordic team members unblinded at the subject level will no longer support the blinded team operation during the follow-up phase.

4.1.4. Baseline

Baseline is defined as the last available measure prior to trial vaccination. Baseline values may come from the screening, vaccination visit, or an unscheduled visit prior to the trial vaccination visit. If multiple pre-vaccination values are available, the one closest in time to the trial vaccination will be used as the baseline value. If no time is collected for a value measured on the date of trial vaccination, measurements required to be collected prior to vaccination per the clinical trial protocol will still be considered eligible for inclusion as baseline measurements. Subjects missing baseline values will not be included in analyses of the change/shift from baseline or ratio to baseline.

Note, as the primary endpoint and analysis for the trial does not require a baseline measurement, but rather a week 2 neutralizing antibody result for the index virus, subjects missing a baseline value are not excluded from the IAS. These subjects will, however, be excluded from analyses presenting geometric mean fold increases from baseline.

4.1.5. Trial Phase and Windowing

The following trial phases are defined for this trial:

Screening Phase: The phase from the subject's signing of informed consent to the trial through the date and time of trial vaccination. AEs collected during the Screening Phase are considered Baseline Signs and Symptoms and are included as Medical History events in the SDTM database.

Active Trial Phase: The phase from the trial vaccination up to and including the week 4 End of Active Phase (EAP) Visit (28-35 days after vaccination). In the event of early withdrawal of a subject from the trial during the Active Trial Phase, the EAP Visit may occur prior to the scheduled EAP Visit window. For safety analyses, any safety information collected within 35 days of trial vaccination will be included in summaries of the Active Trial Phase.

Follow-up Phase: The phase from the EAP Visit through the final FU visit. Subjects have 3 FU visits scheduled per protocol at Weeks 8 (phone), 13, and 26. Subjects may withdraw from the Active Trial Phase early but continue into the FU Phase. Completion of the trial requires all follow-up visits to be attended and can be achieved even if the Active Trial Phase is discontinued early.

For assigning prior and concomitant medications, those ending prior to trial vaccination are considered prior medications. All other medications are considered concomitant medications.

Per protocol, all visits are to occur within the specified window in the schedule of events (Appendix 1). For sensitivity analyses, immunogenicity samples taken out of window will be handled as described in Section 4.2.3.1.

In general, safety analyses will be performed by trial phase. The Active Trial Phase summaries will account for any observations between the vaccination and the EAP visit, inclusive of the EAP visit and any unscheduled visits during this phase. Nominal visits will be used for the

summaries by visit, with the worst/highest toxicity grade value presented for the visit in the case of multiple reported observations.

4.1.6. Baseline Comorbidities

Baseline comorbidities include underlying conditions that increase the risk of severe COVID-19. The following list of conditions are based on the Center for Disease Control and Prevention's Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals (https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html), in which the CDC determined the conditions to be conclusive of higher risk of severe COVID-19. The following table includes how the conditions will be identified from the medical history and baseline signs and symptoms collected for each subject as coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

Table 5: Baseline Comorbidity Definitions

Condition	MedDRA Definition
Asthma, Bronchiectasis, COPD	High Level Term: Bronchospasm and obstruction Preferred Term: Bronchiectasis
Cancer	System Organ Class + High Level Group Term: "Neoplasms benign, malignant and unspecified (incl cysts and polyps)" AND High Level Group Term includes "malignant" Preferred Terms: Cancer surgery Hodgkin's disease Non-Hodgkin's lymphoma
Cerebrovascular disease	High Level Group Term: Central nervous system vascular disorders Aneurysms and artery dissections *(please exclude PTs Aneurysm and Peripheral artery aneurysm)* High Level Terms: Arterial therapeutic procedures (excl aortic) *(please exclude PTs Patent ductus arteriosus repair and Renal artery stent placement)* Preferred Terms: Aortic arteriosclerosis Arteriosclerosis Intermittent claudication Peripheral arterial occlusive disease
Chronic kidney disease	High Level Term: Renal failure and impairment Preferred Terms: Nephropathy Hypertensive nephropathy
Chronic liver disease (cirrhosis, non-alcoholic fatty liver disease, alcoholic liver disease, autoimmune hepatitis)	High Level Terms: Hepatic fibrosis and cirrhosis Hepatocellular damage and hepatitis NEC
Cystic fibrosis	Preferred Term: Cystic fibrosis
Diabetes mellitus, type 1 and type 2	High Level Term: Diabetes mellitus (incl subtypes) Preferred Term: Diabetic neuropathy

Condition	**MedDRA Definition**
Disabilities, including Down Syndrome	High Level Term: Disability issues Preferred Term: Congenital foot malformation
HIV	*Excluded from trial*
Heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies)	High Level Group Term: Cardiac therapeutic procedures *(please exclude PTs Left atrial appendage closure implant, Cardiac operation, Atrial septal defect repair)* High Level Terms: Cardiac disorders NEC Cardiac disorders congenital NEC Aortic valvular disorders Cardiac valve disorders NEC Mitral valvular disorders Pulmonary valvular disorders Coronary artery disorders NEC Ischaemic coronary artery disorders Heart failures NEC Cardiomyopathies Myocardial disorders NEC Preferred Terms: Ventricular fibrillation
Interstitial lung disease	High Level Term: Parenchymal lung disorders NEC
Mental health conditions (such as mood disorders, including depression, and schizophrenia spectrum disorders)	High Level Terms: Adjustment disorders Depressive disorders Mood alterations with depressive symptoms Pervasive developmental disorders NEC Hallucinations (excl sleep-related) Bipolar disorders Fluctuating mood symptoms Mood disorders NEC Psychotic disorder NEC Schizoaffective and schizophreniform disorders Schizophrenia NEC
Neurologic conditions (including Dementia)	High Level Terms: Dementia (excl Alzheimer's type) Dementia NEC Alzheimer's disease (incl subtypes) Central nervous system disorders congenital NEC Preferred Term: Cerebral palsy Paraplegia
Obesity	Preferred Terms: Central obesity Obesity Vital Signs: Baseline BMI of ≥30
Physical Inactivity	*Not collected as a baseline variable*
Pregnancy and Recent Pregnancy	*Excluded from trial*

Condition	MedDRA Definition
Primary Immunodeficiencies	*Excluded from trial*
Pulmonary hypertension and pulmonary embolism	High Level Terms: Pulmonary hypertensions Pulmonary thrombotic and embolic conditions
Smoking, current and former	High Level Term: Tobacco use
Solid organ or blood stem cell transplantation	*Excluded from trial*
Tuberculosis	High Level Term: Tuberculous infections
Use of corticosteroids or other immunosuppressive medications	*Excluded from trial*

4.2. Primary Endpoint Analysis

4.2.1. Definition of Endpoint(s)

Serum samples will be collected from subjects per the trial procedure schedule Appendix 1. Immunogenicity testing will be performed at [redacted], and at contracted laboratories, if needed.

Neutralizing antibody results against SARS-CoV-2 are assumed to be log-normally distributed. Values will be transformed to the $\log_{10}$ scale for the purpose of analysis. Results that are below LLOQ or LLOD will be evaluated based on the algorithm described in Section 4.1.1. Once analyses are performed, estimates will be back transformed to the original scale for reporting.

Foreseeable intercurrent events and handling strategies are described in Section 1.1 for primary and secondary estimands.

4.2.2. Main Analytical Approach

The estimate of the primary estimand will be created using the IAS.

