Clinical Trial Protocol

EudraCT # 2021-005504-36

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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

30-Jun-2023

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1 General Information

1.1 Abbreviations

ACE2	angiotensin-converting enzyme 2
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphokinase
ALT	alanine amino transferase
[redacted]	[redacted]
AST	aspartate aminotransferase
β-HCG	beta-human chorionic gonadotropin
BMI	body mass index
BN	Bavarian Nordic
CBER	Center for Biologics Evaluation and Research
CI	confidence interval
COVID-19	coronavirus disease 2019
CRA	clinical research associate
CRO	contract research organization
CSPV	clinical safety and pharmacovigilance
CSR	clinical study report
CTS	clinical trial site
cVLP	capsid virus-like particles
DMC	data monitoring committee
EAP	end of active phase
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme-linked immunoassay
ELISpot	enzyme-linked immuno spot assay
EU	European Union
EUA	emergency use authorization
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FDA	US Food and Drug Administration
FU	follow-up
GCP	good clinical practice
GMT	geometric mean titer
HBsAG	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	investigator brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee

IgG	immunoglobulin G
IM	intramuscular
IMP	investigational medicinal product
IND	investigational new drug application
IRB	institutional review board
IU	international units
LLOQ	lower limit of quantification
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
NCT	ClinicalTrials.gov national clinical trials number
NHP	nonhuman primates
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PI	principal investigator
PRNT	plaque reduction neutralization test
QTc	QT interval corrected
RBD	receptor-binding domain
SAE	serious adverse event
SAR	serious adverse reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SUSAR	suspected unexpected serious adverse reactions
SOP	standard operating procedure
US	United States
VOC	variant of concern
WOCBP	women of childbearing potential

1.2 Definitions

active control arm	Comirnaty (tozinameran, BNT162b2, Pfizer/BioNTech) SARS-CoV-2 vaccination.
active trial phase	The period from the trial vaccination up to and including the end of active trial phase (EAP) visit at 28 to 35 days after trial vaccination.
locally authorized SARS-CoV-2 vaccines	"Locally authorized" SARS-CoV-2 vaccines include any vaccine that has received market approval or emergency use authorization (EUA) in the country of enrollment at the time of screening for eligibility. Subjects can be eligible if they previously received investigational vaccines that have since been authorized for emergency use or granted full market licensure.
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.
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 above 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.
end of active trial phase (EAP)	The visit (also 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.
end of study/ study completion	The final date on which data are collected (i.e., the last subject's last visit or scheduled assessment).
follow-up period	The period after the active trial phase, up to approximately 6 months after trial vaccination.
SARS-CoV-2 index virus	Wuhan wild type isolate of the severe acute respiratory coronavirus 2.
trial period	The active trial phase plus the follow-up period.
trial vaccination	Part A, randomized component: Single boost or re-boost vaccination with either ABNCoV2 or Comirnaty Part B, single-arm component: Single boost or re-boost with ABNCoV2

1.3 Protocol Synopsis

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
Clinical Phase	Phase 3
Sponsor	Bavarian Nordic A/S Philip Heymans Alle 3 2900 Hellerup Denmark
Trial Identifiers	Sponsor trial code: ABNCoV2-03 EudraCT #: 2021-005504-36 ClinicalTrials.gov #: NCT05329220 IND #: 28466
Trial Design	This trial is composed of a randomized, double-blind, active controlled component (Part A) and an open-label, single-arm component (Part B) conducted in parallel. **Part A** is designed to compare vaccination with a single 100 µg dose of ABNCoV2 to a single 30 µg adult booster dose of Comirnaty (active control) in adult subjects who either previously completed primary vaccination (Cohort 1) or have already received 1 booster dose (Cohort 2) of SARS-CoV-2 locally authorized vaccine(s), and whose last locally authorized SARS-CoV-2 vaccination was at least 3 months prior to the screening visit. Subjects will be randomized in a 1:1 ratio to receive either ABNCoV2 or Comirnaty. **Part B** is designed to collect ABNCoV2 safety and tolerability data from a larger population of adult subjects, as well as additional immunogenicity data from a subset. Part B involves vaccination with the same single 100 µg dose of ABNCoV2 in the same population of adult subjects as the randomized component, and subjects will similarly be enrolled into 2 cohorts according to whether they have completed primary vaccination only or primary plus booster vaccination.
Trial Duration	Approximately 28 weeks for each subject.

Sites and Countries	**Part A:** 13 sites in Belgium and Denmark **Part B:** 45 sites in the United States **Immunogenicity subset:** Select US sites
Vaccination Dose	**Part A:** Either a single 100 µg dose of ABNCoV2 vaccine or a single 30 µg adult boost dose of Comirnaty (tozinameran, BNT162b2) vaccine **Part B:** Single 100 µg dose of ABNCoV2 vaccine
Vaccine Administration	ABNCoV2 and Comirnaty are administered intramuscularly into the deltoid muscle of the non-dominant arm. **Part A:** To blind both subjects and trial staff, preparation of the trial vaccine will be performed by a local, unblinded site staff member, e.g., a local pharmacist.
Sample Size	**Part A**: Healthy adult subjects, who have previously completed primary vaccination with locally authorized SARS-CoV-2 vaccine(s) at least 3 months prior to the screening visit, will be enrolled into 2 cohorts as specified below: • Cohort 1: subjects who previously completed primary vaccination only • Cohort 2: subjects who have completed primary vaccination and have received 1 booster vaccination For each cohort, the targeted enrollment is 500 subjects. Based on data from the ABNCoV2 phase 2 trial, we assume a common standard deviation of 0.52 for $\log_{10}$ transformed neutralizing antibody titers. We further assume 10% of the population will be non-evaluable due to dropout or compromised serum samples. When the sample size is 500 (450 evaluable) with a 1:1 randomization ratio, a one-sided 0.0125 significance level test will have 90% power to reject the null hypothesis for Cohort 1 or Cohort 2 that ABNCoV2 is inferior to Comirnaty, with a non-inferiority margin of 0.67. **Part B:** A total of up to 3000 healthy adult subjects, who have previously completed vaccination with locally authorized SARS-CoV-2 vaccine(s) at least 3 months prior to the screening visit, will be enrolled into 2 cohorts as specified below: • Cohort 1 (at least 250 subjects): subjects who previously completed primary vaccination only • Cohort 2 (at least 250 subjects): subjects who have completed primary vaccination and have received 1 booster vaccination

	The sample size for Part B is not based on a statistical hypothesis test, but rather on the number of subjects exposed to ABNCoV2 considered adequate for safety population analyses and may be adjusted depending on enrolment 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 adverse event 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.
Randomization and Blinding	**Part A only:** At Visit 1, subjects will be randomized in a 1:1 ratio to receive ABNCoV2 or Comirnaty (active control) single dose vaccination. Randomization will be stratified within each cohort by age group (<65 years versus ≥65 years) and previous vaccination regimen. An unblinded member of the local site team will handle the trial vaccine, while the subject and the staff involved in subject evaluation and follow-up will remain blinded. Immunogenicity assessments will be performed by laboratory personnel who have no knowledge of treatment assignment and no access to the trial data. The clinical operational and analysis teams also will be blinded to treatment assignment until the time of the primary and key secondary endpoint analyses.
Primary Objective	**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).
Key Secondary Objective	**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.
Other Secondary Objective	**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.

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).
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. To explore the kinetics of SARS-CoV-2-specific humoral responses in subsets of each Part A cohort. To explore SARS-CoV-2-specific cellular responses at 1 week after ABNCoV2 vaccination within the immunogenicity subsets of each Part B 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.
Primary Endpoint Population-level Summary	**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.
Success Criterion for Primary Endpoint	If the sample size requirement is met in each of the Part A cohorts (minimum of 400 evaluable per cohort), the success criterion will be applied in each of the cohorts as specified below. In the event the sample size requirement is not met in one of the cohorts, the success criterion will only be applied to the cohort meeting the sample size requirement, and results for the under-recruited cohort will be descriptive only. Ratio of GMTs at 2 weeks after trial vaccination, for ABNCoV2 vaccine compared to Comirnaty vaccine, is within the non-inferiority margin of 0.67; specifically, the success criterion will be met within each cohort if the lower bound of the 2-sided 97.5% CI of the GMT ratio is $\geq$0.67. If the non-inferiority criterion is met, a superiority test will be carried out based on the same type I error level.

	If the non-inferiority criterion is met in at least one cohort, supportive analyses will include assessing non-inferiority or superiority in Cohort 1 and Cohort 2 combined.
Key Secondary Endpoint Population-level Summary	**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.
Success Criterion for Key Secondary Endpoint	If both Cohort 1 and Cohort 2 are tested for and meet the success criterion for the primary endpoint, VOCs will be tested in the cohort with the higher number of evaluable subjects, followed by the cohort with the smaller number of evaluable subjects if the success criterion is met in at least one of the tested VOCs in the cohort tested first. In the event only one cohort meets the success criterion for the primary endpoint, VOCs will be formally tested for the successful cohort only. Ratios of GMTs for the VOCs at 2 weeks after trial vaccination, for ABNCoV2 vaccine compared to Comirnaty vaccine, will be tested using the non-inferiority margin of 0.67 as was used for the primary endpoint. The result will be based on the lower limit of a two-sided CI with coverage determined based on the number of VOCs circulating at the time of the trial. A Bonferroni correction will be employed for the simultaneous non-inferiority tests to control the trial-wide type I error. If the non-inferiority criterion is met, a superiority test will be carried out based on the same type I level. If the non-inferiority criterion is met in at least one cohort and one VOC, supportive analyses will include assessing non-inferiority or superiority in Cohort 1 and Cohort 2 combined.
Other Secondary Endpoint Population-level Summary	**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.
Safety Endpoint Population-level Summaries	**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. Safety endpoints:

	• Serious adverse events (SAEs) or adverse events of special interest (AESIs) assessed as related to trial vaccine during the entire trial period, 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 period. • 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 Endpoint Population-level Summaries	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 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. 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. 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.
Trial Halting Criteria	Data Monitoring Committee will review the following to determine whether a temporary halting or termination of the trial is warranted:

	• A serious AESI or other SAE with an at least reasonable possibility of a causal relationship to the administration of ABNCoV2 or Comirnaty vaccine. • An unexpected Grade 3 or higher adverse event (e.g., a systemic reaction or lab toxicity) with an at least reasonable possibility of a causal relationship to the trial vaccination.
Trial Population: Inclusion Criteria	1. Age ≥18 years at screening. 2. Documented, previous completion of a primary vaccination regimen with locally authorized SARS-CoV-2 vaccine(s) or completion of primary plus 1 boost vaccination (see definition of completed primary vaccination regimen and completed primary plus boost vaccination in Section 1.2), with last vaccination at least 3 months before screening. “Locally authorized” SARS-CoV-2 vaccines are those that have received market approval or EUA in the country of enrollment. 3. Absence of acute medical illness, significant physical exam findings, or laboratory abnormalities, as determined by the investigator. 4. Informed consent, provided by the subject prior to performance of any trial-specific procedures; the subject has read, signed, and dated an informed consent form (ICF), having been advised of the risks and benefits of the trial in a language understood by the subject. 5. Body mass index (BMI) ≥18.5 and <40. 6. For female subjects of childbearing potential (WOCBP) and male subjects who are sexually active with a WOCBP, agreement to use an effective method of birth control from at least 30 days prior to administration of the vaccine until 30 days after the vaccination. A woman is considered of childbearing potential unless post-menopausal (defined as ≥12 months without a menstrual period at screening) or surgically sterilized (bilateral oophorectomy, bilateral tubal ligation, hysterectomy). Acceptable contraception methods are restricted to abstinence (only acceptable if refraining from heterosexual intercourse during the period of 30 days prior to administration of the vaccine until 30 days after the vaccination), double barrier contraceptives, vasectomy, intrauterine contraceptive devices, or licensed hormonal products. 7. For WOCBP, a negative serum pregnancy test at screening. 8. Negative tests for human immunodeficiency virus antibody (anti-HIV), hepatitis B surface antigen (HBsAG), and antibody to hepatitis C virus (HCV).

Trial Population: Exclusion Criteria	1. History of COVID-19 infection within the last 3 months before screening. 2. Previous vaccination with a SARS-CoV-2 vaccine other than those mentioned in inclusion criterion #2. 3. Positive test for SARS-CoV-2 infection at screening. 4. Breastfeeding with intent to continue. 5. Acute or chronic medical condition that, in the opinion of the investigator, would render the trial procedures unsafe or would interfere with the evaluation of the responses. 6. History of myocarditis or pericarditis. 7. History of or active autoimmune disease. History of Guillain-Barré syndrome or Reye's syndrome. Persons with vitiligo or thyroid disease taking thyroid replacement are not excluded. 8. Known or suspected impairment of immunologic functions including, but not limited to, known immunodeficiency syndrome. 9. History of malignancy other than squamous cell or basal cell skin cancer, unless there has been surgical excision at least 6 months prior to screening that is considered to have achieved cure. Subjects with history of skin cancer must not be vaccinated at the previous tumor site. 10. Laboratory parameters (such as complete blood count, serum biochemistry including aspartate aminotransferase [AST], alanine amino transferase [ALT], alkaline phosphokinase [ALP], bilirubin, or creatinine values), pulse rate, or blood pressure outside normal range at screening and deemed clinically relevant by the investigator. 11. Clinically significant mental disorder not adequately controlled by medical treatment. 12. Active or recent history (within 6 months before screening) of chronic alcohol abuse, or illicit drug abuse. 13. History of allergic disease or reactions likely to be exacerbated by any component of the vaccine. 14. History of anaphylaxis or severe allergic reaction to any vaccine. 15. History of any vaccinations or plan to receive any vaccinations with a live vaccine within 30 days prior to or after trial vaccination. 16. History of any vaccinations or plan to receive any vaccinations with a non-live vaccine within 14 days prior to or after trial vaccination. 17. Recent blood donation (including platelets, plasma and red blood cells) within 4 weeks prior to screening, or planned blood donations during the active phase of the trial.

	18. Chronic systemic administration (defined as more than 14 days) of >5 mg prednisone (or equivalent)/day, or any other immune-modifying drugs during a period starting 3 months prior to administration of the vaccine and ending 4 weeks after vaccination. The use of topical, inhaled, ophthalmic and nasal glucocorticoids is allowed. 19. History of organ transplantation, whether or not accompanied by chronic immunosuppressive therapy. 20. Administration or planned administration of immunoglobulins and/or any blood products during a period starting 3 months prior to administration of the vaccine and ending 4 weeks after vaccination. Receipt of packed red blood cells given for an emergency indication in an otherwise healthy person, and not required as ongoing treatment is not exclusionary (for example packed red blood cells given in emergency during an elective surgery). 21. Use of any investigational or non-registered drug or vaccine other than the trial vaccine within 30 days preceding the administration of trial vaccine, or planned administration of such a drug or vaccine throughout the trial. 22. Involvement in this trial as site personnel. 23. Known bleeding disorder that, in the opinion of the investigator, would contraindicate intramuscular injection.
Trial Population: Inclusion of Subjects ≥65 Years of Age	Sites will be instructed to pursue a target of 25% of enrollment to be subjects ≥65 years of age in Part A and 33% of enrollment to be subjects ≥65 years of age in Part B. The target is to have approximately 1000 subjects ≥65 years of age who receive ABNCoV2.

1.4 Trial Schedule

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							
SARS-CoV-2 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
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[i]	X[i]
Blood collection for serum antibody titers and nucleocapsid protein antibody testing, Part B immunogenicity subset[k]		X[j]		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
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; SARS-CoV-2 = 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 COVID-19 typical symptoms.

[g] AESIs and MAAEs are not collected until vaccine has been received at visit 1.

[h] During the follow-up period, data collection will be limited to SAEs, AESIs, and MAAEs, and any unsolicited AEs from the active trial period that are not yet resolved.

[i] Nucleocapsid protein antibody testing will be done only on samples collected at V1, V3, FU2, and FU3.

[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.

1.5 Responsibilities

Sponsor	Bavarian Nordic A/S Philip Heymans Alle 3 2900 Hellerup Denmark
Phone (direct office)	[redacted]
E-mail	info@bavarian-nordic.com
Project Leader	[redacted]
Phone	[redacted]
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Medical Monitor ([redacted])	[redacted]
Medical Monitor (BN)	[redacted]
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Trial Statistician	[redacted]
Phone	[redacted]
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CRO Project Manager	[redacted]
Phone	[redacted]
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Laboratory (Immunogenicity testing)	[redacted]
Phone	[redacted]
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2 Background Information and Scientific Rationale

2.1 Introduction to SARS-CoV-2

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which causes coronavirus disease 2019 (COVID-19), is an ongoing worldwide public health emergency. SARS-CoV-2 is not only highly infectious, but infections may lead to humoral immune responses with low virus neutralizing capacity (Chen et al., 2020, Robbiani et al., 2020, Wu et al., 2020).