The geometric mean, 95 % CI, median, minimum, and maximum of SARS-CoV-2 neutralizing antibody results for Part A will be calculated within each cohort. Additionally, in Part A, the ratios of the GMTs between ABNCoV2 and Comirnaty will be provided along with p-values, 95% CI and 97.5% CI from a generalized linear model. Age and baseline neutralizing antibody results will be included as covariates in the model to compare between the vaccination arms. The Least Squares (LS) Means and CIs from the model will be back transformed to their original scale.

GMTs will be obtained by computing the arithmetic means and the corresponding 95% CIs on the $\log_{10}$ scale, and then exponentiating the $\log_{10}$ means and confidence limits to return the results to the original scale.

Figures of neutralizing antibody results with the GMT and fold increase for the index virus and each VOC will be plotted by cohort, and for both cohorts combined, for each vaccination arm in Part A.

4.2.3. Sensitivity Analyses

All results excluded from the primary estimand analysis will be included with the sensitivity analysis for a full account of the trial population, i.e., the safety analysis set. Reasons for exclusion may include, but are not limited to:

- Intercurrent events indicative of SARS-CoV-2 infection prior to 2 weeks after vaccination
- A protocol deviation substantially affecting the immunogenicity outcome (i.e., exclusion from the Immunogenicity Analysis Set)

Another sensitive analysis will further exclude subjects who have significant fold increase in nucleocapsid protein antibody results although neither have positive PCR nor SARS-CoV-2 infection reported as an adverse event.

4.2.3.1. Sensitivity using Multiple Imputation for the Safety Analysis Set

Because the window between vaccination and the primary endpoint measurement is short, the number of subjects with missing data due to intercurrent events or protocol deviations substantially affecting the immunogenicity results is expected to be small. If >5% of data are missing despite the short window, missing values will be imputed via the multiple imputation (MI) method as a sensitivity analysis using the Safety Analysis Set. Missing values will be assumed to be missing at random, such that the reason for the missing value is not dependent on the result itself. As the MI procedure will be performed on the Safety Analysis Set, regardless of protocol deviations, neutralizing antibody results after vaccination that are out of window will be included rather than imputing a "missing" value for full accounting of the available data. Inclusion of serum samples collected out of window will follow the method used for the Sensitivity Analysis using the Safety Analysis Set.

The MI sensitivity analyses will be performed separately for each Part A cohort due to the different background characteristics.

Part A Multiple Imputation Procedure

Assuming the post-vaccination $\log_{10}$ neutralizing antibody results are normally distributed, MI will be used to create 100 complete data sets that will account for the random variability in the $\log_{10}$ neutralizing results. MI sensitivity analyses will only be performed for the Part A cohort(s) formally tested for non-inferiority of ABNCoV2 to Comirnaty, and Cohort 1 and 2 analyses will be performed separately but using the same method. As enrollment in Cohort 1 did not meet the sample size requirement for the formal non-inferiority test, the MI procedure will not be performed for that cohort. Baseline $\log_{10}$ neutralizing antibody results, Week 1 $\log_{10}$ neutralizing antibody results, race group, sex, age group (<65 years versus ≥65 years), and prior vaccination regimen will be used in the joint model to predict the $\log_{10}$ neutralizing antibody value for the primary estimand time point at Week 2.

MI analyses will be performed in SAS using the PROC MI and PROC MIANALYZE procedures, employing a fully conditional specification (FCS) model. A minimum of $\log_{10}$ of half of the LLOD will be set for imputed values to correspond to the observed data range. In addition, a seed of 19201 will be used for the procedure. Analyses will be performed separately for each cohort in Part A. Sample SAS code is provided in Appendix 2.

4.2.4. Supplementary Analyses

There are no supplementary analyses.

4.2.5. Subgroup Analyses

The primary analysis (and similar secondary and exploratory time points listed below) will also be performed and summarized by subgroups for Part A. Subgroups will include:

- Age Group (<65 years and ≥65 years)
- Prior Vaccination Regimen (as randomized groupings)

  Cohort 1:

  - 2 doses of mRNA vaccine,
  - 1 dose or 2 doses of adenovirus-based vaccine,
  - 1 dose of adenovirus-based vaccine followed within 3 months by 1 dose of mRNA vaccine,
  - Other authorized primary vaccination regimen.

  Cohort 2:

  - 2 doses of mRNA primary vaccines plus 1 booster dose of mRNA vaccine,
  - 1 dose or 2 doses of adenovirus-based primary vaccines plus 1 booster dose of mRNA vaccine,
  - Other authorized primary vaccination and boost vaccination combinations.
- Prior Vaccination Regimen (as derived from COVID-19 history data, same categories as above if it is determined that >5% are different from randomized)
- Baseline Neutralizing Antibody Result (< LLOQ, ≥ LLOQ to < median, ≥ median)
  - Median is calculated from the corresponding trial part and cohort values ≥ LLOQ
- Time from Previous Vaccination (time from the most recent COVID-19 vaccination to the trial vaccination)
  - Time is calculated in months as (date of trial vaccination – date of most recent vaccination + 1)/30.4375
  - Times are categorized based on the median within part and cohort
- History of SARS-CoV-2 Infection (Yes vs. No)
- Baseline Comorbidity (Yes vs. No, see Section 4.1.6 for definition)

4.2.6. Supportive Analyses of the Primary Endpoint

The primary analysis will be supported by descriptive summaries (GMT, 95% CI, and median) for each time point (pre- and post-vaccination). Descriptive summaries will be presented for Part A Cohorts 1 and 2 separately and combined.

The proportion of subjects with ≥2-fold and ≥4-fold increase in neutralizing antibody results to the SARS-CoV-2 index virus from baseline to 2 weeks post-trial vaccination will be summarized using frequencies and percentages along with exact Clopper-Pearson 95% CIs within vaccination arm in each cohort. In addition, a similar summary table as a sensitivity analysis using the Safety Analysis Set will also be presented. Subjects missing a value for a time point who did not achieve a response at a previous time point are counted as non-responders for this sensitivity analysis.

4.3. Secondary Estimand Analysis

4.3.1. Key Secondary Estimands

The key secondary variables of interest are the subjects' neutralizing antibody results against circulating SARS-CoV-2 VOCs measured at Week 2 in Part A Cohorts 1 and 2, and they will be summarized as the ratios of GMTs for ABNCoV2 compared to Comirnaty.

The null hypothesis of inferiority will be rejected if the ratio of GMTs against the SARS-CoV-2 VOCs, for ABNCoV2 vaccine compared to Comirnaty vaccine, is within the non-inferiority margin of 0.67. Only Part A cohort(s) that meet the primary success criterion will be formally tested sequentially for non-inferiority of ABNCoV2 to Comirnaty for each VOC, and a Bonferroni correction will be used to control the overall type I error rate for the trial. Details are provided in Section 2.1.

The intercurrent events for the secondary analyses are the same as for the primary analysis and will be handled in a similar fashion described in Section 4.2.1.

4.3.1.1. Definition of Endpoint(s)

The definitions of the primary estimands apply to the secondary estimands.

4.3.1.2. Main Analytical Approach

The VOCs for Part A will be analyzed using the same analysis methods as those for the primary estimand described above. The precision of the CIs will be adjusted based on the number VOCs included in the key secondary analyses. The decision regarding which VOCs to include will be finalized before sample analysis begins. The GMT ratios and CIs with coverage adjusted for the non-inferiority hypothesis testing will also be calculated.

If the non-inferiority success criterion is met for a VOC (lower bound of the adjusted CI is ≥0.67), the p-value from the same model will be reported to assess superiority.

Analyses of other VOCs may also be performed similarly but not subjected to formal testing; such comparisons thus will not affect the trial-wide type I error.

4.3.1.3. Sensitivity Analyses

All results excluded from the secondary estimand analyses will be included with the sensitivity analysis for a full account of the trial population, i.e., the safety analysis set. Reasons for exclusion may include, but are not limited to:

- Intercurrent events indicative of SARS-CoV-2 infection prior to 2 weeks after vaccination

- A protocol deviation substantially affecting the immunogenicity outcome (i.e., exclusion from the Immunogenicity Analysis Set)

Another sensitive analysis will further exclude subjects who have significant fold increase in nucleocapsid protein antibody results although neither have positive PCR nor SARS-CoV-2 infection reported as an adverse event.

4.3.1.4. Supplementary Analyses

There are no supplementary analyses.

4.3.1.5. Subgroup Analyses

For each VOC, the same subgroup analyses as the primary estimand analysis in Section 4.2.5 will be presented for Part A.

4.3.2. Other Secondary Endpoint Analyses

The other secondary endpoints of interest are the GMTs of neutralizing antibodies against the SARS-CoV-2 index virus at 2 weeks after trial vaccination in subjects receiving ABNCoV2 in the immunogenicity subsets of Part B Cohort 1 and Cohort 2.

The geometric mean, 95 % CI, median, minimum, and maximum of SARS-CoV-2 neutralizing antibody results for Part B will be calculated within each cohort at each of the 2 time points. Figures of neutralizing antibody results with GMT and fold increase will be plotted for the individual cohorts and combined. No sensitivity analyses will be performed for Part B subjects; however, the following subgroup analyses will be presented. Note, as prior vaccination regimen was not a randomization factor, it will be derived for the Part B neutralizing antibody analysis.

- Age Group (<65 years and ≥65 years)
- Prior Vaccination Regimen (as derived from COVID-19 history data)

  Cohort 1:

  - 2 doses of mRNA vaccine,
  - 1 dose or 2 doses of adenovirus-based vaccine,
  - 1 dose of adenovirus-based vaccine followed within 3 months by 1 dose of mRNA vaccine,
  - Other authorized primary vaccination regimen.

  Cohort 2:

  - 2 doses of mRNA primary vaccines plus 1 booster dose of mRNA vaccine,
  - 1 dose or 2 doses of adenovirus-based primary vaccines plus 1 booster dose of mRNA vaccine,
  - Other authorized primary vaccination and boost vaccination combinations.
- Baseline Neutralizing Antibody Result (< LLOQ, ≥ LLOQ to < median, ≥ median)

  - Median is calculated from the corresponding trial part and cohort values ≥ LLOQ
- Time from Previous Vaccination (time from the most recent COVID-19 vaccination to the trial vaccination)
  - Time is calculated in months as (date of trial vaccination – date of most recent vaccination + 1)/30.4375
  - Times are categorized based on the median within part and cohort
- History of SARS-CoV-2 Infection (Yes vs. No)
- Baseline Comorbidity (Yes vs. No, see Section 4.1.6 for definition)

Descriptive analyses will be performed for each cohort similar to those described above, as well summaries for Cohort 1+2 combined. Comparisons will not be made for Part B as it has a single arm and is open label.

4.4. Exploratory Endpoints Analysis

4.4.1.1. Definition of Endpoints

Exploratory endpoints include the following:

Part A

ELISA Results

GMT of total binding IgG antibodies against the SARS-CoV-2 index virus at 2 weeks after trial vaccination in subsets of each Part A cohort.

Geometric mean fold increases, from baseline to post-baseline time points after trial vaccination, in total binding IgG antibodies against the SARS-CoV-2 index virus in subsets of each Part A cohort.

Neutralizing Antibody Results

Geometric mean fold increases, from baseline to post-baseline time points after trial vaccination, in neutralizing antibodies against the SARS-CoV-2 index virus and against the SARS-CoV2 VOCs circulating at the time of the trial.

GMT of neutralizing antibodies against the SARS-CoV-2 index virus and the SARS-CoV-2 VOCs circulating at time of the trial, at 1, 4, 13 and 26 weeks after trial vaccination in subsets of each Part A cohort.

Part B

ELISpot Results

Geometric means of SARS-CoV-2-specific T cells secreting interferon-γ / interleukin-4 at 1 week after ABNCoV2 vaccination within the immunogenicity subsets of each Part B cohort.

4.4.1.2. Main Analytical Approach

Geometric means and their corresponding 95% CIs will be used to summarize total IgG binding antibodies measured by ELISA in a subset of Part A subjects by cohort, vaccination arm, and time point. Age and baseline total IgG binding antibody results will be included as covariates in the model to compare the vaccination arms. The LS Means and 95% CIs from the model will be back transformed to their original scale. The difference between the ABNCoV2 and Comirnaty vaccination arms in the Part A cohorts, with respect to total IgG binding antibody results, will be described using the ratio of the GMTs (ABNCoV2 vs. Comirnaty) and corresponding 95% CIs, within each cohort, from the same model.

Cellular immune responses including SARS-CoV-2 specific T cells secreting interferon-γ and interleukin-4 measured by ELISpot in subsets of both Part B cohorts will also be summarized using geometric means and 95% CIs.

Fold increases, defined as post-baseline result divided by the baseline result, for Part A ELISA results and Part B ELISpot results will be summarized by trial part, assay, cohort, vaccination arm (for Part A ELISA only), and time point. Geometric mean fold increases and corresponding 95% CIs will also be calculated.

The Part A ELISA results as well as the Part B ELISpot results will also be plotted as GMTs/GMSFUs and CIs over time for each assay, cohort, and vaccination arm (Part A ELISA) on the $\log_{10}$ scale.

The combined cohort analyses will be similar to the analyses performed for each cohort.

Durability of neutralizing antibody results at 3 months and 6 months will be analyzed within the corresponding kinetics analysis set (Section 3) using GMTs, fold increases, and 95% CIs. These will be produced for subjects who are in the IAS for the primary endpoint analysis and provide serum samples at the 3 month or 6 month follow up visits, respectively. Both tables and figures will be presented by time point starting with baseline.

4.4.1.3. Sensitivity Analyses

There are no sensitivity analyses for the exploratory endpoints.

4.4.1.4. Supplementary Analyses

There are no supplementary analyses planned for the exploratory endpoints.

4.4.1.5. Subgroup Analyses

For the summaries of total IgG antibody response by ELISA, the same subgroup analyses performed for the primary estimand analysis in Section 4.2.5 will be presented for Part A.

4.5. Safety Analyses

4.5.1. Extent of Exposure

Exposure to trial vaccine will be presented as the number of subjects receiving the trial vaccine within trial part, cohort, and vaccination arm (for Part A). The number and percentage of subjects

returning memory aids for the Safety Analysis Set will also be presented. All exposure and diary data will be listed.

4.5.2. Adverse Events

An AE is defined as any untoward medical event occurring after a subject has signed the informed consent form; it does not necessarily have a causal relationship associated with the administration of the trial vaccine.

4.5.2.1. Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that:

- Results in death,
- Is life-threatening,
- Requires in-patient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability or incapacity,
- Results in a congenital anomaly or birth defect, and/or
- Is an otherwise important medical event.

The criteria for an event being serious will be captured in the AE eCRF as reported by the investigator.

4.5.2.2. Causality

Relationship of the trial vaccine to the AE is assessed by the investigator using the categories "none", "unlikely", "possible", "probable", and "definite." An AE assessed as possibly, probably, or definitely related will be counted as a related AE for the purpose of reporting. AEs categorized as none or unlikely related will not be considered related to trial vaccination. All AEs without a causality assessment from the investigator will preliminarily be classified as "possible".