SARS-CoV-2 entry into cells occurs through interaction of the virus spike receptor-binding domain (RBD) with the angiotensin-converting enzyme 2 (ACE2) protein on human cells. Upon binding, ACE2 acts as a receptor, and human proteases are recruited to mediate cell entry (Shang et al., 2020a).

In convalescent COVID-19 patients, despite generally low humoral responses, neutralizing antibodies specific to the RBD of SARS-CoV-2 are recurrently found (Robbiani et al., 2020). Interestingly, SARS-CoV-2 may be more effective in evading an effective immune response than SARS-CoV (the coronavirus that caused the severe acute respiratory syndrome outbreak of 2003) because the SARS-CoV-2 spike more frequently assumes a conformational state that hides the spike RBD (Shang et al., 2020b, Walls et al., 2020, Wrapp et al., 2020). Therefore, displaying the spike RBD of SARS-CoV-2 in a manner that facilitates recognition by the immune system is likely to be protective against COVID-19.

2.2 ABNCoV2 Vaccine

[redacted]

The unique cVLP display platform of the ABNCoV2 vaccine is also referred to as a capsid-like particle and can be modified to present different antigens. [redacted] cVLPs have also been shown to significantly increase murine antibody responses in terms of titer, avidity, and functionality (Thrane et al., 2016, Tissot et al., 2010, Janitzek et al., 2016, Pastori et al., 2012).

[redacted]

[redacted]

[redacted]

[redacted] [redacted]

[redacted]

2.2.1 Nonclinical Studies with ABNCoV2 Vaccine

The immunogenicity of ABNCoV2 has been demonstrated in mice (Fougeroux et al., 2021) and in non-human primates (NHP). A single IM administration of 100 µg ABNCoV2 induced

SARS-CoV-2 neutralizing antibodies in NHP at comparable levels as found in human convalescent samples, while neutralizing antibody titers induced by 15 µg ABNCoV2 remained below convalescent levels. A second administration of 15 µg or 100 µg ABNCoV2 led to a >50-fold increase in titers. While 15 µg ABNCoV2 administered 2 times to NHP resulted in significantly reduced lung viral load after SARS-CoV-2 challenge compared to nonvaccinated control animals, the higher dose of 100 µg ABNCoV2 administered 2 times resulted in complete protection, as evidenced by the majority of animals being completely free of virus in lung and also in nasal swabs.

The safety and good tolerability of 100 µg ABNCoV2 (adjuvanted in a squalene in water emulsion) administered 2 or 3 times in rabbits was demonstrated in a Good Laboratory Practice-compliant repeat dose toxicity and local tolerance study, and no safety concerns for human use were raised.

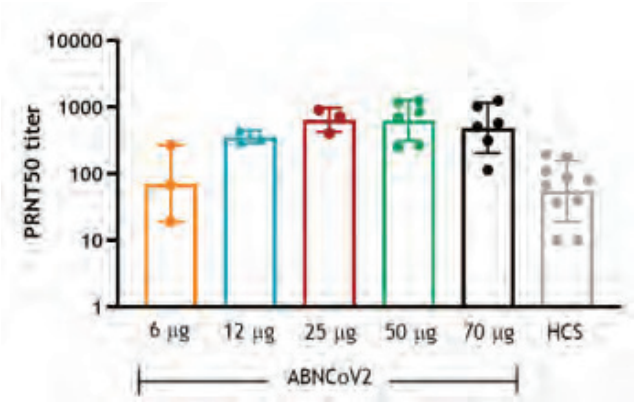
The ABNCoV2 dose administered to rabbits translates to a human equivalent dose based on body surface area (FDA, 2005) of 774 µg for a 60 kg human; this provides a safety margin that is >7× higher than a 100 µg human dose. Even when the use of different methods by different laboratories to determine the ABNCoV2 protein concentration is taken into account, a potentially lower dose of 70 µg instead of 100 µg used in the toxicity study translates to a human equivalent dose of 542 µg for a 60 kg human and still provides a safety margin that is >5x higher than a 100 µg human dose. Further, the number of vaccine applications (3) suggests further safety for the 1 to 2 administrations used in the human studies (see Section 2.2.2).

See further details in the current effective ABNCoV2 IB.

2.2.2 Clinical Trials with ABNCoV2 Vaccine

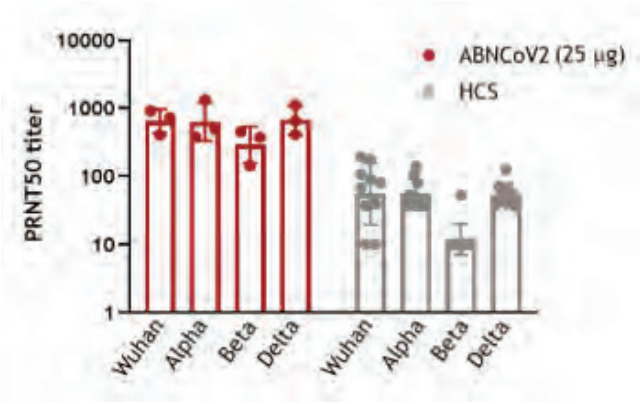
A first-in-human trial was conducted in 45 subjects (COUGH-1, EudraCT no. 2020-004621-22/ NCT04839146). In a predefined dose escalation, SARS-CoV-2-naïve subjects received up to 70 µg of the ABNCoV2 vaccine in this phase 1 trial. Preliminary safety results did not show any relevant safety findings. Final results from this trial are not yet available at the time of completion of this protocol, but the currently available data indicate that humoral immune responses were elicited at all dose levels after completion of the 2-dose schedule in the initially seronegative population. While there was a dose-response effect between 6 µg and 25 µg, for the dose levels between 25 µg and 70 µg a dose saturation was observed (see Figure 2) based on preliminary data from a small subset of subjects (3 subjects in each of the 6, 12, and 25 µg groups and 6 subjects in each of the 50 and 70 µg groups). With the serum samples of the subjects in the 25 µg dose group, a broad immune response against the variants of concern (VOCs) Alpha, Beta and Delta was observed in the neutralization assay (see Figure 3). For further dose justification, please refer to Section 2.2.1.

Figure 2 Neutralizing Antibody Titers from Phase 1 by Dose



Titers obtained 14 days after second dose in 2-dose schedule in initially seronegative subjects.
Abbreviations: HCS = human convalescent sera; PRNT50 = 50% plaque reduction neutralization test.

Figure 3 Neutralizing Antibody Titers for SARS-CoV-2 Wildtype and Alpha, Beta and Delta Variants



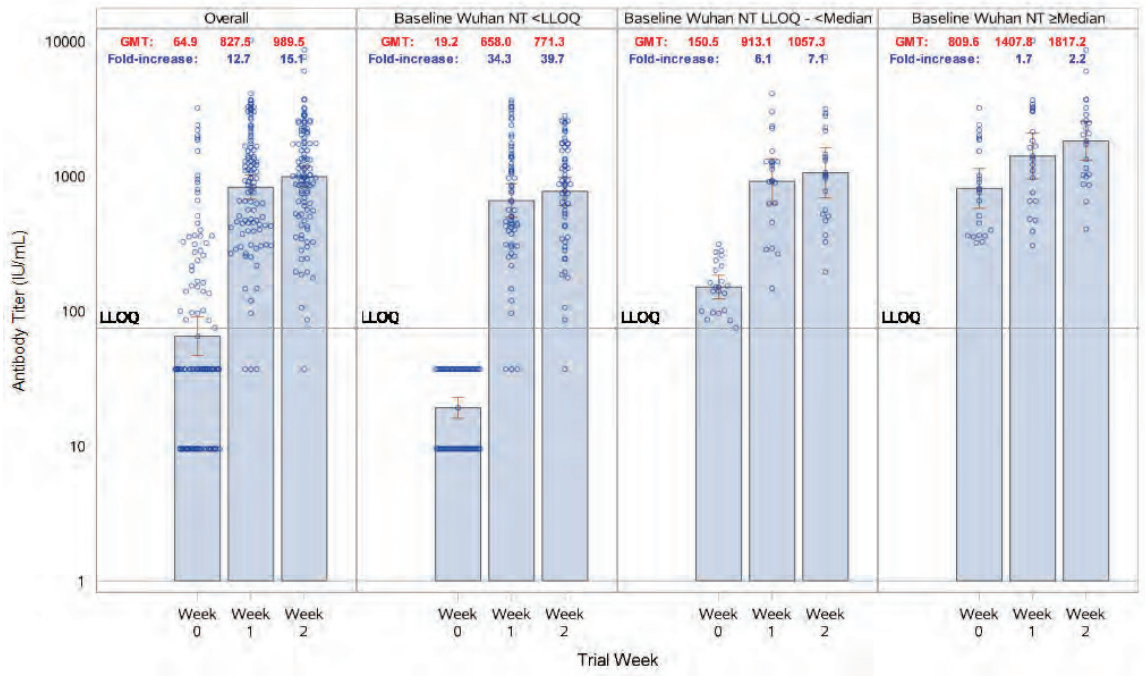
Titers obtained 14 days after second dose in 2-dose schedule at 25 µg per dose.
Abbreviations: HCS = human convalescent sera; PRNT50 = 50% plaque reduction neutralization test.

An open-label phase 2 study (ABNCoV2-01, EudraCT no. 2021-001393-31, NCT05077267) to evaluate safety, tolerability and immunogenicity of the ABNCoV2 vaccine is in progress. The trial is evaluating a homologous prime-boost regimen in seronegative subjects with the 100 µg high dose supported by animal studies. The trial also is evaluating both a 100 µg single dose boost regimen and a 50 µg single dose boost regimen in subjects who had either completed their primary vaccination or had confirmed SARS-CoV-2 infection at least 3 months prior. The intent is to evaluate whether the 2-dose primary regimen elicits an immune response that is as good as expected, based on the available nonclinical and phase 1 data, and whether a single dose boost regimen elicits a comparably high immune response in seropositive subjects.

In addition, the phase 2 trial also serves as the basis for the dose decision between 50 and 100 µg in this phase 3 trial.

Preliminary humoral immunogenicity data for the 100 µg single dose seropositive group from phase 2 has been analyzed by the time of completion of this protocol. Overall, across the 101 subjects with data from 2 weeks after boost vaccination, there was a 15.1-fold increase over baseline in geometric mean titer (GMT) of neutralizing antibodies against the SARS-CoV-2 index virus. Subgroup analysis showed a 39.7-fold GMT increase over baseline in those subjects with a baseline titer below the lower limit of quantification (LLOQ), a 7.1-fold GMT increase over baseline for those subjects with a baseline antibody titer above the LLOQ but below 319 IU/mL (the median among those above the LLOQ), and a 2.2-fold GMT increase over baseline in those subjects with a baseline antibody titer at or above the median (see Figure 4).

Figure 4 Neutralizing Antibody Titers Against the Wuhan Strain at Baseline, Week 1, and Week 2 in Initially Seropositive Subjects Who Received 100 µg of ABNCoV2



Abbreviations: GMT = geometric mean titer; LLOQ = lower limit of quantification; NT = neutralizing titer.

Preliminary data from the 50 µg dose group of the phase 2 trial suggest a similar immunogenicity response to a single boost administration overall, with some slight trends towards higher fold increases with the 100 µg dose, particularly in subjects who were primed with mRNA-based vaccines. The tolerability was roughly comparable between the 50 and 100 µg dose groups. For further details on the 50 µg results of phase 2, please refer to the IB.

SARS-CoV-2-specific T-cell responses, e.g., SARS-CoV-2-specific T cells secreting interferon-γ /interleukin-4 upon restimulation, were assessed in the Phase 2 trial, using enzyme-linked immuno spot technique (ELISpot).

Results of the cellular immunogenicity analysis using interferon-γ and interleukin-4 ELISpot showed a clearly Th1-focused boost response, with a broad and consistent response across all VOCs tested. Importantly, the ratio of Th1 to Th2 increased after administration of the ABNCoV2 boost vaccination for all VOCs. The results of the interferon-γ and interleukin-4 ELISpot analysis for the 100 µg dose group of the Phase 2 trial are displayed in Figure 5 and Figure 6.

Figure 5 Interferon-γ (Th1) ELISpot for SARS-CoV-2 RBD of Index Virus and Variants of Concern (data from 100 µg dose group of Phase 2)

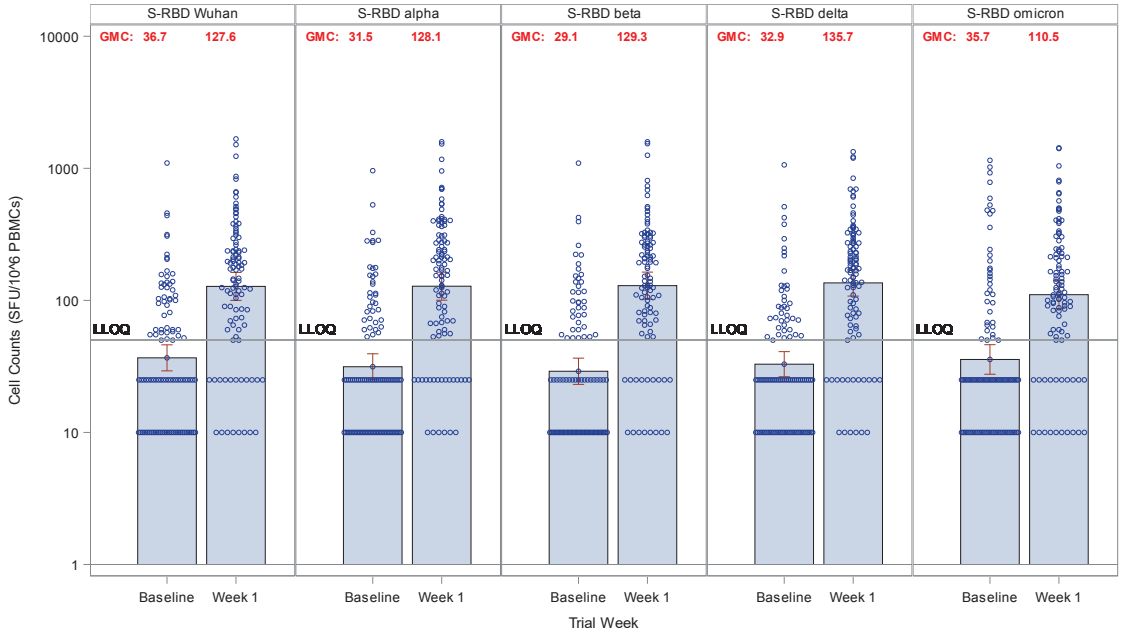
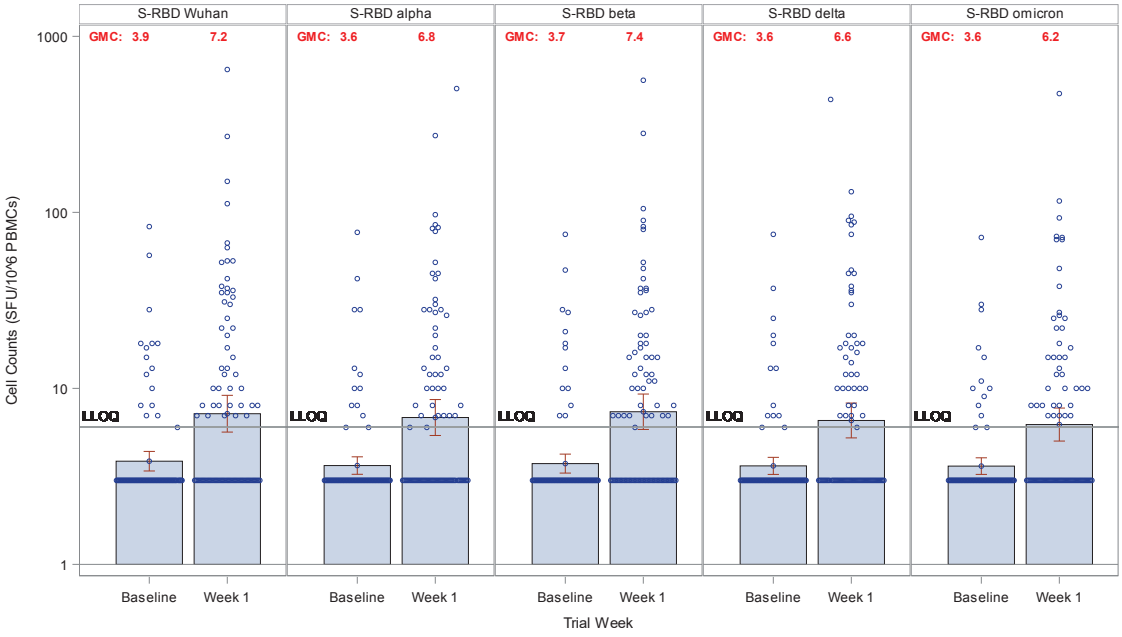


Figure 6 Interleukin-4 (Th2) ELISpot for SARS-CoV-2 RBD of Index Virus and Variants of Concern (data from 100 µg dose group of Phase 2)



The preliminary safety data from phase 2 as of 15-Feb-2022 are presented below. Summary safety data for the active trial phase (4 weeks following vaccination) are presented in Table 1 for Groups 2 and 3 (the 2 dose groups of seropositive subjects). The preliminary data show that the solicited local and general vaccine side effects that occurred in 30% or more of subjects were injection site pain (79.9%), fatigue (45.0%), headache (43.2%), myalgia (36.1%), and injection site induration and erythema (30.8% each). The most commonly reported unsolicited AEs were nasopharyngitis (10), headache (5), oropharyngeal pain (4), and rhinitis, dizziness, diarrhea, and COVID-19 disease (3 occurrences each). (At this time, a Topline Interim Clinical Study Report [CSR] only is available.)

There were 2 serious adverse events (SAEs) reported in the phase 2 study, both of which were assessed not to be related to trial vaccine. One event of metatarsal fracture and repair occurred in an elderly subject subsequent to a fall during their follow-up phase. The second was an event of a slipped cervical disc, which also occurred during follow-up. The subject underwent corrective surgery, and the SAE resolved.

The Topline Interim Clinical Safety Report presented AESIs from the entire vaccinated phase 2 trial population. A total of 11 AESIs were reported by 6 subjects; all were non-serious. There were 4 events of ageusia, 5 of anosmia, and 2 of thrombocytopenia. Only the 2 events of thrombocytopenia were assessed as related to the trial vaccine; they were mild grade, clinically

non-significant and transient, and they resolved without any treatment administered to subjects. The sponsor in agreement with the data monitoring committee (DMC) concluded that those cases represented minor fluctuations slightly below the reference range. An overall look at all platelet counts of all subjects throughout the trial confirmed that there was no trend toward declines in platelet counts. Therefore, no safety signal with regards to thrombocytopenia was confirmed. (Note: one of the cases of thrombocytopenia occurred in a Group 1 [initially seronegative] subject and is not included in Table 1.)

Table 1 Overall Summary of Adverse Events in Seropositive Subjects During the Active Trial Period

	Group 2[a] (N = 103) n (%) [Events]	**Group 3[b] (N = 66) n (%) [Events]**	**Overall (N = 169) n (%) [Events]**
All AEs	88 (85.4) [411]	60 (90.9) [264]	148 (87.6) [675]
SAEs	0	0	0
AEs leading to withdrawal	0	0	0
Solicited local AEs	82 (79.6) [179]	56 (84.8) [124]	138 (81.7) [303]
Solicited local AEs Grade ≥3[c]	5 (4.9) [5]	5 (7.6) [5]	10 (5.9) [10]
Solicited general AEs	72 (69.9) [190]	41 (62.1) [110]	113 (66.9) [300]
Solicited general AEs Grade ≥3[c], related	13 (12.6) [29]	4 (6.1) [13]	17 (10.1) [42]
Unsolicited AEs, related	5 (4.9) [5]	7 (10.6) [10]	12 (7.1) [15]
Unsolicited AEs Grade ≥3[d], related	0	0	0
AESIs[e], related	0	1 (1.5) [1]	1 (0.6) [1]

Abbreviations: AE = adverse event; AESI = adverse event of special interest; N = number of subjects in the Safety Analysis Set for the group of interest; n = number of subjects experiencing the event; SAE = serious adverse event.

Data are not final; the data cutoff date is 15-Feb-2022. Data are presented for Groups 2 and 3 only (the two dose groups of seropositive subjects), as these are the topline study results to support use as a booster vaccine, and active phase data for Group 1 are not yet available.

[a] Group 2 = Seropositive, 1 dose 100 µg

[b] Group 3 = Seropositive, 1 dose 50 µg

[c] Solicited AE grading based on trial-specific definitions for solicited local and general AEs

[d] Unsolicited AE grading based on Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

[e] AESIs are adopted as per the Safety Platform for Emergency vACcines (SPEAC) Project generated list of AESI for safety monitoring.

For further details about phase 1 and phase 2 preliminary results, please refer to the IB.

2.3 Scientific Rationale

Despite the recent approval of several SARS-CoV-2 vaccines using different technologies, such as mRNA-based or adenovirus-vectored vaccines, there is still substantial spread of COVID-19

disease and related disease burdens. These burdens include fatal outcomes as well as the need for social distancing measures, causing a high economic and societal impact.

The recent emergence of variant strains with yet unknown susceptibility to the currently available vaccines highlights the potential need for continuous adaptation of vaccines and the necessity to administer re-vaccinations (boosts) in populations considered at relevant risk.

In developed countries, large parts of the population have obtained at least an initial SARS-CoV-2 vaccination regimen. Therefore, the medical need is expected to be for boost vaccinations for previously vaccinated subjects in order to maintain or adapt immunity to continuously circulating strains of SARS-CoV-2. Indeed, boost vaccinations have already been demonstrated to increase waning neutralizing antibody titers (Atmar et al., 2021, Munro et al., 2021). This phase 3 trial is designed to test ABNCoV2 in the boost setting in two parallel parts. The first is a randomized, double-blind, non-inferiority comparison of ABNCoV2 100 µg to an active control group that will receive a standard adult booster dose of Comirnaty (Pfizer/BioNTech), an authorized SARS-CoV-2 vaccine. The second is an open-label, single-arm trial of ABNCoV2 100 µg.

Based on results from the phase 2 trial of ABNCoV2, the single 100 µg dose was selected as the appropriate phase 3 dose, due to its slight trend towards higher fold increases versus the 50 µg dose in seropositive subjects, as well as its comparable reactogenicity.

Comirnaty was chosen for the active control in the randomized component because mRNA SARS-CoV-2 vaccines were the first to be specifically authorized in the boost setting, and because certain European governments have agreed to make it available for this research. The analysis of Part A will provide comparison to a vaccine authorized in the boost setting and for which prior clinical trial data are available.

2.4 Risk/Benefit Assessment

2.4.1 Risks

Based on the available data obtained in the nonclinical rabbit toxicology study and in the phase 1 and 2 clinical trials, the 100 µg dose level planned for this phase 3 trial is not expected to cause any major risks.

One suspected unexpected serious adverse reaction (SUSAR) of basal cell carcinoma was reported from phase 1 (COUGH-1) in a subject with a history of basal cell carcinoma and melanoma. In this subject, following 2 doses of ABNCoV2, 1 dose of Janssen COVID-19 vaccine was administered as well.

Overall safety data for ABNCoV2 is limited and preliminary, as the phase 1 and phase 2 studies are not yet completed. However, based on the currently available data (see Section 2.2.2), local

and systemic side effects are overall in line with the expected safety profile of already licensed COVID-19 vaccines.

Myocarditis and pericarditis have so far not been observed in the phase 1 and phase 2 clinical development program of ABNCoV2. However, available data regarding myocarditis or pericarditis reported in individuals vaccinated with some licensed COVID-19 vaccines containing the S antigen strongly support a plausible causal relationship to the vaccines and have warranted inclusion of a warning statement and additional safety information about these events in EUA Fact Sheets and labeling of those approved vaccines.

Blood drawing may cause discomfort, bruising, light-headedness, or fainting. Rarely, a blood draw may result in infection at the site of venipuncture.

As with all vaccines, there is a risk of an allergic reaction or an anaphylactic event. Trial site staff will observe all trial subjects for at least 30 minutes after the boost vaccination. If a severe allergic reaction and/or dyspnoea occurs, appropriate medical treatment and supervision will be provided.

As with all vaccines, there is a risk of temporary mild to moderate injection site reactions, such as injection site pain and/or tenderness, erythema, swelling, pruritus, or induration. The above mentioned were reported most commonly in the phase 1 and phase 2 studies. Also, systemic inflammatory reactions including flu-like symptoms such as fever, headache, nausea, muscle pain, chills or fatigue can occur. For further details on the safety results for the phase 1 and phase 2 studies, please refer to the IB.

2.4.2 Potential Benefits

Trial subjects will contribute significantly to the development of a vaccine targeting COVID-19 disease. Subjects assigned to receive the ABNCoV2 vaccine might potentially acquire similar immunity against SARS-CoV-2 as with approved vaccines. However, it cannot be said yet whether ABNCoV2 vaccine is efficacious against COVID-19 disease in humans. Thus far, efficacy data for the ABNCoV2 vaccine are available from animal models only; human data are preliminary but provide support for immunogenicity of the vaccine at levels shown to confer protection (Gilbert et al., 2021). Subjects randomized to the active control will receive the same authorized Comirnaty booster vaccine that is available outside the trial.

Analysis of the samples collected will not directly benefit the subject. Neither subjects nor their physicians will receive results of sample analyses.

2.4.3 Risk/Benefit Balance

For existing SARS-CoV-2 vaccines, the favorable risk-benefit balance is well established. Thus, for a new vaccine candidate such as ABNCoV2 without safety issues identified to date, the macro-level risk for an active controlled trial is that the vaccine may be found to be inferior to

approved vaccines and not provide adequate protection against COVID-19 disease, or that unforeseen safety concerns may arise that are greater than for approved vaccines. However, both preclinical and clinical data to date for ABNCoV2 suggest the vaccine induces appropriate measures of immunity against SARS-CoV-2 and has a favorable safety profile. The risk of inferiority of this candidate vaccine is balanced by the potential benefit to public health to have another vaccine in the armamentarium for the prevention and mitigation of COVID-19 disease.

3 Trial Design

The design of the two parts of this phase 3 trial is provided below in Sections 3.1 and 3.2.

3.1 Part A: Randomized, Double-blind, Active Controlled Component

The randomized, double-blind, active controlled component will compare vaccination with a single dose of 100 µg ABNCoV2 to a single 30 µg adult boost dose of Comirnaty in adult subjects previously vaccinated for SARS-CoV-2.

Healthy adult subjects who have previously completed vaccination with locally authorized SARS-CoV-2 vaccine(s) at least 3 months prior to the screening visit will be enrolled into 2 cohorts based on the extent of prior SARS-CoV-2 vaccination:

- Cohort 1: subjects who previously completed primary vaccination only
- Cohort 2: subjects who have completed primary vaccination and have received 1 booster vaccination

Sample size calculations are based on hypothesis testing in Part A (ABNCoV2 versus Comirnaty), yielding a sample size of 500 enrolled (450 evaluable) within each cohort (see Sections 12.2 and 12.6).

Subjects will be randomized in a 1:1 ratio (see Section 12.1) to either ABNCoV2 or Comirnaty (active control arm).

3.2 Part B: Open-label, Single-arm Component

The open-label, single-arm component will collect safety and tolerability data from a larger trial population of subjects receiving ABNCoV2, as well as additional immunogenicity data from a subset of this population. A single 100 µg dose of ABNCoV2 will be administered to up to 3000 healthy adult subjects who have previously received their most recent locally authorized SARS-CoV-2 vaccination at least 3 months prior to the screening visit. These subjects will be enrolled into 2 cohorts:

- Cohort 1 (at least 250 subjects): subjects who previously completed primary vaccination only

- Cohort 2 (at least 250 subjects): subjects who have completed primary vaccination and have received 1 booster vaccination

Additionally, a subset of sites in the US will collect blood for serum and peripheral blood mononuclear cells (PBMCs) from approximately 500 subjects (200 to 250 from each cohort).

3.3 End of Study / Study Completion

Study completion is defined as the final date on which data are collected (i.e., the last subject's last visit or scheduled assessment).

4 Objectives

4.1 Primary Objective

The primary objective of this phase 3 trial is to assess the non-inferiority of vaccination with ABNCoV2 compared to Comirnaty in terms of neutralizing antibodies against the SARS-CoV-2 index virus (Wuhan wild type isolate). This objective will be carried out in the randomized, double-blind component (Part A), 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. If for any reason, the minimum sample size of 400 is not met in one cohort, data from that cohort will be summarized descriptively.

4.2 Secondary Objectives

The key secondary objective is to assess the non-inferiority of vaccination with ABNCoV2 compared to Comirnaty in terms of neutralizing antibodies against VOCs circulating at the time of the trial, again in Part A Cohort 1 and Cohort 2. Variants of concern might include Omicron (B.1.1.529), Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and/or Delta (B.1.617.2). If the non-inferiority margin is met for a VOC, superiority comparison will be carried out in the same cohort with the same type I error level.

Another secondary objective is to assess the neutralizing antibody titers against the SARS-CoV-2 index virus in the immunogenicity subsets of the single-arm component (Part B), for Cohort 1 and Cohort 2.

4.3 Safety Objectives

There are two safety objectives. The first is to compare, in the randomized, double-blind setting (Part A), the safety and tolerability of ABNCoV2 to Comirnaty. The second is to assess the same safety and tolerability endpoints among all subjects who receive ABNCoV2 (Parts A and B).

4.4 Exploratory Objectives

Objectives to be explored in subsets of each Part A cohort are the following:

- Vaccination with ABNCoV2 compared to Comirnaty in terms of total binding IgG antibodies against the SARS-CoV-2 index virus.
- Kinetics of SARS-CoV-2-specific humoral responses.

SARS-CoV-2-specific cellular responses 1 week after ABNCoV2 vaccination will be explored within the immunogenicity subsets of each Part B cohort.

Another exploratory objective is 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.

5 Endpoints and Population-level Summaries

5.1 Primary Endpoint

The endpoint of subject titer of serum neutralizing antibodies against the SARS-CoV-2 index virus will be measured from blood samples collected 2 weeks after trial vaccination in each Part A cohort. The primary endpoint will be summarized as the GMTs for ABNCoV2 and Comirnaty. In each Part A cohort, formal hypothesis testing will be performed if a minimum of 400 evaluable subjects has primary endpoint data available for analysis. If the sample size requirement is not met in one of the cohorts, formal hypothesis testing will only be performed in the cohort meeting the sample size requirement; results for the under-recruited cohort will be descriptive only. The success criterion for the null hypothesis that ABNCoV2 is inferior to Comirnaty will be rejected if the ratio of GMTs for ABNCoV2 versus Comirnaty is within the non-inferiority margin of 0.67; that is, the lower bound of the 2-sided 97.5% CI of the GMT ratio is $\geq$0.67.

5.2 Secondary Endpoints

If both Part A cohorts are tested for and meet the success criterion for the primary endpoint, VOCs will be tested in the cohort with the higher number of evaluable subjects, followed by the cohort with the smaller number of evaluable subjects if the success criterion is met in at least one of the tested VOCs in the cohort tested first. In the event only one cohort meets the success criterion for the primary endpoint, VOCs will be formally tested for the successful cohort only.

Serum from blood samples collected for Part A at 2 weeks after trial vaccination will be analyzed for neutralizing antibodies against the SARS-CoV-2 VOCs (e.g., omicron, alpha to delta) circulating at time of the trial. Additional variants could be included in the assessment based on their further emergence. Those variants to be targeted for formal testing will be specified prior to the start of sample analysis. These key endpoints will be summarized as GMTs for ABNCoV2 and Comirnaty. The null hypothesis of inferiority for each VOC will be rejected if the ratio of

GMTs against the SARS-CoV-2 VOC, for ABNCoV2 vaccine compared to Comirnaty vaccine, is within the non-inferiority margin of 0.67. A Bonferroni correction will be used to adjust for the simultaneous non-inferiority test to maintain the trial-wide type I error.

To address the remaining secondary objective pertaining to Part B, serum from blood samples collected at 2 weeks after trial vaccination in the immunogenicity subset of each Part B cohort will be analyzed for neutralizing antibodies against the SARS-CoV-2 index virus. The endpoints will be summarized as GMTs for each cohort.