4.5.2.3. Adverse Events of Special Interest

Adverse events of special interest (AESIs) are generally defined as AEs that meet the following criteria:

- Known association with immunization or a specific vaccine platform;
- Theoretical association based on animal models;
- Occurrence during wild type disease as a result of viral replication and/or immunopathogenesis.

AESIs for ABNCoV2-03 are defined per Section 11.9 of the clinical trial protocol. An AE cannot be considered an AESI unless it occurs after the trial vaccination. For analyses, the investigator flagging of the AESI in the eCRF will be used to define AESIs.

4.5.2.4. Medically Attended Adverse Events

Medically attended AEs (MAAEs) are defined as AEs with medically attended visits that were not routine visits for physical examination or vaccination, such as visits for hospitalization, an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason. MAAEs for non-serious AEs are flagged on the eCRF. SAEs requiring hospitalization are also considered MAAEs for analysis purposes.

4.5.2.5. Solicited Adverse Events

Solicited AEs are defined as all symptoms specifically listed in the memory aid provided to the subjects following vaccination. After vaccination, the subjects are requested to monitor and record local symptoms (i.e., erythema, swelling, induration, pruritus and pain at the injection site) as well as general symptoms (i.e., body temperature increase/pyrexia, headache, chills, myalgia, nausea and fatigue) in the memory aid daily for the day of vaccination and the following 7 days (Days 1 to 8, an 8-day period). If symptoms persist at Day 8, daily symptoms and temperatures will be documented each day until resolved. Solicited AEs that meet the criteria for SAEs will be documented in the AE eCRFs.

There will be 2 sets of grading for solicited local (Table 6) and general (Table 7) AEs. Memory aids for solicited AEs were reviewed and collected using the Bavarian Nordic (BN) standard grading scale, but in an effort to align with the FDA's *Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials*, events that were collected in millimeters (mm) or degrees (°) will be mapped to the FDA grading scale for the primary analysis of solicited AEs. Grading using the BN standard grading scale will also be presented as a sensitivity analysis to compare to the FDA grading scale analysis and to prior trial results. In the grading tables for solicited AEs, the primary analysis scale using the FDA grading is labeled "Grading for Analyses" and the historical BN standard grading scale is labeled "Grading Assessed at Diary Review."

Solicited Local AEs

Occurrence, intensity, and duration of solicited local AEs during the 8-day period after vaccination will be summarized for each vaccination arm within cohorts and combined cohorts. Note, solicited local AEs are always assumed to be related to vaccination so no summaries based on causality will be performed.

Injection site erythema, swelling, and induration will be measured using a provided ruler, and the maximum diameter will be recorded for each day on the memory aid. The intensity for these symptoms u be graded as follows:

Table 6: Solicited Local Event Grading

	Grading for Analyses		Grading Assessed at Diary Review	
	Grade	**Severity Measure[a]**	**Grade**	**Severity Measure**
Injection site erythema, Injection site swelling, and Injection site induration[b] (longest diameter)	0	0 cm	0	0 mm
	1	2.5 - 5.0 cm	1	<30 mm
	2	5.1 – 10 cm	2	≥30 – <100 mm

	3	> 10 cm	3	≥100 mm
Injection site pruritus	Same as assessed at diary review		0	Absent
			1	Mild
			2	Moderate
			3	Severe
Injection site pain	Same as assessed at diary review		0	Absent
			1	Pain on touch
			2	Painful when limb is moving
			3	Spontaneously painful/prevents normal activity

[a]Per FDA "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials", September 2007. Available at https://www.fda.gov/media.73679/download. Note, values measured in cm between 0 and 2.5, exclusive, will be assigned a grade of 0.

[b]Per FDA guidance, injection site swelling, and induration are combined into one scale (i.e., injection site swelling/induration).

Solicited General AEs

Occurrence, relationship, intensity, and duration of solicited general AEs during the 8-day period after vaccination will be summarized for each vaccination arm within cohorts and combined cohorts based on the grades defined below:

Table 7: Solicited General Event Grading

MedDRA coded Preferred Term	**Grading for Analyses**		**Grading Assessed at Diary Review**	
	Grade	**Severity Measure[a]**	**Grade**	**Severity Measure**
Body temperature (oral)[b]	0	<38.0°C (<100.4°F)	0	< 37.5°C (< 99.5°F)
	1	38.0 – 38.4°C (100.4 – 101.1°F)	1	≥ 37.5 – < 38.0°C (≥99.5 – <100.4°F)
	2	38.5 – 38.9°C (101.2 – 102.0°F)	2	≥ 38.0 – < 39.0°C (≥100.4 – <102.2°F)
	3	39.0 – 40.0°C (102.1 – 104.0°F)	3	≥ 39.0 – < 40.0°C (≥102.2 – <104.0°F)
	4	>40.0°C (>104.0°F)	4	≥ 40.0°C (≥ 104.0°F)
Headache, Myalgia, Nausea, Chills and Fatigue		Same as assessed at diary review	0	None
			1	Mild: easily tolerated, minimal discomfort and no interference with daily activity

			2	Moderate: Some interference with daily activity
			3	Severe: Prevents daily activity

[a]Per FDA "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials", September 2007. Available at https://www.fda.gov/media/73679/download.
[b]Pyrexia is defined as oral temperature ≥ 38.0^{0}C (≥ 100.4^{0}F), which is fever Grade ≥1 by FDA grading and oral temperature Grade ≥2 as assessed at diary review.

Causal relationship between solicited general AEs and the vaccine will be assessed by the investigator as described in Section 4.5.2.2.

Analysis

Solicited AEs will be summarized by AE term for overall occurrence and by maximum intensity using frequencies and percentages. Note, only solicited events with intensity grades above 0 are considered AEs; however, subjects reporting intensity grades of 0 for the collection period will be included in summaries to account for all observed memory aid data. As intensity is still collected daily for ongoing events after day 8 of the memory aid reporting period, the maximum intensity used in summaries will be derived from the entire duration of the event and not just from the 8-day reporting period.

Summaries will be presented by cohort and vaccination arm (ABNCoV2 versus Comirnaty) for Part A, and by cohort for Part B separately using 2 different grade scales (Grading for Analyses per FDA Guidance and Grading Assessed at Dairy Review) according to Table 6 for local AEs and Table 7 for general AEs.

In addition, duration of solicited events will be summarized only for subjects experiencing the event of interest using n, mean, SD, median, Min, and Max. Although the collection period is 8 days including the day of vaccination, durations may be longer than 8 days if the solicited event is ongoing at Day 8.

Additional summaries of the subset of general AEs determined to be related to vaccination, as well as those considered both related and ≥ Grade 1 and related and ≥ Grade 3 using the Grading for Analysis scale per FDA Guidance, will also be presented using frequencies and percentages.

The solicited AE information from the memory aid as well as the physician's assessments and durations will be included in subject-level listings.

Figures will be presented for all solicited local and general AEs overall and for the subset of ≥ Grade 3 (based on Grading for Analysis scale per FDA Guidance) solicited AEs by cohort (Parts A and B) and vaccination arm within cohort (Part A only).

4.5.2.6. Unsolicited Adverse Events

Unsolicited AEs will be assessed and documented from ICF signature through EAP, and if ongoing at that time followed until resolution or until the subject's last trial visit, at the latest. SAEs, AESIs, and MAAEs will be collected through the end of the trial, including during the FU phase, and followed-up until resolution or achievement of stable clinical conditions.