5.3 Safety Endpoints

Safety endpoints will be summarized in Part A for all subjects receiving ABNCoV2 compared to those receiving Comirnaty and in both parts for all subjects receiving ABNCoV2. The endpoints include the frequency and percentage of subjects who report the following:

- SAEs or adverse events of special interest (AESIs) assessed as related to trial vaccine during the entire trial period, 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 period.
- 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.

5.4 Exploratory Endpoints

GMTs of total binding IgG antibody against the SARS-CoV-2 index virus will be summarized at baseline and post-baseline time points for ABNCoV2 and Comirnaty in subsets of each Part A cohort.

Immunogenicity of ABNCoV2 and Comirnaty will be explored as the geometric mean fold increases from baseline to each scheduled post-baseline time points in:

- Neutralizing antibodies against the SARS-CoV-2 index virus.
- Neutralizing antibodies against the SARS-CoV-2 VOCs circulating at time of the trial.
- Total binding IgG antibodies against the SARS-CoV-2 index virus (in subsets of each Part A cohort).

In addition, the kinetics of neutralizing antibody responses over time for ABNCoV2 and Comirnaty will be explored by calculating GMTs of neutralizing antibodies against the SARS-CoV-2 index virus and VOCs circulating at time of the trial at 1, 4, 13, and 26 weeks after trial vaccination in subsets of the Part A cohorts.

Cellular immune responses at 1 week after vaccination with ABNCoV2 within the immunogenicity subsets of each Part B cohort will be explored by calculating the geometric means of SARS-CoV-2-specific T cells secreting interferon-γ and interleukin-4 upon restimulation, as measured by ELISpot.

6 Study Population

6.1 Inclusion Criteria

Subjects must meet all the inclusion criteria listed in the Synopsis (Section 1.3) to be enrolled in either Part A or Part B of the trial.

6.2 Exclusion Criteria

The criteria that will exclude subjects from eligibility for both Parts A and B of the trial are provided in the Synopsis (Section 1.3).

6.3 Inclusion of Older Subjects

Sites will be instructed to pursue a target of 25% of enrollment to be subjects that are ≥65 years of age for Part A and 33% to be ≥65 years of age for Part B. The end goal is to have at least 1000 subjects ≥65 years of age who receive ABNCoV2.

6.4 Selection of Subjects

The investigator will keep a log of subjects screened for the trial and will provide the reason in case of exclusion. Information about every screened subject will be documented in the electronic case report form (eCRF).

For subjects who enter screening but do not proceed to vaccination, the information documented in the eCRF will be limited to the date of informed consent form (ICF) signature, demographics, and reason for screen failure, including any (S)AEs that led to the screen failure.

6.5 Recruitment and Retention

Subjects will be actively recruited. Recruitment strategies, including advertisements approved by the Independent Ethics Committee (IEC) and Institutional Review Board (IRB), will be evaluated by the Sponsor.

Individuals identified as potential subjects for the trial will be provided with all the necessary information required to make an informed decision about their participation.

7 Study Intervention

7.1 Vaccine Dosage and Administration

In Part A, each subject will be randomized to receive 1 dose of 100 µg ABNCoV2 vaccine or 1 adult boost dose of 30 µg Comirnaty (tozinameran, BNT162b2) vaccine. An unblinded member of the local site team will handle the trial vaccine, while the subject and the staff involved in subject evaluation and follow-up will remain blinded. In case of an emergency that makes unblinding necessary (i.e., the subject's safety is dependent on unblinding), a mechanism that permits rapid unblinding but does not permit undetectable breaks of the blinding will allow the Investigator the possibility of learning the treatment assignment for a subject. The detailed process for emergency unblinding will be described in a trial-specific procedure.

In Part B, all subjects will receive the same single dose of 100 µg ABNCoV2 as in Part A but as an open-label trial vaccination. All vaccinations will be administered at the investigational sites and injected intramuscularly into the deltoid muscle of the non-dominant arm.

7.2 Subject Discontinuation

A subject may be discontinued early from the active trial phase or the overall trial for different reasons. Reasons for early discontinuation of a subject may include, but are not limited to:

- Clinical need for or receipt of concomitant or ancillary therapy not permitted in the trial as outlined in Section 11.4.
- Subject's receipt of an approved booster vaccination for SARS-CoV-2 outside the protocol.
- Subject's request to discontinue (withdrawal of consent to participate).
- Subject unwilling or unable to comply with trial requirements.
- Any reason that, in the opinion of the investigator, requires or supports early discontinuation of a subject.

Each subject has the right to terminate their trial participation completely at any time for any reason, and the investigator may also terminate a subject's trial participation. Subjects whose trial participation is terminated during the active trial phase of either Part A or Part B should undergo a concluding end of active phase (EAP) visit, including safety laboratory testing and pregnancy test for women of childbearing potential (WOCBP). The subject has the right to refuse the EAP visit; however, the clinical trial site (CTS) should make every effort to collect any safety data possible for the subject. If the subject is willing, the 2-month follow-up (FU) phone call (FU1), the 3-month FU visit (FU2), and/or the 6-month visit (FU3) should still be performed to collect

any potential SAEs/AESIs which occurred after vaccination. Subjects who discontinue after receiving trial vaccine will not be replaced.

8 Schedule of Procedures by Visit

The trial procedures will be conducted according to the trial procedure schedule (Section 1.4) and as described on the following pages. Visits must be scheduled within the protocol-allowed visit windows.

8.1 Screening Visit

All subjects must be thoroughly informed about all aspects of the trial (e.g., trial visit schedule, required evaluations and procedures, risks and benefits) as described in the ICF. Written informed consent must be obtained according to local requirements before any trial-related assessments may be carried out.

After the written informed consent has been obtained, subjects will enter a screening period of up to 14 days before the trial vaccination. Screening procedures are listed in the trial procedure schedule in Section 1.4.

If a subject has been screened and cannot be vaccinated because of a certain transient condition (e.g., abnormal lab value due to an acute condition or a missing lab evaluation due to mishandling of the sample), the respective test(s) should be repeated. The re-test must be performed, and eligibility determined within the 14-day window started by the initial screening visit.

If a subject cannot be vaccinated due to other circumstances (e.g., completion of a wash-out period for a medication or vaccine not allowed during the trial) leading to a delay over the 14-day window, a complete re-screening must be performed, and a new subject number will be assigned. The clock then re-starts at the new screening visit within 14 days before randomization. A subject may be fully re-screened only once.

8.2 Active Phase

8.2.1 Visit 1

After successfully passing the screening evaluations, the eligible subjects for Part A can be randomized and vaccinated with ABNCoV2 or Comirnaty, no later than 14 days after the start of screening. Eligible volunteers for Part B can be vaccinated with ABNCoV2, again no later than 14 days after the start of screening. The procedures performed at Visit 1 are listed in the trial schedule in Section 1.4. With respect to timing, procedures listed above the randomization event in the trial schedule should be performed prior to randomization and vaccination; of greatest importance is that collection of samples for serum antibody titers, PBMC testing, and

nucleocapsid protein antibody testing must always be performed prior to vaccine administration. Refer to Section 12.1 for randomization procedures.

Investigational sites will be provided with instructions for administration of trial vaccine. Subjects will be observed for 30 minutes after vaccine administration, and AEs that occur immediately following trial vaccination will be collected. The site coordinator also will give the memory aid (along with appropriate instruction) to subjects at Visit 1 for them to record any solicited AEs that occur after vaccination, for a period of 8 days (the day of vaccination and the next 7 days).

8.2.2 Visit 2

Visit 2 is to occur 5 to 7 days after trial vaccination. The procedures performed at Visit 2 are listed in the trial schedule in Section 1.4. Core procedures performed in the active phase visits following trial vaccination include the evaluation of vital signs, recording of concomitant medications, targeted physical examination, and AE recording. Blood samples are collected for serum antibody titers from subjects in Part A and for PBMCs from subjects in the Part B immunogenicity subset.

Subjects are asked if they have any SARS-CoV-2 symptoms or tested positive between Visit 1 and Visit 2, and if so, responses will be recorded as AEs. A SARS-CoV-2 infection polymerase chain reaction (PCR) test may be performed if it is determined to be clinically indicated.

As Visit 2 is the first visit following trial vaccination, site personnel are to examine the injection site and review the memory aid with the subject. Expected injection site reactions are to be recorded by the subject with solicited AEs on the memory aid. Unexpected findings are to be recorded by site personnel as AEs. All completed pages of the memory card are collected. If there are any symptoms that have not yet resolved the site should counsel the subject regarding continued collection of symptoms using the memory aid.

8.2.3 Visit 3

Visit 3 is to occur 2 weeks after trial vaccination, ±2 days. The procedures performed at this visit are listed in the trial procedure schedule in Section 1.4. In addition to the core set of trial procedures listed above, a blood draw is performed at this visit for safety labs in all subjects, and for serum antibody titers and nucleocapsid protein antibody testing in Part A and in the Part B immunogenicity subset. The subjects are asked if they have any SARS-CoV-2 symptoms or tested positive since the last visit. If there were any unresolved solicited symptoms at the prior visit, the memory aid is reviewed with the subject and all completed pages collected.

8.2.4 Visit 4 / End of Active Phase

Visit 4 is the last visit in the active phase of both parts of the trial, and it occurs 4 to 5 weeks after trial vaccination. As shown in Section 1.4, the core trial procedures are performed at this visit, a final pregnancy test is done for WOCBP, and blood is collected for serum antibody titers in Part A. The subjects are asked if they have any SARS-CoV-2 symptoms or tested positive since the last visit. If there were any unresolved solicited symptoms at the prior visit, the memory aid is reviewed with the subject and all completed pages collected.

8.3 Follow-up Phase

To monitor safety and immunogenicity, all subjects will receive 1 phone call at 2 months (FU1, days 56 to 70) and attend 2 visits, at 3 months (FU2, days 91 to 105) and 6 months (FU3, days 182 to 196) after trial vaccination. The phone call involves collection of AESIs and SAEs only. For the follow-up visits, as shown in the trial schedule in Section 1.4, the core procedures from the active phase are repeated, including collection of MAAEs, AESIs, and SAEs, but concomitant medications and other AEs are no longer recorded, and blood collection for serum antibody and nucleocapsid protein testing occurs only in Part A. The subjects are asked if they have any SARS-CoV-2 symptoms or tested positive since the last visit. The memory aid may be collected at the FU2 visit if not collected previously and all symptoms have resolved. At the FU3 visit, the memory aid will be collected regardless of ongoing symptoms for recording.

8.4 Unscheduled Visit

Clinically indicated additional procedures or visits may be necessary at any time, including between scheduled visits. Unscheduled visits may be performed, e.g., to repeat laboratory testing or physical exams due to a new development, to do PCR testing for suspected COVID-19 infection, or to perform any clinically indicated evaluation, such as an electrocardiogram (ECG). Examinations performed at unscheduled visits will be recorded in the source documents as well as in the respective eCRF sections for unscheduled visits.

9 Investigational Medicinal Product

9.1 Production, Packaging and Labeling

ABNCoV2 drug product is released by Bavarian Nordic A/S, DK.

Address: Bavarian Nordic A/S
[redacted]

The packages and vials of ABNCoV2 vaccine are labeled according to regulatory requirements. Vials contain at least 100 µg in 0.5 mL.

Comirnaty is a commercially available product and will not be relabeled for trial purposes. For further details, please refer to the prescribing information for Europe and the US:

- https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf
- https://www.fda.gov/media/151707/download

9.2 Shipment, Storage and Handling

Usage of the investigational medicinal product (IMP) is only allowed upon final approval of all shipment relevant paperwork by Bavarian Nordic (BN) or its authorized designee. Only subjects enrolled in the trial may receive IMP.

ABNCoV2 and Comirnaty vaccine will be temperature controlled and monitored during shipment to the CTS. Once at the site, the package should be handed over to the personnel in charge of IMP preparation (e.g., the pharmacist). Site personnel are responsible for proper storage of IMP upon receipt. All IMP must be stored in a secure, environmentally controlled and monitored area in accordance with the required storage conditions, with access limited to the investigator and authorized site staff.

ABNCoV2 vaccine is shipped and stored at -20°C (±5°C). Comirnaty vaccine is shipped and stored according to package leaflet instructions. For further details see the pharmacy manual.

9.3 Preparation

The preparation of trial vaccine will be performed by authorized personnel only. An unblinded member of the local site team will handle the trial vaccine, while the subject and the staff involved in subject evaluation and follow-up will remain blinded. Trial-specific details on preparation of the ABNCoV2 and Comirnaty vaccines are provided in the pharmacy manual.

9.4 Accountability and Disposal

Used (if allowed by institutional policy) and unused vials of all IMP need to be retained in a place with limited access until appropriate drug accountability has been performed. Drug accountability must be documented whenever the IMP is either prepared or administered.

BN will provide a Drug Accountability Log for recording receipt, dispensation, and destruction of IMPs (see separate pharmacy manual). Alternative systems used to track drug accountability are acceptable for use in the trial provided the aforementioned items are adequately captured and records are available for review during scheduled monitoring visits to the site.

After drug accountability has been performed, used and unused vials should either be returned to the designated drug depot, a vendor selected by BN or discarded according to local regulations.

Destruction or return of IMP must be agreed upon with BN and appropriately documented. Documentation should be reviewed and signed off by the pharmacist and Clinical Research Associate (CRA) assigned to monitor the site.

Sites are responsible for the proper destruction and disposal of used needles and syringes, which should be performed according to local regulations. If local disposal is not possible, used clinical supplies may be returned to BN or to the designated drug depot after prior consultation with BN.

10 Assessment of Immunogenicity

The immunogenicity of ABNCoV2 and Comirnaty will be assessed by measuring humoral responses on serum samples collected from all subjects in Part A and from an immunogenicity subset of subjects in Part B.

Immunogenicity testing will be performed at [redacted] and at contracted laboratories, where applicable. Testing will be conducted according to applicable standard operating procedures (SOPs) that are in effect at the time of testing. A list of applicable SOPs in effect will be included in the electronic Trial Master File.

The procedures for collection, preparation, storage and shipment of specimens for immunogenicity testing (serum and PBMC) are specified in lab manuals/study-specific instructions, which will be provided to the investigators/CTS personnel as well as to the processing laboratories before recruitment commences. Additionally, investigators and CTS staff will be trained in the procedures during the investigator meeting/site initiation visit.

10.1 Humoral Immune Response

As outlined in Section 1.4, serum samples for Part A will be collected from subjects at all active trial phase and in-person follow-up visits, and for the Part B immunogenicity subset, enrolled at select investigational sites, at baseline (Visit 1) and Visit 3. In both parts, samples for immunogenicity testing obtained at Visit 1 will be drawn prior to vaccination.

SARS-CoV-2-specific antibody responses will be assessed in trial subjects using neutralization tests (e.g., pseudo virion assay; neutralizing antibodies) and enzyme-linked immunosorbent assay (ELISA; total antibodies)

10.2 Cellular Immune Response

PBMC samples will be collected as outlined in the trial procedure schedule in Section 1.4 (at Visits 1 and 2) at selected investigational sites participating in the Part B immunogenicity subset. Samples for immunogenicity testing obtained at Visit 1 will be drawn prior to vaccination.

SARS-CoV-2-specific T-cell responses, e.g., SARS-CoV-2-specific T cells secreting interferon-γ / interleukin-4 upon restimulation, will be assessed using enzyme-linked immuno spot technique (ELISpot).

10.3 Nucleocapsid Protein Antibody Testing

Serum samples also will be used to analyze nucleocapsid protein antibody titers as outlined in the trial procedure schedule in Section 1.4 at Visits 1 and 3 and Follow-up 2 and 3 in Part A and at Visits 1 and 3 at selected investigational sites participating in the Part B immunogenicity subset. Samples for nucleocapsid protein antibody testing obtained at Visit 1 will be drawn prior to vaccination.

10.4 Future Use of Lab Specimens

Specimens remaining after completion of immunogenicity testing as per protocol might be stored for possible future research and analysis supporting the licensure path of ABNCoV2 vaccines. Future testing will facilitate the bridging of trial results to animal immunogenicity results and/or to immune response data collected from subjects vaccinated with other COVID-19 vaccines. Further, remaining samples might be used for assay development and controls. Subjects will be invited to consent to storage/future use of their samples and will be informed about data protection measures. Specimens will be stored in BN's secured laboratory area in [redacted] or at an external storage facility in a coded, pseudonymized manner to ensure data protection. Genetic testing will not be performed.

11 Safety and Reactogenicity

Safety will be monitored in both Part A and Part B by collection of medical history and performance of an electrocardiogram (ECG) at baseline, physical examination including vital signs at in-person visits, and routine laboratory measurements (including pregnancy testing and counseling on avoidance of pregnancy for WOCBP). Local and general solicited AEs and unsolicited AEs will be recorded. AESIs are defined as per Section 11.9 and are reported following the same workflow as SAEs, with the exception that AESI collection begins after receipt of vaccination.

11.1 Definitions

11.1.1 Medical History

Symptoms, relevant laboratory findings and ongoing medical conditions present before and/or at screening will be documented as medical history.

11.1.2 Adverse Events

Adverse events are defined by the International Council for Harmonisation (ICH) E6(R2) as any untoward medical occurrence in a subject administered a medical product, regardless of whether there is a causal relationship associated with the administration of the IMP. For this study, any new signs, symptoms, laboratory findings or changes in health starting after informed consent are documented in the subjects' records and the AE section of the eCRF. Adverse events are recorded based on unsolicited and solicited questioning (Sections 11.1.3 and 11.1.4).

11.1.3 Unsolicited AEs

Unsolicited AEs are defined as AEs which are not pre-listed on the memory aid. Adverse events (e.g., feeling of ill-health, subjective symptoms and objective signs, intercurrent diseases, accidents, etc.) observed by the investigator and/or reported by the subject must be recorded in the eCRF regardless of the assessment of causality in relationship with the IMP/MP.

After vaccination, abnormal laboratory findings assessed as being clinically significant by the investigator are to be documented as AEs. In addition, after vaccination abnormal laboratory findings fulfilling the Grade 3 or Grade 4 criteria according to the toxicity scale (Appendix 1) are to be documented as AEs in the eCRF, regardless of whether they are considered clinically relevant. For lab values fulfilling the Grade 3 or Grade 4 criteria, the decision to repeat the labs is left to the discretion of the principal investigator (PI). Toxicity grade and seriousness of an AE will be assessed separately, i.e., a Grade 3 or Grade 4 AE will not automatically be regarded as serious.

The investigator should ask the subjects at each visit if they have experienced any AEs since their last visit. All intercurrent diseases reported by the subject need to be recorded by the investigator in the appropriate section of the eCRF.

11.1.4 Solicited AEs

In this clinical trial protocol, 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 or pyrexia, headache, chills, myalgia, nausea and fatigue) in the memory aid daily for the day of vaccination and the following 7 days (an 8-day period). Any symptoms that persist at the end of this period will continue to be measured and documented each day until resolved.

11.1.5 Serious Adverse Events, Serious Adverse Reactions, Adverse Events of Special Interest, and Medically Attended Adverse Events

An SAE is any untoward medical occurrence or effect in a subject administered the trial vaccine that may or may not have a causal relationship with the study vaccine and that is serious, meaning that it:

- Results in death;
- Is life-threatening;

  The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death, if it were more severe.
- 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; or
- Is an otherwise important medical event, e.g., leads to suspicion of transmission of an infectious agent.

Though SAEs, as specified above, include all serious events independent of whether they have a suspected causal relationship to the IMP or not, serious adverse reactions (SARs) are defined as a subset of SAEs that include all noxious and unintended responses to the IMP related to any dose administered that at any dose results in any of the serious outcomes listed above. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

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 this trial are defined as per Section 11.9.

All AEs are collected from signing of ICF but should not be considered by the investigator to be an AESI unless occurring since receipt of trial vaccination.

MAAEs are defined as adverse events 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.

11.2 Relevant Medical History

Relevant medical history will be self-reported and documented at screening and will focus particularly on any important diseases and in the case of infections or tumors, the pathogen involved or the pathological diagnosis, if available. In particular, for subjects with prior COVID-19 infection, the infection and dates must be included in the eCRF. Additionally, laboratory reports need to be documented during screening. All ongoing conditions for which the subjects are taking medications, and/or which may exacerbate during the trial period should be considered as important. Special attention should be given to history of prior allergic reactions, especially to vaccines.

11.3 Prior and Concomitant Medication

All concomitant (ongoing) medication except homeopathic substances and dietary supplements must be recorded in the subject's medical record and in the eCRF including information about the indication, dosage regimen, and the onset and end of treatment.

The following medications taken within 3 months prior to screening will also be recorded in the eCRF and the subject's medical record: vaccines (e.g., influenza/pneumococcal), corticosteroids (via any route of administration), other immune-modulating drugs, immunoglobulin and/or any blood products, investigational drugs, and depot preparations that are still active at the date of screening. In addition, previous SARS-CoV-2 vaccination record will include the specific vaccine received with dose and date(s) in the eCRF, regardless of the time elapsed prior to screening.

11.4 Prohibited Medications

Prohibited medication or medication where washout periods need to be adhered to are (see also eligibility criteria in the Synopsis [Section 1.3]):

- Administration of any SARS-CoV-2 vaccine other than the trial vaccine for the entire trial period.
- Vaccination with any licensed live vaccine within 30 days prior to or after trial vaccination or any licensed non-live vaccine within 14 days prior to or after trial vaccination.

- Chronic systemic administration (defined as more than 14 days) of >5 mg prednisone (or equivalent) per day or any other systemic use of immune-modifying drugs during a period starting 3 months prior to administration of the trial vaccine and ending at the last visit of the active trial phase. The use of topical, inhaled, ophthalmic and nasal corticoids will be permitted.
- Administration of immunoglobulins and/or any blood products during a period starting 3 months prior to administration of the trial vaccine and ending at the last visit of the active trial phase.
- Use of any investigational or non-registered drug or vaccine other than the trial vaccine within 30 days preceding the administration of the trial vaccine, or planned administration of such a drug or vaccine during the entire trial period (i.e., through 6 months after the trial vaccination).

11.5 Physical Examination

11.5.1 Complete Physical Examination

A complete physical examination (excluding breast, genital, and rectal examinations) will be performed at screening. The examination includes a review of major organ systems as well as body height and weight. The examination should be directed at finding evidence of any infections, tumors and lymphadenopathy (a grading scale for lymphadenopathy is included in Appendix 2). In addition, auscultation of the heart and lungs will be performed to check specifically for signs of any heart condition or respiratory disorders.

Any clinically significant findings at the screening physical examination will be recorded as medical history events. The only data captured in the eCRF for the physical examination itself will be the date it was performed. Any new or worsening clinically significant findings post-treatment will be captured as AEs.

11.5.2 Targeted Physical Examination

A targeted physical examination, guided by any signs or symptoms previously identified or any new symptoms that the subject has experienced since the last visit, is required according to the trial schedule (Section 1.4). In addition, auscultation of the heart and lungs will be performed to check specifically for signs of any heart condition.

Any new or worsening of clinically significant findings from the active trial phase physical examinations will be recorded as AEs.

11.6 Vital Signs

At screening and every other in-person trial visit as defined in the trial schedule (Section 1.4), blood pressure and pulse rate will be taken after the subject has been sitting upright for approximately 2 minutes. Body temperature will be measured orally.

11.7 Unsolicited AEs

All intercurrent diseases reported when the investigator actively questions the subject will be documented and all required details (e.g., start and stop date, intensity) will be assessed. Unsolicited AEs will be reported in the subject's medical record and respective section of the eCRF (for requirements for screen failures, see Section 15.1).

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 throughout the entire trial, including during the FU period.

(S)AEs would only be considered as AESIs once subject has received the trial vaccination. SAEs and AESIs will be followed-up until resolution or achievement of stable clinical conditions.

Assessment of Intensity

For all unsolicited AEs not represented in the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (FDA, 2007), the maximum intensity will be based on the following descriptions:

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.

Assessment of Causality

The relationship between the occurrence of an AE and the IMP will be assessed using the categories presented below. For expedited reporting and all other purposes, the categories "not related" and "unlikely" will represent no evidence or argument to suggest a causal relationship,

while “possible”, “probable” and “definite” will be seen to convey that there is evidence or argument to suggest a causal relationship. To ensure reporting, all AEs without a causality assessment from the investigator will preliminarily be classified as “possible”.

In terms of binary causality assessments unlikely and not related in clinical trials is lumped to “not related” whereas other causality assessments as per below are lumped to “related”.

Not related	The time interval between administration of the IMP and the occurrence or worsening of the AE rules out a relationship, and/or alternative cause is established and there is no evidence of a (concomitant) causal connection with or worsening caused by the IMP.
Unlikely	The time interval between administration of the IMP and the occurrence or worsening of the AE makes a causal relationship unlikely, and/or the known effects of the IMP or substance class provide no indication of a (concomitant) causal connection with or worsening caused by the IMP and there is another cause which serves as an adequate explanation, and/or although the known effects of the IMP or substance class make it possible to derive a plausible causal chain with regard to a (concomitant) causal connection or worsening, however, another cause is considerably more likely, and/or another cause of the AE has been identified and a (concomitant) causal connection with or worsening caused by the IMP is unlikely.
Possible	A plausible causal chain regarding a (concomitant) causal connection with / worsening of the AE can be derived from the pharmacological properties of the IMP or substance class. However, other approximately equally likely causes are known, or although the pharmacological properties of the IMP or substance class provide no indication of a (concomitant) causal connection with / worsening of the AE, there is no other known cause which provides an adequate explanation.
Probable	The pharmacological properties of the IMP or substance class, and/or the course of the AE after discontinuation of the IMP and possible subsequent re-exposure, and/or specific findings (e.g., positive allergy test or antibodies against the IMP / metabolites) suggest a (concomitant) causal connection with / worsening of the AE resulting from the IMP, however another cause cannot completely be ruled out.
Definite	The pharmacological properties of the IMP or substance class and/or the course of the AE after discontinuation of the IMP and possible subsequent re-exposure, and/or specific findings (e.g., positive allergy test or antibodies against the IMP / metabolites) definitely indicate that there is a (concomitant) causal connection with / worsening of the AE resulting from the IMP and there are no indications of other causes.

11.8 Solicited AEs

After the vaccination, subjects receive a memory aid to record solicited local and general AEs most likely to occur on the day of vaccination and the following 7 days (Days 1 to 8).

All solicited symptoms observed after vaccination with details concerning the intensity and the course of the symptom should be documented in the memory aid. The CTS will review the memory aid with the subject, and when it is completed (all symptoms have resolved), will transfer the results to the eCRF and the subject's medical record. The investigator's assessment of the symptoms will also be recorded in the eCRF including causality (for solicited general AEs), seriousness, outcome, and any intervention required. Local and general symptoms still ongoing after 8 days will continue to be measured and documented each day until resolved on the memory aid.

To standardize procedures uniform rulers will be handed out to subjects for measurements of erythema, swelling and induration diameters, as will digital thermometers for oral measurements of body temperature.

In case of severe and unexpected local and/or general reactions, the subject should be instructed to contact the trial physician outside of scheduled trial visits.

11.8.1 Solicited Local AEs

The solicited local symptoms erythema, swelling, induration, pruritus and pain at the injection site are to be documented in the memory aid by the subjects.

Assessment of Intensity

Injection site erythema, swelling, and induration will be assessed based on the longest diameter as measured by the subject in mm and recorded in the memory aid. Subjects are asked to document the solicited local AEs in the memory aid. For injection site erythema, injection site swelling, and injection site induration, subjects are asked to record longest diameters; for injection site pruritus and injection site pain, subjects are asked to record level of severity as described in Table 2 below.

Table 2 Grading of Local Symptoms from the Subject's Memory Aid

MedDRA coded Preferred Term Local Adverse Events	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 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	Painful on touch
			2	Painful when limb is moved
			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.

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

Assessment of Causality

Solicited local AEs are defined as being related to the vaccine.

11.8.2 Solicited General AEs

The solicited general symptoms body temperature, headache, myalgia, nausea, chills and fatigue are to be documented in the memory aid by the subjects.

Assessment of Intensity

Subjects are asked to document the solicited general AEs in the memory aid. Subjects are asked to record temperature and severity of symptoms as described in Table 3 below. In the subject's memory aid, the grading of symptom intensity is described in basic, easily understood language based on the following descriptions:

Table 3 Grading of General Symptoms from the Subject's Memory Aid

MedDRA coded Preferred Term General Adverse Events	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°C (102.1 – 104°F)	3	≥39.0 – <40.0°C (≥102.2 – <104.0°F)
	4	>40°C (>104°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°C (≥100.4°F), which is fever Grade ≥1 by FDA grading and oral temperature Grade ≥2 as assessed at diary review.

Assessment of Causality

Causal relationship between solicited general AEs and the vaccine will be assessed by the investigator using the same categories as for unsolicited AEs (see Section 11.7).

11.9 Adverse Events of Special Interest

11.9.1 General AESI Definitions

For this trial, AESIs are defined according to the following lists of AESIs available:

1. Brighton Collaboration SPEAC – Safety Platform for Emergency vACcines (SPEAC) Project generated list of AESI for safety monitoring (accessible via https://brightoncollaboration.us/covid-19/). This list is updated on a quarterly basis and the current effective list of AESIs is applicable for this trial. Links to the Brighton

Collaboration's case definitions for AESIs applicable for COVID-19 vaccine trials are provided in Appendix 3.

2. ACCESS Project List of Adverse events of special interest and case definitions (accessible via http://www.encepp.eu/documents/DraftReport.pdf).
3. CBER Surveillance Program – List of Adverse Events of Special Interest (accessible via https://www.bestinitiative.org/wp-content/uploads/2021/02/C19-Vaccine-Safety-AESI-Background-Rate-Protocol-FINAL-2020.pdf).
4. Additionally, confirmed COVID-19 infection is also considered as AESI. Confirmed COVID-19 infection requires laboratory confirmation of SARS-CoV-2 using reverse transcription PCR methods (ECDC, 2020).

BN has compiled an all-inclusive list of AESIs based on references provided above, which is part of investigator training materials.

For timelines for reporting and follow-up of AESIs, see Section 11.14.1. The same timelines and reporting processes as for SAEs are applicable.

11.9.2 Myocarditis and Pericarditis

Myocarditis and pericarditis are a subset of AESIs of particular interest. Postmarketing data from mRNA vaccine recipients have demonstrated increased risks of myocarditis and pericarditis in males under the age of 40 years following a second dose of mRNA vaccine. Cases have been reported in older males and in females as well, and also following other doses. Available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management, although information is not yet available about potential long-term sequelae.

The spike (S) protein antigen can induce antibodies to SARS-CoV-2 spike glycoproteins that cross-react with myocardial contractile proteins, including myocardial α-myosin heavy chain (Vojdani and Kharrazian, 2020). In contrast to the currently licensed COVID-19 vaccines, the ABNCoV2 candidate vaccine does not contain the full-length S protein of the SARS-CoV-2 virus, but specifically the receptor binding domain (RBD) of the S protein. However, as the pathomechanism for myocarditis or pericarditis following COVID-19 vaccination is not fully understood, and the specific role of the RBD remains unclear, precautionary measures will be implemented for this trial.

Symptoms of myocarditis or pericarditis include chest pain, shortness of breath, or feelings of having a fast-beating, fluttering, or pounding heart, with onset of symptoms most commonly reported within a few days following vaccination. While some cases required intensive care support, available data from short-term follow-up suggest that symptoms resolve in most individuals with conservative management. Information is not yet available about potential long-term sequelae. Subjects will receive educational materials explaining the symptoms of

myocarditis and pericarditis and instructing them to seeking medical attention if they occur. Subjects reporting acute chest pain, shortness of breath, palpitations, or other signs or symptoms of myocarditis or pericarditis within 4 to 6 weeks after vaccination will be referred to a cardiologist for evaluation and management. Cases of myocarditis and pericarditis will be followed until resolution of symptoms and abnormal test findings.

Determination of myocarditis and pericarditis will be performed based on the case definitions and guidelines from the Brighton Collaboration Myocarditis/Pericarditis Working Group (Sexson Tejtel et al., 2022). Reference to the publication of these case definitions is provided in Appendix 3. Cases of myocarditis or pericarditis occurring in temporal association with vaccination will be considered as potentially related, unexpected, and serious (as important medical events, even if other seriousness criteria are not met). These will be included in expedited reporting for the trial.

An adverse event follow-up questionnaire for cardiac events (Appendix 4) will be used during the study.

The DMC will review cases of myocarditis and pericarditis, with details as to the timelines for review and ad-hoc meetings to be described in the DMC charter (Section 13.3.1). In addition, recommendations for pausing or halting the trial will be in line with the stopping rules described in Section 13.3.2.