Unsolicited AEs are graded based on the *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials*. The maximum toxicity grade over the duration of the AE will be reported in the eCRF. If a subject has multiple AEs

within the same PT, the highest toxicity grade will be used for subject-level summaries. Grading will be based on the descriptions listed in Table 8.

Table 8: Adverse Event Grading

Grade	Definition
Grade 1	An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with daily activities.
Grade 2	An AE which is sufficiently discomforting to interfere with daily activities, but does not require medical intervention (non-narcotic pain reliever or other nonprescription medication are not considered "medical intervention" for this purpose).
Grade 3	An AE which prevents daily activities and which requires medical intervention (non-narcotic pain reliever or other nonprescription medication are not considered "medical intervention" for this purpose)
Grade 4	Life-threatening, or disabling.

Analysis

In general, AEs will be summarized separately by trial part for the Safety Analysis Set in each phase (the Entire Trial Phase, Active Trial Phase, and Follow-up Phase). Within each part, cohort, and vaccination arm (Part A only), AEs will be further presented by SOC and PT. AEs occurring between ICF signature and trial vaccination will be considered Baseline Signs and Symptoms and will be reported in a similar fashion to medical history events.

Summary tables for all AEs by SOC and PT will be presented including subject and event counts, as well as percentages of subjects for the Active Trial Phase:

- AEs
- Related AEs
- AEs ≥ Grade 3
- Related AEs ≥ Grade 3
  - Related AEs ≥ Grade 3 Occurring within 8 Days of Trial Vaccination
- SAEs
- Related SAEs
  - Related SAEs Occurring within 8 Days of Trial Vaccination
- AESIs
  - Related AESIs
- MAAEs
  - Related MAAEs
- AEs Leading to Discontinuation of the Active Trial Phase
- Non-serious AEs in > 5% of Subjects

In addition, a combined summary of AEs will be presented for related SAEs, related unsolicited AESIs, related ≥ Grade 3 AEs, and AEs leading to discontinuation within 8 days after vaccination. Grading for analysis per FDA guidance will be used for all combined summaries including solicited AEs.

An overall combined summary of solicited and unsolicited AEs including subject counts, event counts, and percentages of subjects experiencing the AE will be created for the following event categories:

Solicited and Unsolicited AEs

- All AEs
- SAEs
- AEs ≥ Grade 3 (using Grading for Analysis per FDA Guidance for solicited AEs)
- AESIs
- MAAEs
- Related AEs
- Related SAEs
- Related AEs ≥ Grade 3
- AEs Leading to Withdrawal from Trial

Solicited AEs

- Local AEs
  - AEs ≥ Grade 3 Within 8 Days of Vaccination
  - SAEs
- General AEs
  - SAEs
  - AEs ≥ Grade 3
  - Related AEs
  - Related AEs within 8 Days of Vaccination
  - Related AEs ≥ Grade 3
  - Related AEs ≥ Grade 3 within 8 Days of Vaccination
  - AEs Leading to Deferral or Discontinuation of Vaccine

Unsolicited AEs

- All AEs
  - SAEs
  - Related AEs

  - AESIs
  - AEs ≥ Grade 3
  - AEs ≥ Grade 3 within 8 Days of Vaccination
  - Related SAEs
  - Related AESIs
  - Related AEs ≥ Grade 3
  - Related AEs ≥ Grade 3 within 8 Days of Vaccination
  - MAAEs
  - AEs Leading to Withdrawal from Trial
  - Fatal AEs
- SAEs
  - Within 8 Days of Vaccination
  - Related SAEs
  - Fatal
- AESIs
  - Within 8 Days of Vaccination
  - Related AESIs
- Related AEs ≥ Grade 3
  - Within 8 Days of Vaccination

Tables summarized by SOC and PT will be sorted in order of descending incidence of SOCs in the ABNCoV2 column under the combined Cohorts 1+2 column for Parts A and B, and descending order of incidence of PTs within the SOCs. For subject level frequencies and percentages, subjects experiencing an event more than once will be counted only once within SOC and PT; however, all events will be counted in the event column.

All AEs will be listed by trial part, cohort, vaccination (Part A only), subject, onset date, SOC, and PT. Separate listings will be created for SAEs, AESIs, AEs ≥Grade 3, AEs leading to discontinuation of the Active Trial Phase, and fatal AEs. Listings will include all AEs regardless of trial phase. Both grading scales for the solicited AEs will be listed.

4.5.3. Laboratory

A list of laboratory parameters collected is included in Section 11.11 of the Clinical Trial Protocol. For the purpose of analysis, laboratory data will be converted to standard Système International d'Unités (SI) units during creation of the SDTM datasets. The original laboratory values and units will also be stored in the SDTM datasets. Only the SI units will be used in tables and listings. SI units and conversions will be included in the SDTM documentation.

All measured laboratory values will be listed and summarized at each scheduled visit using descriptive statistics. Laboratory values out of normal range will be flagged as either "L" for below normal range or "H" for above normal range in listings. Clinically significant abnormal laboratory values are recorded as AEs and summarized along with the unsolicited AEs.

Toxicity will be graded based on the *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials*. Grade 1 or Grade 2 toxicity is only graded according to this scale if the value is outside of the institutional normal range applicable for this trial.

All laboratory tables will be presented by each trial part separately and within each part, by cohort and vaccination arm for Part A and by cohort for Part B.

Shift tables will be used to evaluate categorical changes in toxicity levels from baseline to each scheduled time point, as well as to worst toxicity grade during the Active Trial Phase, for laboratory parameters graded per the above toxicity scale.

For laboratory parameters not graded per the above toxicity scale, similar shift tables will be created based on the laboratory provided normal ranges (Low, Normal, High). Summary tables will be produced for the number of high and low laboratory values at each scheduled time point by laboratory category and parameter.

All laboratory results will be listed. Pregnancy test results will only be included in listings.

4.5.4. Vital Signs

Vital signs will be graded as described in Table 9 below, per the *Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials.* Summaries will focus on subject level changes using shifts from baseline in toxicity grade or normal range indicator. Summaries will be performed within trial part (A or B), cohort (Cohort 1, Cohort 2, and Cohort 1+2), and by vaccination arm for Part A.

Table 9: Vital Signs Grading

Vital Signs	Units	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life Threatening (Grade 4)
Fever	(°C)	38.0 – 38.4	38.5 – 38.9	39.0 – 40.0	> 40.0
	(°F)	100.4 – 101.1	101.2 – 102.0	102.1 – 104.0	> 104.0
Tachycardia	beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia	beats per minute	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic)	mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant

					hypertension
Hypertension (diastolic)	mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic)	mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock

ER = emergency room; mm Hg = millimeters of mercury.

Note, the Grade 4 categories requiring a corresponding emergency room visit or hospitalization will not be included in this analysis, as they should be reported separately as SAEs. The frequency and percentage of subjects experiencing Fever, Tachycardia, Bradycardia, Hypertension (systolic and diastolic), and Hypotension (systolic) will be summarized for the Active Trial Phase for any occurrence and by grade within vaccination arm (part A), cohort, and trial part.

4.5.5. Electrocardiograms

ECGs are only required to be performed at screening to confirm the subject is eligible for the trial. Post-vaccination ECGs are performed only if clinically indicated; therefore, results from ECGs will be included only in subject level listings.

4.5.6. Other Safety Endpoints

4.5.6.1. SARS-CoV-2 Infection Results via PCR

The frequency and percentage of subjects testing positive for COVID-19 infection via PCR test by visit any time after trial vaccination will be summarized by vaccination arm for each of the cohorts in Part A. For Part B, proportions will be summarized for each cohort by timepoint and overall. As collection may occur during unscheduled visits, frequencies and percentages will include all subjects who tested positive between the prior visit through the summarized visit. PCR testing and results will also be listed.