11.10 Confirmed COVID-19 Infection with Severe Manifestations or Resulting in Critical Illness

All cases of COVID-19 disease with severe manifestations or resulting in critical illness will be reviewed periodically by the DMC.

Severe COVID-19 in adults is defined as dyspnea, a respiratory rate of 30 or more breaths per minute, a blood oxygen saturation of 93% or less, a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (Pao2:Fio2) of less than 300 mm Hg, or infiltrates in more than 50% of the lung field (Berlin et al., 2020). Critical illness is defined as respiratory failure, septic shock, and/or multiple organ dysfunction (NIH, 2021).

11.11 Safety Laboratory Measurements

The intensity of laboratory/systemic toxicities measured quantitatively will be graded according to the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (FDA, 2007). The laboratory values provided in this toxicity grading scale serve as guidelines and are dependent upon institutional parameters. Institutional specific toxicity gradings will be included in site specific manuals as needed.

Safety laboratory measurements are obtained at Screening and Visit 3 and at any other visit(s) if clinically indicated. For subjects who discontinued during the trial and are coming for the EAP

visit so that final safety data can be collected, safety labs may be done at this time. Safety laboratory parameters to be evaluated are:

Hematology:

Red blood cell count, hemoglobin, total and differential white blood cell count (WBC), platelet count, hematocrit, mean corpuscular/cell volume (MCV), mean corpuscular/cellular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) and red blood cell distribution width (RDW) are routinely performed as part of the complete blood cell count and will be included in the laboratory report.

Serum chemistry:

Total bilirubin, ALP, AST, ALT, serum creatinine, sodium, potassium, calcium, c-reactive protein.

Pregnancy test:

A β-human choriogonadotropin (β-HCG) pregnancy test will be conducted for all WOCBP at screening, prior to vaccination, and at EAP. At screening a serum β-HCG pregnancy test will be performed; other pregnancy tests will be conducted as urine β-HCG tests.

Virology:

The following parameters will only be evaluated during the screening period for assessment of inclusion/exclusion criteria:

- Human immunodeficiency virus antibody (anti-HIV)
- Hepatitis B surface antigen (HbsAG)
- Hepatitis C antigen (HCV)

SARS-CoV-2 Testing:

Testing by PCR for SARS-CoV-2 infection will be done at screening. It also will be performed at any time throughout the trial starting after vaccination if clinically indicated (e.g., in the presence of typical COVID-19 symptoms; see the trial schedule, Section 1.4).

Positive SARS-CoV-2 infections, whether detected by testing within the trial or outside the trial, should be reported as AESIs (see Section 11.10).

11.12 Cardiac Assessment

A standard 12-lead ECG will be required at screening. An ECG may be performed at any other visit if clinically indicated. The investigator will assess the clinical significance for abnormal ECGs.

11.13 Pregnancy

As per inclusion criteria, WOCBP must have a negative serum pregnancy test at screening and a negative urine pregnancy test at randomization. In addition, WOCBP and male subjects who are sexually active with WOCBP must have used an acceptable method of contraception for 30 days prior to the trial vaccination, must agree to use an acceptable method of contraception during the trial, and must avoid pregnancy for at least 30 days after the vaccination. Nevertheless, IMP-exposed pregnancies cannot be excluded with certainty. Subjects who become pregnant prior to vaccination will be excluded from the trial and are regarded as screening failure. Subjects who become pregnant during the active trial phase (up to and including 1 month [minimum 28 days] after receiving trial vaccine) may continue trial procedures at the discretion of the investigator. All reports, where the embryo or fetus may have been exposed to the IMP will be followed-up until delivery to collect information on the outcome of the pregnancy (see Section 11.14.3).

Subjects will be instructed to notify the investigator if it is determined (also after completion of the trial) that they became pregnant during the trial.

11.14 Reporting

11.14.1 Reporting of SAEs and AESIs

All SAEs (collection starts at signing of ICF) and AESIs (collection starts upon vaccination) occurring throughout the entire course of the trial, to include the active trial and follow-up period, must be entered in the eCRF within 24 hours of awareness by the investigators, which triggers an autogenerated output to the drug safety department of [redacted], the contract research organization (CRO) for this trial.

In case the eCRF is unavailable, the SAE/AESI must be reported to [redacted] by telephone or fax within 24 hours of becoming aware of the SAE and/or AESI as follows:

SAE/AESI Hotline:

- [redacted]
- [redacted]

SAE/AESI Hotline Fax:

- [redacted]
- [redacted]

The investigator should not delay reporting because of missing information. Nonetheless, the report should be as complete as possible. This initial report should include, at a minimum, sufficient information to permit identification of the following:

- The reporter (investigator's name and contact information)
- The subject
- Involved trial medication
- AE(s)
- Seriousness criterion
- Date of onset

[redacted] is responsible for expedited reporting to the involved regulatory authorities according to applicable laws and guidelines, and for safety report distribution to participating investigators, IECs or IRBs and Human Research Protection Offices.

Regulatory authorities will be notified as soon as possible but no later than 7 days after date of first receipt of fatal or life-threatening SUSAR (Suspected Unexpected Serious Adverse Reaction) with an at least possible relationship to the IMP and no later than 15 days after knowledge of any non-fatal or non-life-threatening SUSAR.

11.14.2 Reporting of MAAEs

All MAAEs will be collected for the trial duration, including the follow-up period. MAAEs must be entered in the eCRF within 24 hours of awareness by the investigators. If an MAAE is considered serious or meets criteria for an AESI, reporting procedures in Section 11.14.1 are to be followed.

11.14.3 Reporting of Pregnancies

If a subject becomes pregnant during the active trial phase (up to and including 1 month [minimum 28 days] after receiving the trial vaccination), this must be reported to [redacted] within 24 hours of the investigator becoming aware of the event (Section 11.13).

A pregnancy will be followed to term, any premature terminations reported, and the health status of the mother and child including date of delivery and the child's sex and weight will be reported by the investigator to [redacted] as soon as possible.

Any event during pregnancy fulfilling the criteria for an SAE or AESI will be reported to [redacted] (see Section 11.14.1). However, hospitalization for delivery is a prospectively planned hospitalization and is not considered a SAE, per se.

12 Statistical Considerations

12.1 Randomization Procedure and Blinding Consideration, Part A Only

At Visit 1, subjects enrolled in Part A of the trial will be randomized in a 1:1 ratio to receive vaccination with a single 100 µg dose of ABNCoV2 or a 30 µg adult dose of Comirnaty, stratified by age (<65 years versus ≥65 years) and prior vaccination regimens.

Randomization strata in Cohort 1 include the following prior vaccination regimens, completed at least 3 months prior to trial vaccination: 1) 2 doses of mRNA vaccine (Comirnaty or Spikevax), 2) 1 dose or 2 doses of adenovirus-based vaccine (Vaxzevria or Janssen COVID-19 Vaccine), 3) 1 dose of adenovirus-based vaccine followed within 3 months by 1 dose of mRNA vaccine, and 4) other authorized primary vaccination regimen, if applicable.

Randomization strata in Cohort 2 include the following prior vaccination regimens, completed at least 3 months prior to trial vaccination: 1) 2 doses of mRNA primary vaccines plus 1 booster dose of mRNA vaccine (Comirnaty or Spikevax), 2) 1 dose or 2 doses of adenovirus-based primary vaccines (Vaxzevria or Janssen COVID-19 Vaccine) plus 1 booster dose of mRNA vaccine, and 3) other authorized primary vaccination and boost vaccination combinations.

Randomized assignments for subjects will be performed via an interactive voice or web response system (IVRS/IWRS) after confirmation of subject's eligibility as specified in Section 1.3.

To minimize the potential for bias, site personnel and subjects are blinded to vaccination assignment. Additionally, the BN and CRO study teams and statistical programming team will not have unblinded data until database lock/freeze for the primary analyses.

12.2 Sample Size Calculation

12.2.1 Part A

The primary and key secondary analyses will be tested in the randomized, double-blind component of the trial (Part A) in both Cohort 1 and Cohort 2. Two non-inferiority tests will be performed. Therefore, the sample size calculation is based on a one-sided, 0.0125 type I error, α,

to control for both tests. This will maintain the trial-wide α at 0.025 for the one-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 titers in both the ABNCoV2 and Comirnaty arms. 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 two groups. We further assume a 10% non-evaluable rate due to dropouts or invalid samples. With an evaluable sample size of 450, a one-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%. In the event that the minimum sample size is not met in one 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 of interest circulating at the time of the trial. VOCs will only be formally tested sequentially in the separate Part A cohorts and in the 2 cohorts combined. Discussion of the gatekeeping procedures with regards to the multiple hypothesis tests for the key secondary endpoints is in Section 12.3.

12.2.2 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.

12.3 Multiplicity

The hypothesis test of noninferiority 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 confidence limit 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%.

12.4 Variables

Endpoint variables are provided in Section 5.

12.5 Analysis Populations

The Safety Analysis Set for all safety endpoints and population-level summaries includes all subjects who received a trial vaccination with either ABNCoV2 or Comirnaty.

The Immunogenicity Analysis Set for immunogenicity endpoints includes all subjects who are in the Safety Analysis Set, have at least a baseline and 1 post-vaccination neutralizing antibody titer result, have not tested positive for SARS-CoV-2 infection, and have not received a booster outside of the trial within 2 weeks of trial vaccination.

12.6 Primary Analysis

12.6.1 Primary Estimand

The primary variable of interest is the subjects' neutralizing antibody titers 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 GMTs for ABNCoV2 compared to Comirnaty in subjects meeting the immunogenicity analysis set 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) A positive test for SARS-CoV-2 infection prior to Visit 3 (12 to 16 days after vaccination), by PCR and

2) Discontinuation from the trial due to AEs.

For the primary estimand, the second 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 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 and should result in exclusion of data points from the primary analysis. Strategies to handle these additional intercurrent events will be determined in a blinded fashion.

12.6.2 Primary Analysis Methods

The neutralizing antibody titers to the SARS-CoV-2 index virus will be collected and quantified as described in Section 10. As all subjects are previously vaccinated, it is not expected that a large number of titer values will be below the limits of quantitation or detection. In the case a titer result is below the limit of detection, a value of half the limit of detection will be used for analysis purposes. In the event a titer value is at least the limit of detection but below the limit of quantitation, a value of half the limit of quantitation will be used for analysis purposes.

A generalized linear model will be used to compare the SARS-CoV-2 neutralizing antibody titers (on the $\log_{10}$ scale) at 2 weeks after trial vaccination between the vaccination groups with age and baseline titers included as covariates. The least squares means and the corresponding 97.5% CI from the model will be back transformed to their original scale via exponentiation for ease of interpretation.

If the non-inferiority success criterion is met (lower bound of the 97.5% CI is $\geq$0.67), the p-value from the same model will be reported to assess superiority.

12.6.3 Sensitivity and Supportive Analyses

The primary analysis will be supported by descriptive summaries (GMT, their 95% CIs and the median) for each time point (pre- and post-vaccination). Besides summarizing data by cohort, summaries and the 95% CI will also be presented for combined Part A Cohorts 1 and 2.

The proportion of subjects with $\geq$2-fold and $\geq$4-fold increase in neutralizing antibody titers to the SARS-CoV-2 index virus from baseline to 2 weeks after trial vaccination will be summarized using frequencies and percentages within cohort and arm.

Nucleocapsid protein test results will be used to perform additional sensitivity analyses of the primary endpoint. Test results that are indicative of SARS-CoV-2 infection will be used to exclude subjects from the analysis population as potential additional subjects experiencing the intercurrent event of COVID-19 infection prior to the 2 week timepoint.

Since the window between vaccination and the primary endpoint measurement is short, the number of subjects with missing data is expected to be small. If there are any, missing data will be imputed using a multiple imputation method as a sensitivity analysis for subjects who meet the Safety Analysis Set definition.

12.6.4 Subgroup Analyses

The primary analysis will also be repeated for the following subgroups: prior vaccination regimen (per randomization strata in Section 12.1), age (<65 years and ≥65 years), baseline neutralizing titer to SARS-CoV-2 index virus (<Limit of Quantification, <median of all subjects in Part A, ≥median of all subjects in Part A), time from previous vaccination, history of SARS-CoV-2 infection and baseline comorbidity. If the number of subjects with known history of SARS-CoV-2 infection is small, the analysis for this subgroup will only be performed for subjects without known history of SARS-CoV-2 infection.

12.7 Secondary Analyses

12.7.1 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 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 12.3.

The intercurrent events for the secondary analyses are the same as for the primary analysis and will be handled in a similar fashion (Section 12.6.1).

Besides the key secondary variables of interest, other secondary variables include the subjects' neutralizing antibody titers against the SARS-CoV-2 index virus measured at 2 weeks after ABNCoV2 vaccination in the immunogenicity subsets of Part B Cohort 1 and Cohort 2. These will be summarized descriptively using GMTs, 95% CIs, and medians.

12.7.2 Secondary Analysis Methods

The VOCs for Part A will be analyzed using the same analysis methods as those for the primary estimand described in Section 12.6.2. 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, adjusted CIs for the non-inferiority hypothesis testing, as well as 95% CIs will also be calculated as descriptive information.

If the non-inferiority success criterion is met for a VOC (lower bound of the 97.5% 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.

Analyses of Part B Cohort 1 and Cohort 2 will consist of descriptive summaries (GMTs, 95% CIs, and medians) for each time point (pre- and post-vaccination).

12.7.3 Sensitivity and Supportive Analyses

The same sensitivity and supportive analyses described for the primary estimand in Section 12.6.3 will also be repeated for each of the VOCs in Part A. Multiple imputation sensitivity analyses will only be performed for the Part A cohort formally tested for non-inferiority of ABNCoV2 to Comirnaty.

12.7.4 Subgroup Analyses

The same subgroup analyses described for the primary estimand in Section 12.6.4 will be performed for each of the VOCs in Part A.

12.8 Exploratory Endpoints

Geometric mean titers of neutralizing antibodies against the SARS-CoV-2 index virus and VOCs, along with their corresponding 95% CIs, will be summarized by time point and cohort for Part A to explore the kinetics of humoral responses over time. Like for the primary analysis, COVID-19 infection is an intercurrent event for analyses of later time points due to its effect on humoral responses. Subjects with evidence of infection after the 2 week peak time point therefore will be removed from the Immunogenicity Analysis Set for these exploratory kinetic analyses. That is, not only will subjects with AEs of COVID-19 and positive PCR tests be removed, but additionally, due to the longer duration between follow-up visits and the possibility of asymptomatic COVID-19 infections, nucleocapsid protein testing will be used to remove subjects who have evidence of COVID-19 infection. Results will be presented in both tabular and graphical format.

Total antibody titers measured by ELISA in subsets of the Part A cohorts and cellular immune responses measured by ELISpot in the immunogenicity subsets of the Part B cohorts will also be summarized using geometric means and their 95% CIs. The difference between the ABNCoV2 and Comirnaty vaccination groups in the Part A cohorts with respect to total antibody titers will also be described by the ratio of their GMTs (ABNCoV2 vs. Comirnaty) and corresponding 95% CIs within each cohort. All analyses will be considered descriptive. The GMTs and 95% CIs will also be plotted as a function of time for each assay and vaccination group for the applicable parts and cohorts on the $\log_{10}$ scale.

Fold increases, defined as post-baseline titers divided by the baseline titers, will be summarized by assay, vaccination group (if applicable), and timepoint within each part and cohort. They will further be summarized by subgroups (age, baseline titer category, baseline comorbidity, previous vaccination regimen, history of known SARS-CoV-2 infection, and time from previous vaccination). Similar to the titers, fold increases will also be summarized by geometric means and corresponding 95% CIs.

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

12.9 Analyses of Safety

Safety data will be summarized descriptively. Adverse event data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Solicited and unsolicited AEs will be summarized by system organ class, preferred term, and cohort. Solicited and unsolicited AEs that meet certain criteria, e.g., ≥Grade 3, serious, related to vaccination, within 8 days after trial vaccination, or during the active trial phase, will be summarized similarly.

Based on AE and SARS-CoV-2 PCR testing results in Part A, the proportion of subjects testing positive for COVID-19 infection by timepoint, and at any time after trial vaccination, will be summarized by vaccination group for each of the cohorts. For Part B, proportions will be summarized for each cohort by timepoint and overall.

Vital signs and laboratory data will be graded according to the scales in “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials” (FDA, 2007) and reported by toxicity type and grade. Summaries will focus on subject level changes, thus shifts from baseline in toxicity grade or normal range indicator will be summarized by vaccination group and cohort.