4.5.6.2. SARS-CoV-2 Infection Results via Nucleocapsid Protein Testing

Nucleocapsid protein IgG results will be listed. The results will support a sensitivity analysis of the primary immunogenicity endpoint excluding subjects with an increase in nucleocapsid protein IgG levels potentially indicative of a natural SARS-CoV-2 infection prior to the immunogenicity testing visit.

4.5.6.3. Physical Examinations

The performance of physical examinations will be listed. Findings upon physical examination at screening will be added to the Medical History case report form if they started prior to the signing of the ICF, and to the AE case report form page if starting afterward.

4.6. Other Analyses

4.6.1. Disposition

All subjects screened will be accounted for in disposition summaries. A summary table will be presented specifying the number of subjects who were screened, were vaccinated, completed the active trial phase, completed the trial, completed each FU visit, and are included in each analysis set. Subjects who discontinued will also be summarized by reason for discontinuation from the active trial phase and/or the trial. Subjects who completed or discontinued early during the Active Trial Phase but completed all FU visits will be considered as having completed the trial.

A listing will be presented for all vaccinated subjects by trial part and cohort.

4.6.2. Analysis Populations

Frequencies and percentages of each analysis population will be presented by vaccination arm (for part A) and by cohort. All subjects who signed ICF but are not eligible for the trial will be listed, including the reason for ineligibility. Reasons for exclusion from the IAS will be presented in a table.

4.6.3. Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol. The non-compliance may be either on the part of the subject, the investigator, or the trial site staff. Protocol deviations are collected on both the site level and the subject level. Subject-level deviations will be databased and listed. Categorized deviations will be presented using frequencies and percentages for the Safety Analysis Set.

4.6.4. Demographics and Baseline Characteristics

Tables of descriptive statistics for demographics will be produced for the Safety Analysis Set and the IAS. Descriptive statistics will be presented for the continuous demographic variables. Categorical demographic and baseline variables will be summarized using frequencies and percentages. The following demographic variables will be presented.

Demographic Variables

- Age at Informed Consent (years)
- Age Group (18 to <65 years, ≥ 65 years)
- Sex (Male, Female)
- Race (White, Black or African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, Multiple, Not Reported)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- BMI [kg/m^2]
- Prior vaccination regimen
    - Cohort 1:
        - 2 doses of mRNA vaccine,

        - 1 dose or 2 doses of adenovirus-based vaccine,
        - 1 dose of adenovirus-based vaccine followed within 3 months by 1 dose of mRNA vaccine,
        - Other authorized primary vaccination regimen.
    - Cohort 2:
        - 2 doses of mRNA primary vaccines plus 1 booster dose of mRNA vaccine,
        - 1 dose or 2 doses of adenovirus-based primary vaccines plus 1 booster dose of mRNA vaccine,
        - Other authorized primary vaccination and boost vaccination combinations.
- Baseline Neutralizing Antibody Result (< LLOQ, ≥ LLOQ to < median, ≥ median)
    - Median is calculated from the corresponding trial part and cohort values ≥ LLOQ
- Time from Previous Vaccination (time from the most recent COVID-19 vaccination to the trial vaccination)
    - Time is calculated in months as (date of trial vaccination – date of most recent vaccination + 1)/30.4375
- History of SARS-CoV-2 Infection (Yes vs. No)
- Baseline Comorbidity (Yes vs. No, see Section 4.1.6)

4.6.5. Prior and Conc omitant Medications

Displays of **prior** medications include medications where end date is before date of administration of trial vaccine. Displays of **concomitant** medications include all ongoing medications, medications with missing end dates, or medications with end date after administration of trial vaccination. Tables by ATC Level 2 class and preferred name will be presented for the Safety Analysis Set. If ATC Level 2 class is not available, the next highest class available will be used. Subject level listings will be created by trial part, cohort, vaccination received (Part A only) subject, ATC Level 2 class, preferred name, verbatim term, medication start and end dates, and medication ongoing status.

4.6.6. Medical History and Baseline Signs and Symptoms

Medical history data are collected at screening and include conditions that started prior to signing of the ICF. Baseline signs and symptoms are adverse events that occurred between signing of the ICF through the time just prior to trial vaccination. These data are coded according to MedDRA similarly to AEs. Medical history events and baseline signs and symptoms combined will be summarized by trial part, cohort, and vaccination arm (Part A only) within SOC and PT for the Safety Analysis Set to give a full accounting of pre-vaccination prevalence of events in the trial population. SOCs and PTs within SOCs will be sorted by descending frequency in the overall column for Cohorts 1+2 combined.

Separate subject level listings will be generated for Medical History and Baseline Signs and Symptoms as they were collected separately.

4.6.7. Prior COVID-19 Vaccination and History

Prior vaccination for SARS-CoV-2 was recorded at baseline and will be reported separately from prior medications, but in the same fashion as prior medications.

Prior COVID-19 infection and prior hospitalization for COVID-19 infection will be included as a baseline COVID-19 related characteristic. Individual infection events and associated hospitalizations will be included in a listing, including the start and end date of the events.

For Part A subjects, prior COVID-19 vaccination regimen was a randomization stratification factor. The subgroup analysis for the primary objective by prior vaccination will be performed both as randomized as well as by the derived prior vaccination regimen from the COVID-19 vaccination data.

4.6.8. Time to COVID-19 Infection

Time to COVID-19 infection in days will be summarized within trial part for each cohort and vaccination arm (for Part A only) using the safety analysis set as an exploratory safety analysis. PCR results and AE data will be used to determine the occurrence of COVID-19 infection for each subject, as well as the date of COVID-19 infection. Subjects with multiple infections during the trial will be analyzed using their earliest detected infection. Subjects who do not have a positive COVID-19 result will be censored at the date of the last visit attended prior to the analysis.

The date of earliest detected infection will be calculated as the minimum of a positive PCR sample collection date or the start date of an AE of COVID-19.

Time to COVID-19 infection will be calculated in days as (Date COVID-19 infection – Date of trial vaccination) + 1. Median time to COVID-19 infection within each cohort and vaccine arm (for Part A only), as well as for both cohorts combined, will be based on Kaplan-Meier estimates and corresponding 95% CIs based on the Brookmeyer-Crowley method. Along with the time to COVID-19 analyses, frequencies of subjects with COVID-19 infections will also be presented by visit. Time to COVID-19 infection plots will be created for each cohort and vaccination arm (for Part A only).

4.6.9. Thrombocytopenia

An exploratory safety analysis of thrombocytopenia will be performed for the active trial phase. To explore prevalence at baseline, both Medical History and Baseline Signs and Symptoms will be reviewed for pre-existing cases. Events will be queried based on the MedDRA high level term of “Thrombocytopenias” and the MedDRA preferred term of “Platelet count decreased”.

Post vaccination AE data will also be reviewed for incidences of thrombocytopenia using the same MedDRA high level term of “Thrombocytopenias” and the MedDRA preferred term of “Platelet count decreased”.

A summary of changes from baseline in platelet counts to the worst post-vaccination value (based on the lowest post-vaccination platelet count) will also be analyzed by trial part, cohort,

and vaccination arm (Part A only). Continuous summary statistics will be provided for both the actual values at baseline and worst value post-vaccination, as well as for the change from baseline to worst post-vaccination value. A histogram of the changes from baseline for the combined cohorts will be created with groupings for vaccination arm in Part A, and overall for Part B.