12.10 Timing of Analyses

12.10.1 Primary Analysis

The primary analysis for the trial will occur after all subjects have completed the 2 months of follow up. All planned immunogenicity and safety analyses will be performed. A data review meeting will take place once all data are entered into the database prior to database lock. 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. A full CSR will be written for this analysis.

12.10.2 Final Analysis

The data collected at the 3 month and 6 month follow up visits will be analyzed at the end of the trial after the database lock. As limited immunogenicity and safety data are collected at these time points, a CSR addendum may be written in place of a full CSR.

13 Ethical Aspects

13.1 Ethical and Legal Regulations

The PI is to ensure that this clinical trial is conducted in complete accordance with the provisions of the 2013 version of the Declaration of Helsinki, national laws, and other guidelines for the conduct of clinical trials, such as the ICH Good Clinical Practice (GCP), to guarantee the greatest possible subject protection.

13.2 Approval by IEC/IRB

The clinical trial protocol must be reviewed by the competent IEC/IRB according to the national laws of the respective CTS before the CTS enrolls its first subject in the trial.

If one of the investigators is a member of one of these committees, he/she may not vote on any aspect of the review of this protocol.

The Sponsor will assure that the IEC/IRB is informed of any amendment to the protocol and any unanticipated problems involving risks to human subjects included in the trial. Such information will be provided to the IEC/IRB at intervals appropriate to the degree of subject risk involved, but not less than once a year. Copies of all correspondence between the investigator and the IEC/IRB must be forwarded immediately to the Sponsor. If IEC/IRB approval of the trial is withdrawn, the Sponsor must be contacted immediately by facsimile, e-mail or telephone.

13.3 Data and Safety Monitoring

13.3.1 Data Monitoring Committee

The DMC is an independent board that oversees the safety of subjects participating in the trial. The members of the DMC are independent experts with experience in infectious diseases. The primary responsibility of the DMC is to review and evaluate the accumulated trial safety data and make recommendations whether to continue the trial to its planned conclusion.

If an event occurs which fulfills the trial halting rules (see Section 13.3.2 for further details), the DMC will review the event in a timely manner and agree whether to recommend halting or terminating the trial participation of the affected subject(s) and/or the trial as a whole. If the trial as a whole or participation of specific subjects is halted, the DMC also will decide if and when to recommend resuming the trial or subject participation in it.

A separate charter will describe in detail the relevant operational procedures, communication pathways, roles and responsibilities of the DMC.

13.3.2 Stopping Rules

The events or criteria listed below would trigger a DMC review to determine whether a temporary halting or termination for the trial as a whole is warranted:

- A serious AESI or other SAE with an at least reasonable possibility of a causal relationship to the administration of trial vaccine
- An unexpected Grade 3 or higher adverse event (e.g., a systemic reaction or lab toxicity) with at least a reasonable possibility of a causal relationship to the administration of trial vaccine
- Any case of myocarditis or pericarditis in temporal association to the administration of trial vaccine

The Medical Monitor or safety physician will review cases of Grade 3 or higher adverse events at least weekly. Any issues identified during this review can be brought to the DMC for review.

In general, any member of the DMC, the PI, and/or the BN Medical Monitor or safety physician may request a DMC review based on any observation. The DMC Chair may convene an ad-hoc meeting to review events and make recommendations with respect to the study whether or not the study stopping rules are met.

If an event fulfilling the DMC review criteria reaches the investigator's attention, the investigator has the responsibility to alert the Clinical Safety and Pharmacovigilance (CSPV) Department at email [redacted] within 24 hours and provide comprehensive

documentation of the event. A DMC meeting should be convened within 48 hours after the sponsor receives the relevant safety information.

13.4 Confidentiality and Data Protection

The PI of the respective CTS is obliged to make sure that all documents provided to third parties (e.g., in the course of a marketing authorization procedure) contain no personally identifying information.

Only a subject and site number may identify subjects. Their name or clinic and subject's medical record number may not be used. The PI keeps a separate confidential subject log for trial recruitment that allows subject numbers to be matched with names and addresses of subjects at any time. Documents not meant to be passed on to third parties must be stored securely by the PI.

Information collected during the trial may be made available to persons directly involved in this trial (PI and his staff members, monitors, statisticians), to persons authorized by the Sponsor, or to authorities. The Sponsor of the trial will only receive pseudonymized data for analysis.

14 Informed Consent

The ICF and process must comply with ICH GCP guidelines, as well as specific national regulations and/or local laws in the countries where the trial is conducted and must be approved by the appropriate IEC/IRB.

The ICF will document the trial-specific information that the investigator or his/her designee (designee must be listed on the Delegation of Authority log) provides to the subject and the subject's agreement to participate. The investigator, or designee, must explain in terms understandable to the subject the purpose and nature of the trial, trial procedures, anticipated benefits, potential risks, possible adverse effects, and any discomfort that participation in the trial may entail.

Subjects must be informed unequivocally that they may refuse participation in the trial, that they may withdraw from the trial at any time and for whatever reason, and that withdrawal of consent will not affect their subsequent medical treatment or relationship with the treating physician.

Subjects also consent to authorize the monitor, quality assurance personnel, and regulatory authorities to inspect source documents for data verification and quality assurance purposes. Such verifications will always be conducted in compliance with regulations and the terms of the informed consent and under the ethical supervision of the investigator. All aspects of the confidentiality of the subject's data will be guaranteed.

This ICF process must be documented in the subject's source record. Each subject must provide a signed and dated informed consent before any trial-related (nonstandard of care) activities are performed (such as baseline testing and data collection). The initial and any amended signed and

dated consent forms must remain in each subject's trial file at the CTS and be available for verification by trial monitor, Sponsor/CRO auditor or competent regulatory authorities at any time. A copy of each signed consent form must be given to the subject at the time that it is signed by the subject.

15 Electronic Case Report Forms and Retention of Records

15.1 Electronic Case Report Forms

Electronic case report forms will be used to collect the clinical trial data.

All eCRFs are to be filled out completely by authorized CTS personnel. It is the investigator's responsibility to ensure that all subject data entered in the eCRF (including discontinuations or changes in trial vaccine or other medications) are accurate, complete and supported by the subject's medical records. The investigator attests to this by providing electronic signature within the electronic data capture (EDC) system.

All effort will be made by trial personnel and the PI to enter the eCRFs within the contractually agreed-upon time frame for subject visits/contacts. For any subject leaving the trial, any remaining eCRF and open queries should be completed at the time of the final visit or shortly thereafter. For subjects not fulfilling the eligibility criteria, the minimum information documented in the eCRF is the ICF information, demographics, and reason for screen failure.

The eCRFs exist within an EDC system with controlled access managed by BN or its authorized representative for this trial. Trial staff will be appropriately trained in the use of eCRFs and application of electronic signatures before the start of the trial and before being given access to the EDC system. Original data and any changes of data will be recorded using the EDC system, with all changes tracked by the system and recorded in an electronic audit trail. After database lock, the investigator will receive a copy of the subject data (e.g., paper, CD-ROM or other appropriate media) for archiving at the CTS.

15.2 Retention of Records

The investigator/trial staff must maintain adequate and accurate records to enable the conduct of the trial to be fully documented and the trial data to be subsequently verified. All essential documents, as listed in ICH GCP guidelines, will be retained by the investigator for at least 2 years after the date the last marketing application is approved for the drug in the indication being investigated and until there are no pending or contemplated marketing applications; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after formal discontinuation of clinical development of the drug.

The investigator must notify and obtain written approval from BN before destroying any clinical trial documents or images (e.g., scan, radiograph, ECG tracing). The Sponsor will inform the investigator of the date that the trial records may be destroyed or returned to BN.

Should an investigator wish to assign trial records to another party, advance written notice must be given to the Sponsor. Bavarian Nordic must also be notified in advance and provide express written approval of any change in the maintenance of clinical trial documents, should the investigator choose to move trial records to another location.

If the investigator cannot guarantee the aforementioned archiving requirements at the CTS for all such documents, special arrangements must be made between the investigator and BN to store these documents in secure sealed containers away from the CTS. These documents must be able to be returned in their secure sealed containers to the CTS for auditing purposes.

16 Monitoring of the Trial

16.1 Monitoring Plan

A CRO (contact information to be found in the “Responsibilities” section in the beginning of this protocol) will be contracted to perform monitoring services according to ICH GCP. Monitoring will be conducted according to the monitoring plan, which must be approved by BN. The monitoring plan will outline the monitoring strategy (including rationale) and will specify in detail the items for source data verification and other tasks, to be performed by the CRA.

Monitoring will be conducted through onsite visits with the investigator and site staff, remote monitoring, as well as any appropriate communications by mail, fax, email, or telephone. The purpose of monitoring is to ensure that the trial is conducted in compliance with the protocol, SOPs, and other written instructions and regulatory guidelines, and to ensure the quality and integrity of the data.

To assure the accuracy of data collected in the eCRFs, it is mandatory that the monitor have direct access to all original source documents, including all electronic medical records at reasonable times and upon reasonable notice. During the review of source documents, every effort will be made to maintain the privacy and confidentiality of all subjects during this clinical trial.

The site needs to maintain records to identify the nature and location of all source documents as well as essential documents.

16.2 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the participant, the investigator, or the trial site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

The PI or designee will be responsible for identifying and recording all deviations that are defined as isolated occurrences involving a procedure that did not follow the protocol or a protocol-specific procedure. All deviations from the protocol and actions taken will be recorded in the source data and placed in the trial-specific regulatory file. Protocol deviations must be sent to the local IEC/IRB per their guidelines. The site PI/trial staff is responsible for knowing and adhering to their IEC/IRB requirements. Further details about the handling of protocol deviations will be included in a trial-specific procedure.

17 Audits and Inspections

Site audits may be carried out by the BN quality assurance department or designee at any time during or after completion of this trial. All documents pertinent to the trial must be made available to the designated auditor. Subject privacy must, however, be respected. The investigator and clinical staff are to be present and available for consultation during routinely scheduled site audit visits conducted by the Sponsor or designee.

In addition, representatives from local, state, or federal regulatory authorities may choose to inspect a trial site at any time before, during, or after completion of the clinical trial. The investigator should immediately notify the Sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection. In the event of such an inspection, BN will be available to assist in the preparation. All pertinent trial data should be made available as requested by the Regulatory Authority for verification, audit, or inspection purposes.

18 Responsibility of the Investigator

The investigator should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae or other relevant documentation requested by the Sponsor, the IRB/IEC, or the regulatory authority(ies).

The PI agrees to carry out the trial in accordance with the guidelines and procedures outlined in this clinical trial protocol. The PI especially consents to strictly adhere to the ethical aspects of this protocol (see Section 13).

Changes to the protocol require written “Amendments to the protocol” issued by the Sponsor and written approval by the IEC/IRB and the PI. Changes are allowed only if the trial value is not

reduced and if they are ethically justifiable. If required by the IEC/IRB, subjects will be informed of protocol changes and reconsented regarding changes that could affect subjects' willingness to continue participation in the trial.

It is within the responsibility of the investigator to ensure that the eCRF is completed in a timely manner after each subject visit and that all subject data entered in the eCRF are accurate, complete, and supported by the subject's medical records. The investigator attests to this by providing electronic signature within the electronic data capture (EDC) system.

At the conclusion of the trial, the investigator will return all partially used, unused and empty drug containers as directed by BN, or the drug containers will be destroyed at the CTS according to local legal requirements.

The investigator may ask to terminate participation in the trial due to administrative or other reasons. If this should be the case, appropriate measures that safeguard the interests of the participating subjects must be taken after verification and consultation with the PI.

The investigator will maintain appropriate medical and research records for this trial, in compliance with the ICH E6 Guideline for GCP and regulatory and institutional requirements for the protection of confidentiality of subjects. He/she will permit authorized representatives of the Sponsor and regulatory authorities to review (and, when required by applicable law, to copy) clinical records for the purposes of quality reviews, audits/inspections, and evaluation of the trial safety and progress.

The PI agrees to follow the detailed publication policy included in the clinical trial agreement.

By signing this protocol, the PI confirms that he/she has read the entire clinical trial protocol, agrees to its procedures, and will comply strictly with the formulated guidelines.

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20 Appendices

Appendix 1: Toxicity Scale for Laboratory Values

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

Estimating severity grade
For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

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

Serious or life-threatening AEs
ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a Grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: Seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

Appendix 2: Grading Scale for Lymphadenopathy

A grading scale for lymphadenopathy would apply as follows:

Grade 0 (normal finding):	No palpable lymph nodes or lymph nodes up to a diameter of 1 cm, soft, non-tender
Grade 1 (mild):	Slightly palpable lymph nodes or lymph nodes up to a diameter of 1 cm, bilaterally enlarged lymph nodes, signs of tenderness
Grade 2 (moderate):	Markedly palpable lymph nodes or lymph node diameter exceeds 1 cm, bilaterally enlarged lymph nodes, pain, skin redness, warmth, limiting instrumental daily life activities
Grade 3 (severe):	Markedly palpable lymph nodes or lymph node diameter exceeds 2 cm, generalized enlargement of lymph nodes, severe pain, general symptoms like fever and sweating limiting self-care daily activities

Appendix 3: Myocarditis and Pericarditis Scale, Case Definitions for COVID-19 Adverse Events of Special Interest, Brighton Collaboration

Brighton Collaboration publications are provided at the link below:

Brighton Collaboration Publications - Google Sheets

As of the date of this protocol edition, case definitions have been published for the below AESIs at the links provided in Table 4, which were excerpted from the above website.

Table 4 Brighton Collaboration Publications of COVID-19 AESI Case Definitions

Publication Organization		Information on Publication				Case Definition Companion Guide[a]
Category	**Sub-category**	**Title**	**Year**	**PMID**	**DOI**	**Link**
Cardiac	Myocarditis Pericarditis	Myocarditis and pericarditis: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data	2022	35105494	10.1016/j.vaccine.2021.11.074	Myocarditis and Pericarditis Case Definition Companion Guide
Hematologic	Thrombocytopenia	Thrombocytopenia: case definition and guidelines for collection, analysis, and presentation of immunization safety data.	2007	17493712	10.1016/j.vaccine.2007.02.067	Thrombocytopenia Case Definition Companion Guide
Neurologic	Aseptic meningitis	Aseptic meningitis: case definition and guidelines for collection, analysis and presentation of immunization safety data.	2007	17574313	10.1016/j.vaccine.2007.04.058	Aseptic Meningitis Case Definition Companion Guide
Neurologic	Encephalitis / myelitis / ADEM	Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and presentation of immunization safety data.	2007	17570566	10.1016/j.vaccine.2007.04.060	Myelitis Case Definition Companion Guide
						ADEM Case Definition Companion Guide
						Acute Encephalitis Case Definition Companion Guide

Publication Organization		Information on Publication				Case Definition Companion Guide[a]
Category	**Sub-category**	**Title**	**Year**	**PMID**	**DOI**	**Link**
Neurologic	Facial nerve palsy	Facial nerve palsy including Bell's palsy: Case definitions and guidelines for collection, analysis, and presentation of immunisation safety data	2017	27235092	10.1016/j.vaccine.2016.05.023	Facial Nerve Palsy Case Definition Companion Guide
Neurologic	Guillain Barre Syndrome (GBS)	Guillain-Barre syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data	2011	20600491	10.1016/j.vaccine.2010.06.003	GBS and Miller Fisher Syndrome Case Definition Companion Guide
Neurologic	Seizure	Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation	2004	14741144	10.1016/j.vaccine.2003.09.008	Generalized Convulsion Case Definition Companion Guide
Neurologic	Sensorineural hearing loss (SNHL)	Sensorineural hearing loss (SNHL) as an adverse event following immunization (AEFI): Case definition & guidelines for data collection, analysis, and presentation of immunization safety data	2020	32418788	10.1016/j.vaccine.2020.05.019	
Respiratory	ARDS	Acute respiratory distress syndrome (ARDS) as an adverse event following immunization: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data	2021	33583673	10.1016/j.vaccine.2021.01.053	
Systemic	VAED	Vaccine-associated enhanced disease: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data	2021	33637387	10.1016/j.vaccine.2021.01.055	
Systemic reactions	Anaphylaxis	Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data	2007	17448577	10.1016/j.vaccine.2007.02.064	Anaphylaxis Case Definition Companion Guide

Publication Organization		Information on Publication				Case Definition Companion Guide[a]
Category	**Sub-category**	**Title**	**Year**	**PMID**	**DOI**	**Link**
Vasculitis	Single organ cutaneous vasculitis	Single organ cutaneous vasculitis: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data	2016	28029543	10.1016/j.vaccine.2016.09.032	

[a] Where case definitions are provided in supplemental materials, links to the case definition companion guides are provided.