4.6.10. Hyperkalaemia

An exploratory safety analysis of hyperkalemia will be performed for the active trial phase in a similar fashion to thrombocytopenia. To explore prevalence at baseline, both Medical History and Baseline Signs and Symptoms will be reviewed for pre-existing cases. Events will be queried based on the MedDRA preferred terms of "Hyperkalaemia" and "Blood potassium increased".

Post-vaccination AE data will also be reviewed for incidences of hyperkalaemia using the same MedDRA preferred terms of "Hyperkalaemia" and "Blood potassium increased".

A summary of changes from baseline in potassium levels to the worst post-vaccination value (based on the highest post-vaccination potassium level) will also be analyzed by trial part, cohort, and vaccination arm (Part A only). Continuous summary statistics will be provided for both the actual values at baseline and worst value post-vaccination, as well as for the change from baseline to worst post-vaccination value. A histogram of the changes from baseline for the combined cohorts will be created with groupings for vaccination arm in Part A, and overall for Part B.

4.7. Interim Analysis

The primary analysis for the trial will occur after subjects have completed the 2 months of follow-up within a trial part. A data review meeting will take place to review any potential exclusions from the Immunogenicity Analysis Set. Once the trial data are clean and any queries resulting from the data review meeting are resolved, the database will be locked and unblinded for the analysis. Planned immunogenicity and safety analyses will be performed once the lock has occurred and the immunogenicity results are available. A full CSR will be written for this analysis.

4.8. Changes to Protocol-planned Analyses

Nucleocapsid Protein IgG Testing

A change from the protocol on the use of the nucleocapsid antibody testing to define intercurrent events for the primary estimand has been incorporated into this SAP. The intercurrent event of COVID-19 infection, and use of the "while on treatment" strategy, is only intended to exclude the significant effects an infection would have on the immunogenicity response for a subject. The antibody response to the trial vaccine could not be distinguished from the antibody response to a SARS-CoV-2 infection in this situation. As no current vaccines contain the nucleocapsid protein, the nucleocapsid IgG test was added to ensure subjects with recent infections were not included in the analyses.

Nucleocapsid protein IgG testing results in a study of the kinetics of these antibodies after SARS-CoV-2 infection show the average peak occurred 72 days after a positive PCR test result,

and a 90.8% sensitivity in samples collected >14 days after the start of symptoms (Loesche, 2022). This suggests that subjects who had SARS-CoV-2 infection prior to baseline may continue to have increases in antibody levels against the nucleocapsid protein during the 2-week period from baseline to the primary endpoint time point. On the other hand, subjects who had new infection after baseline may not have significant increases during the short period of time. Thus, the nucleocapsid protein antibody results are not a good indicator for natural infection acquired between baseline and Week 2.

The risk of missing natural COVID-19 infections by not accounting for nucleocapsid IgG test results is low. Subjects are required to test negative for COVID-19 at screening via PCR test. Additionally, those attending the Week 1 or Week 2 visits with clinically relevant symptoms are tested by PCR for infection, such that concurrent infections during the 2 week period should be captured either by PCR test or adverse event reporting.

The risk of excluding subjects who had older infections that may have occurred prior to baseline is not negligible due to the kinetics of the nucleoprotein protein IgG test. Therefore, in the interest of having a more inclusive primary analysis it has been decided to remove the nucleocapsid protein IgG testing from the intercurrent event of COVID-19 infection and retain the results for a sensitivity analysis.

Analysis Sets

The following analysis sets were added to better define how the kinetic analyses will be performed:

- Kinetics Analysis Set – 3 Months
- Kinetics Analysis Set – 6 Months

Additional Analyses

An analysis of time to COVID-19 infection was added as an exploratory safety analysis. In addition, analyses of thrombocytopenia and hyperkalemia have been added as exploratory safety analyses.

5. SAMPLE SIZE DETERMINATION

5.1. Part A

The primary and key secondary analyses are planned to be tested in the randomized, double-blind component of the trial (Part A) in both Cohort 1 and Cohort 2. Two non-inferiority tests are planned. Therefore, the sample size calculation is based on a 1-sided, 0.0125 type I error, α, to control for both tests. This will maintain the trial-wide α at 0.025 for the 1-sided null inferiority hypotheses.

Based on data from the ABNCoV2 phase 2 trial, we assume the common standard deviation to be 0.52 for $\log_{10}$ transformed neutralizing antibody results. The test of non-inferiority of ABNCoV2 compared with Comirnaty will be performed by comparing the lower end of the 97.5% CI with a non-inferiority margin of 0.67 in the ratio of neutralizing antibody GMTs between the 2 arms. We further assume a 10% non-evaluable rate due to dropouts or invalid samples. With an evaluable sample size of 450, a 1-sided test with an α of 0.0125 will have approximately 90% power to reject the null hypothesis that ABNCoV2 is inferior to Comirnaty.

A minimum sample size of 400 evaluable subjects will be required for the non-inferiority hypothesis test to be performed for the primary endpoint within each cohort. In the event the evaluable sample size is as low as 400, the power to reject the null hypothesis that ABNCoV2 is inferior to Comirnaty is approximately 86%. If the minimum sample size is not met in 1 of the cohorts regardless of recruitment effort, data from the cohort will be summarized descriptively and will be integrated in the combined-cohort analyses.

For the key secondary analyses, the number of hypothesis tests to be performed will depend on the number of VOCs with immunogenicity results available. VOCs will only be formally tested sequentially in the separate Part A cohorts and in the 2 cohorts combined.

5.2. Part B

The sample size for Part B is not based on formal statistical hypothesis testing, but rather on the number of subjects exposed to ABNCoV2 considered adequate for safety population analyses and may be adjusted depending on enrollment in Part A. A total of 3000 subjects (for example, 2500 from Part B plus 500 from Part A who will receive ABNCoV2) would allow for 95% power to detect an AE with an incidence rate as low as 0.1%.

The immunogenicity subset in Part B will consist of approximately 200 to 250 subjects in each cohort. This subset sample size is based on feasibility alone, i.e., the number of participating sites and consenting subjects.

5.3. Immunogenicity Sampling

As the sample size needed for safety endpoints is larger than those needed for the immunogenicity endpoints, the following table includes a summary of the number of samples used for the individual immunogenicity endpoint analyses:

Table 10: Immunogenicity Sampling and Analysis by Endpoint

Endpoint	Part A		Part B	
	Cohort 1	Cohort 2	Cohort 1	Cohort 2
Index Virus Serum Samples Baseline and Week 2	All	All	~250 subjects	~250 subjects
VOCs Serum Samples Baseline and Week 2	All	All	N/A	N/A
Index Virus Serum Samples for Exploratory Timepoints: Weeks 1, 4, 13, and 26	All	~250 subjects	N/A	N/A
VOCs Serum Samples for Exploratory Timepoints: Weeks 1, 4, 13, and 26	All	All	N/A	N/A
ELISA	All	~250 subjects	N/A	N/A
ELISpot	N/A	N/A	All PBMC subset subjects with matching baseline and post baseline visits	All PBMC subset subjects with matching baseline and post baseline visits

6. SUPPORTING DOCUMENTATION

APPENDIX 1. SCHEDULE OF EVENTS

Visit	**SCR**	**V1**	**V2**	**V3**	**V4/ EAP**	**FU1 (phone)**	**FU2**	**FU3**
Day / Visit +… Days	**V1 -14 – -1**	**Day 1**	**V1[a] +5–7**	**V1[a] +12–16**	**V1[a] +28–35**	**V1[a] +56–70**	**V1[a] +91–105**	**V1[a] +182–196**
Target week	-2	0	1	2	4	8	13	26
Target month		0			1	2	3	6
Informed consent	X							
Eligibility assessment	X	X						
Demographics collection	X							
Medical history review	X							
Physical examination (including height, weight, BMI)[b]	X							
ECG[b]	X							
Evaluation of vital signs[b]	X	X	X	X	X		X	X
Recording of prior and concomitant medication	X	X	X	X	X			
Blood draw for safety labs[b]	X			X	(X)[c]			
Pregnancy test for WOCBP[d]	X	X			X			
Counseling on avoidance of pregnancy for WOCBP[e]	X	X						
Hep-B, HCV, HIV test	X							
SARSCoV2 infection PCR test	X		(X)[f]	(X)[f]	(X)[f]		(X)[f]	(X)[f]
Targeted physical exam (including auscultation of the heart and lungs)[b]		X	X	X	X		X	X

Visit	SCR	V1	V2	V3	V4/ EAP	FU1 (phone)	FU2	FU3
Day / Visit +… Days	**V1 -14 – -1**	**Day 1**	**V1[a] +5–7**	**V1[a] +12–16**	**V1[a] +28–35**	**V1[a] +56–70**	**V1[a] +91–105**	**V1[a] +182–196**
Target week	-2	0	1	2	4	8	13	26
Target month		0			1	2	3	6
AE/SAE/SAR/AESI/MAAE recording	X	X[g]	X	X	X	X[h]	X[h]	X[h]
Blood collection for serum antibody titers and nucleocapsid protein antibody testing[i], Part A		X[i,j]	X	X[i]	X		X	X
Blood collection for serum antibody titers and nucleocapsid protein antibody testing, Part B immunogenicity subset		X[j]		X				
Blood collection for PBMCs, Part B immunogenicity subset[k]		X[j]	X					
Randomization[l]		X						
Handout of memory aid		X						
Trial vaccine administration and subject observation (≥30 minutes)		X						
Recording of immediate AEs		X						
Review/collection of memory aid[m]			X	(X)	(X)		(X)	(X)
Examination of injection site			X					

Abbreviations: AE = adverse event; AESI = adverse event of special interest; BMI = body mass index; EAP = end of active phase visit; ECG = electrocardiogram; FU1/FU2/FU3 = follow-up visits; Hep-B = hepatitis B; HCV = hepatitis C virus; HIV = human immune deficiency virus; MAAE = medically attended adverse event; PBMC = peripheral blood mononuclear cells; PCR = polymerase chain reaction; SAE = serious adverse event; SAR = serious adverse reaction; SARSCoV2 = severe acute respiratory syndrome coronavirus 2; SCR = Screening; V1-V4 = active phase, Visits 1 to 4; WOCBP = woman of childbearing potential.
X: mandatory; (X): if indicated/if applicable
Part A: randomized component; Part B: single-arm component
a The visit windows for V2, V3, V4/EAP, FU1, FU2, and FU3 will be calculated based upon the date of vaccination (V1) with either ABNCoV2 or Comirnaty.
b If clinically indicated, additional safety measures can be taken at any other trial visits or at unscheduled visits. Auscultation of the heart and lungs is to be performed at any physical examinations to check specifically for signs of any heart condition or respiratory disorders.
c Only for subjects who discontinued during the trial and are coming for EAP visit to obtain final safety data.

d At SCR, a serum pregnancy test must be performed. At V1 and EAP, a urine pregnancy test will be performed.
e Review of acceptable contraceptive methods and recent menstrual history with WOCBP.
f At any time during the trial starting after vaccination if clinically indicated, e.g., in the presence of COVID19 typical symptoms.
g AESIs and MAAEs are not collected until vaccine has been received at V1.
h During the follow-up period, data collection will be limited to SAEs, AESIs, and MAAEs, and any unsolicited AEs from the active trial phase that are not yet resolved.
i Nucleocapsid protein antibody testing will be done only on samples collected at V1 and V3.
j Any blood collected for serum or PBMC samples at V1 must be collected before vaccination. Baseline serum samples will also be tested for antibodies suggestive of previous COVID-19 infection.
k Immunogenicity subset blood samples will be collected at select US sites.
l Only for subjects enrolled in Part A.
m If symptoms persist at 7 days after vaccination, daily symptoms and temperature will continue to be measured and documented each day until resolved. Memory aid will be collected once it is complete.

APPENDIX 2. SAS CODE FOR MULTIPLE IMPUATION SENSITIVITY ANALYSIS

If >5% of Week 2 neutralizing antibody results are missing for Part A, the multiple imputation code will be run separately for both Part A cohorts, with the appropriate values for prior regimen, shown below, included in each model.

At the time of finalization of the statistical analysis plan, enrollment has completed, and Cohort 1 of Part A did not reach the required sample size for the primary analysis. The MI analysis of Cohort 2 of Part A only will be performed if there are >5% of Week 2 neutralizing antibody results missing.

titersl: the dataset containing the $\log_{10}$ neutralizing antibody results data along with the covariates used in the analysis, one record per subject.

- sex: Male vs. Female
- racegroup: White vs. Other
- agegroup: <65 years vs. ≥65 years
- priorreg (categories different by cohort):

  Cohort 1:
  - 2 doses of mRNA vaccine,
  - 1 dose or 2 doses of adenovirus-based vaccine,
  - 1 dose of adenovirus-based vaccine followed within 3 months by 1 dose of mRNA vaccine,
  - Other authorized primary vaccination regimen.

  Cohort 2:
  - 2 doses of mRNA primary vaccines plus 1 booster dose of mRNA vaccine,
  - 1 dose or 2 doses of adenovirus-based primary vaccines plus 1 booster dose of mRNA vaccine,
  - Other authorized primary vaccination and boost vaccination combinations.
- ltiterBL: Log_{10} Baseline Neutralizing Antibody Result
- ltiterW1: Log_{10} Week 1 Neutralizing Antibody Result
- ltiterW2: Log_{10} Week 2 Neutralizing Antibody Result

```
proc mi data=titersl out=titermi nimpute=100 seed=19201
                                 minimum=[log10(LLOD/2)];
    class sex racegroup agegroup priorreg;
    var sex racegroup agegroup priorreg ltiterBL ltiterW1;
```

```
    fcs nbiter=20 reg(ltiterW2 = ltiterBL ltiterW1 agegroup priorreg sex
racegroup /details);
run;

proc means data=titermi noprint nway;
 by _imputation_;
 var ltiterW2;
 output out=summ(drop=_type_ _freq_) n=n mean=logmn stderr=logse;
run;

ods output parameterestimates=PartACohort1Est;
proc mianalyze data=summ;
    modeleffects logmn;
    stderr logse;
run;
data PartACohort1Est2;
    set PartACohort1Est;
    GMT=10**estimate;
    GMT_LCL=10**LCLmean;
    GMT_UCL=10**UCLMean;
    keep estimate lclmean uclmean gmt:;
    label estimate='Mean Log10 Titers'
          lclmean='Lower 95% CI of the Mean Log10 nAb Result'
          uclmean='Upper 95% CI of the Mean Log10 nAb Result'
          gmt='Geometric Mean Titer'
          GMT_LCL='Lower 95% CI of the Geometric Mean nAb Result'
          GMT_UCL='Upper 95% CI of the Geometric Mean nAb Result'
run;
```

(Repeat for Part A Cohort 2 if sample size for cohort meets minimum for non-inferiority testing.)

7. REFERENCES

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