Appendix 4: Adverse Event Follow-up Questionnaire — Inflammatory Cardiac Disorders

Please enter all dates in the following format: DD/MMM/YYYY (e.g., 01/MAR/2019)

Patient			
Initials/Subject ID	Sex ☐ M ☐ F	DOB	Study ID (if applicable)

Suspect Product Administration			
ABNCoV2	Date of dose		Batch no.
Comirnaty	Date of dose		Batch no.
Other (specify):	Therapy dates	Dose/frequency:	Indication
Other (specify):	Therapy dates	Dose/frequency:	Indication

Cardiovascular Adverse Event(s) – enter a diagnosis or signs/symptoms if a diagnosis is not available						
Cardiovascular Adverse Events(s)	**New onset (Y/N)**	**Start Date**	**Stop Date**	**CTCAE Grade[a]**	**Serious Criteria[b]**	**Outcome[c]**
Key symptoms (mark N/A if not present)		**Start Date**	**Stop Date**	**CTCAE Grade[a]**	**Serious Criteria[b]**	**Outcome[c]**
Cough						
Dizziness/Fainting						
Dyspnea						
Palpitations						

Chest pain, pressure or discomfort							
Typical chest pain made worse when lying down and relieved by sitting up							
Any other symptoms, please specify							

Key:	CTCAE Grade[a] 1 = Grade 1 (mild) 2 = Grade 2 (moderate) 3 = Grade 3 (severe) 4 = Grade 4 (life-threatening) 5 = Fatal	Serious Criteria[b] D = Death L = Life-threatening H = Hospitalization/prolonged hospitalization S = Significant disability M = Medically significant N/A = Not applicable (non-serious)	Outcome[c] 1 = Recovered/resolved 2 = Recovering/resolving 3 = Not recovered/not resolved 4 = Recovered/resolved with sequelae 5 = Fatal 6 = Unknown

If one of the events resulted in death Date of death: Cause:

Was an autopsy performed? ☐ No ☐ Yes (if available please attach report)

Hospitalization Admission date: Discharge Date:

Cardiac Diagnostic Results – enter N/A if not performed

Test Method	**Test Date**	**Test Results (please include reference range for lab values)**
Chest X-ray		
Auscultation		
ECG		
Echocardiography		
Troponin I or T		
Cardiac MRI		
Cardiac CT scan		
Pericardial Endomyocardial biopsy		
Other diagnostic tests (please specify, e.g., Angiography, Ergometry, etc.)		

Was any pericardial effusion identified?	☐ Yes ☐ No	If yes, please provide details (date, how diagnosed, estimated volume etc.):
Was an endomyocardial biopsy performed?	☐ Yes ☐ No	If yes, please provide details (date, histology results etc.):
Minimum left ventricular ejection fraction (LV-EF)	%	Date and method of measurement:

Were vasopressors or positive inotropic agents administered? ☐ **Yes** ☐ **No**

Name of treatment	Route	Dose	Therapy Dates	Response

Were any other agents to treat heart failure administered? ☐ Yes ☐ No

(e.g., diuretics, vasodilators, ACE inhibitors, ß-blocking agents, etc.)

Name of treatment	Route	Dose	Therapy Dates	Response

Were any other treatments administered? ☐ Yes ☐ No

Name of treatment	Route	Dose	Therapy Dates	Response

Were any non-drug treatments applied? ☐ Yes ☐ No

Description of treatment	Therapy Dates	Response

Risk factors (list below) or ☐ No risk factors		
Recent episodes of viral (e.g., adeno, coxsackie), bacterial or fungal infections	☐ Yes ☐ No	If yes, please provide details
Chronic infections (e.g. HIV, tuberculosis, Hepatitis B/C)	☐ Yes ☐ No	If yes, please provide details
Previous hypersensitivities (incl. but not limited to sulfonamides, NSAIDs etc.)?	☐ Yes ☐ No	If yes, please provide details
Previous autoimmune disorders (e.g. celiac disease, rheumatoid diseases, etc.)	☐ Yes ☐ No	If yes, please provide details
History of malignancies (e.g. incl. anthracyclin treatment)	☐ Yes ☐ No	If yes, please provide details
Known ischemic disorders, incl. cardiac/coronary	☐ Yes ☐ No	If yes, please provide details
Chronic alcohol or tobacco use	☐ Yes ☐ No	If yes, please provide details
Recent pregnancy (female patients)	☐ Yes ☐ No	If yes, please provide details
Family history of inflammatory cardiac disorders?	☐ Yes ☐ No	If yes, please provide details
Other risk factors (specify):	☐ Yes ☐ No	If yes, please provide details

Medical History potentially relevant for assessment of cardiac conditions, in addition to the risk factors specifically listed above:	
Condition	**Start date, intensity, treatments, further relevant details**

Relevant current condition: Please indicate below whether the patient currently has, or has had in the past, any of the following cardiovascular conditions. If any apply, please provide the additional details requested

Condition	Yes/No/Unk	Start date	Stop date	Ongoing (Yes/No)	Details, including treatments received
Myocarditis					
Pericarditis					
Hypertension					
Thrombosis					
Cardiac arrhythmia					
Myocardial infacrtion					
Coronary artery disease					
Other heart/vascular condition (specify)					
Bacterial Infections in the last 6 months (e.g., Streptococcal (Strep) or Staphylococcal (Staph) infections)					

Condition	Yes/No/Unk	Start date	Stop date	Ongoing (Yes/No)	Details, including treatments received
Viral Infections in the last 6 months (COVID-19, Influenza (Flu), Parvovirus, Enterovirus (Cocksackie virus), etc.)					
Viral Infections in the last 6 months (COVID-19, Influenza (Flu), Parvovirus, Enterovirus (Cocksackie virus), etc.)					
Fungal Infections in the last 6 months (e.g., yeast infections (Candida), Aspergillus, Histoplasma, etc.)					
Tick-borne disease (Lyme disease, Ehrlichiosis, Babesiosis, etc.)					
Autoimmune disorders (e.g., systemic lupus erythematosus (SLE), Sjogren's syndrome, giant cell arteritis, rheumatoid arthritis, mixed connective tissue disease, rheumatic fever, etc.)					
HIV					

Condition	Yes/No/Unk	Start date	Stop date	Ongoing (Yes/No)	Details, including treatments received
Use of Immunosuppressant medications					
Cancer					
Radiation and/or Chemotherapy treatment					

Additional Medications (including concomitant medications). If space is not sufficient, please include a printout of the patient's medications.

Drug Name	Indication	Dose and Frequency	Start Date	Stop Date

Additional Event Information		
In your opinion, what is the causal relationship between the inflammatory cardiac adverse event and the ABNCoV2 vaccination? ☐ Related ☐ Not Related	If not related, what was the cause of the inflammatory cardiac adverse event?	
In your opinion, what is the causal relationship between the inflammatory cardiac adverse event and the Comirnaty vaccination? ☐ Related ☐ Not Related	If not related, what was the cause of the inflammatory cardiac adverse event?	
Were alternate causes for the signs and symptoms ruled out?	☐Yes ☐No	If yes, please describe how these were ruled out:

Please provide any additional, relevant information on a separate page.

Signature of person completing form:	Date Completed:
Name and function of person completing form (Print):	
Email:	Phone:

Appendix 5: Signature Page

Investigator Signature Page

Herewith I agree that I have read and fully understand this 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

This protocol describes necessary information to conduct the trial. I agree that I will conduct the trial according to the instructions given within this protocol. Furthermore, I agree that I will conduct this trial according to International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), the 2013 version of the Declaration of Helsinki, as well as applicable local legal and regulatory requirements in the respective countries. Additionally, I will follow all applicable national regulations requirements (e.g., German Arzneimittelgesetz). I agree that all information revealed in this protocol is handled strictly confidential.

Additionally, I will permit trial-related monitoring, audits, Institutional Review Board (IRB) / Independent Ethics Committee (IEC) review and regulatory inspections, providing direct access to source data/documents.

(Date) (Signature) Name, MD

Principal Investigator (PI)

Address

Coordinating Investigator Signature Page

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

I agree that the protocol was written according to international ethical and scientific quality standards (ICH GCP), in compliance with the 2013 version of the Declaration of Helsinki and local legal and regulatory requirements applicable in the respective country.

(Date) (Signature) [Name, Department]

Coordinating Investigator

Address

Sponsor Signature Page

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

By signing the protocol:

the undersigned parties agree that the protocol was written according to international ethical and scientific quality standards (ICH GCP), in compliance with the 2013 version of the Declaration of Helsinki and local legal and regulatory requirements applicable in the respective country.

Coordinating Author and Medical Monitor

[redacted]

Biostatistician

[redacted]

Appendix 6: Summary of Changes for Amendment#1 to the Clinical Trial Protocol

A Randomized, Active Controlled Phase 3 Trial to Evaluate the Immunogenicity, Safety, and Tolerability of a Single Boost Dose of ABNCoV2 Vaccine in Adult Subjects Previously Vaccinated for SARS-CoV-2

Date of Edition 2.0: 01-Apr-2022

Rationale

The protocol Edition 2.0 has been created to implement corrections to the previous edition.

Changes

Changes/added terms are highlighted in **bold** letters in the text (see Table 5 below), deleted terms are marked using ~~strikethrough~~.

Table 5 Description of Changes from Edition 1.0 to Edition 2.0

Clinical Trial Protocol Edition 1.0, dated 28-Feb-2022 Previously written:	Clinical Trial Protocol Edition 2.0, dated 01-Apr-2022 Changed to:
1.3 Trial Synopsis Trial Design (page 11) This phase 3 trial will compare vaccination with a single dose of 100 µg ABNCoV2 to a single standard adult dose of Comirnaty in previously vaccinated adult subjects who are eligible to receive a boost or re-boost (applies to Cohort 3 only) vaccination ~~according to local guidelines~~, and whose last authorized SARS-CoV-2 vaccination is at least 3 months (Cohorts 2 and 3) or 6 months (Cohort 1) prior to the screening visit.	**1.3 Trial Synopsis** Trial Design (page 11) This phase 3 trial will compare vaccination with a single dose of 100 µg ABNCoV2 to a single standard adult dose of Comirnaty in previously vaccinated adult subjects who are eligible to receive a boost or re-boost (applies to Cohort 3 only) vaccination, and whose last authorized SARS-CoV-2 vaccination is at least 3 months (Cohorts 2 and 3) or 6 months (Cohort 1) prior to the screening visit. **Where local guidelines are available, subjects should be eligible for boost or re-boost vaccination according to those guidelines.**

Clinical Trial Protocol Edition 1.0, dated 28-Feb-2022 Previously written:	Clinical Trial Protocol Edition 2.0, dated 01-Apr-2022 Changed to:
1.3 Trial Synopsis Sample Size (page 12) • Cohort 1: subjects who previously completed a primary vaccination regimen with Comirnaty at least 6 months prior to the screening visit ~~and in accordance with local guidelines regarding vaccine eligibility~~ • Cohort 2: subjects who previously completed a primary vaccination regimen with authorized SARS-CoV-2 vaccines (defined in Section 1.2) at least 3 months prior to the screening visit ~~and in accordance with local guidelines regarding vaccine eligibility~~; this includes subjects who completed a primary Comirnaty regimen at least 3 months but less than 6 months before the screening visit • Cohort 3: subjects who have received at least 1 booster vaccination with an authorized SARS-CoV-2 vaccine (defined in Section 1.2) at least 3 months prior to the screening visit ~~and in accordance with local guidelines regarding booster eligibility~~	**1.3 Trial Synopsis** Sample Size (page 12) • Cohort 1: subjects who previously completed a primary vaccination regimen with Comirnaty at least 6 months prior to the screening visit • Cohort 2: subjects who previously completed a primary vaccination regimen with authorized SARS-CoV-2 vaccines (defined in Section 1.2) at least 3 months prior to the screening visit; this includes subjects who completed a primary Comirnaty regimen at least 3 months but less than 6 months before the screening visit • Cohort 3: subjects who have received at least 1 booster vaccination with an authorized SARS-CoV-2 vaccine (defined in Section **1.2**) at least 3 months prior to the screening visit
1.4 Trial Schedule	**1.4 Trial Schedule** **Demographics collection** row added, **X** added in SCR column
2.2.2 Clinical Trials with ABNCoV2 Vaccine **Table 1 Overall Summary of Adverse Events in Seropositive Subjects During the Active Trial Period** Row 6: Solicited general AEs~~, related~~	**2.2.2 Clinical Trials with ABNCoV2 Vaccine** **Table 1 Overall Summary of Adverse Events in Seropositive Subjects During the Active Trial Period** Row 6: Solicited general AEs

Clinical Trial Protocol Edition 1.0, dated 28-Feb-2022 Previously written:	Clinical Trial Protocol Edition 2.0, dated 01-Apr-2022 Changed to:
3 Trial Design This is a randomized, active controlled phase 3 trial to compare vaccination with a single dose of 100 µg ABNCoV2 to a single standard adult dose of Comirnaty in adult subjects previously vaccinated for SARS-CoV-2~~ who are eligible to receive a boost vaccination according to local guidelines~~. … • Cohort 1: approximately 625 to 1000 subjects with a previously completed primary vaccination regimen with Comirnaty (Pfizer/BioNTech SARS-CoV-2 vaccine) at least 6 months prior to the screening visit~~ and in accordance with local guidelines regarding vaccine eligibility~~ • Cohort 2: subjects who previously completed a primary vaccination regimen with authorized SARS-CoV-2 vaccines (e.g., 2 doses of Spikevax, 1 dose of Janssen, 2 doses of Vaxzevria, or any mix-and-match vaccinations) at least 3 months prior to the screening visit~~ and in accordance with local guidelines regarding vaccine eligibility~~; this includes subjects who completed a primary Comirnaty vaccination regimen at least 3 months but less than 6 months before the screening visit • Cohort 3: subjects who have received at least 1 booster vaccination with an authorized SARS-CoV-2 booster vaccine at least 3 months prior to the screening visit ~~and in accordance with local guidelines regarding booster eligibility~~	**3 Trial Design** This is a randomized, active controlled phase 3 trial to compare vaccination with a single dose of 100 µg ABNCoV2 to a single standard adult dose of Comirnaty in adult subjects previously vaccinated for SARS-CoV-2. **Where local guidelines are available, subjects should be eligible to receive a boost or re-boost vaccination according to those guidelines.** … • Cohort 1: approximately 625 to 1000 subjects with a previously completed primary vaccination regimen with Comirnaty (Pfizer/BioNTech SARS-CoV-2 vaccine) at least 6 months prior to the screening visit • Cohort 2: subjects who previously completed a primary vaccination regimen with authorized SARS-CoV-2 vaccines (e.g., 2 doses of Spikevax, 1 dose of Janssen, 2 doses of Vaxzevria, or any mix-and-match vaccinations) at least 3 months prior to the screening visit; this includes subjects who completed a primary Comirnaty vaccination regimen at least 3 months but less than 6 months before the screening visit • Cohort 3: subjects who have received at least 1 booster vaccination with an authorized SARS-CoV-2 booster vaccine at least 3 months prior to the screening visit

Clinical Trial Protocol Edition 1.0, dated 28-Feb-2022 Previously written:	**Clinical Trial Protocol Edition 2.0, dated 01-Apr-2022 Changed to:**
9.1 Production, Packaging and Labeling The packages and vials of ABNCoV2 vaccine are labeled according to regulatory requirements. Vials contain at least 100 µg in ~~0.3~~ mL.	**9.1** Production, Packaging and Labeling The packages and vials of ABNCoV2 vaccine are labeled according to regulatory requirements. Vials contain at least 100 µg in **0.5** mL.

Appendix 7: Summary of Changes for Amendment#2 to the Clinical 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

Date of Edition 3.0: 01-Jun-2022

Rationale

The protocol Edition 3.0 has been created to implement a title change and major design changes to the previous edition.

Changes

Changes are extensive and throughout the document. They are summarized at a high level below in Table 6.

Table 6 Description of Changes from Edition 2.0 to Edition 3.0

Change
Trial is to be conducted in two parts: • Part A: randomized, double-blind component • Part B: single-arm, open-label component
Cohorts in each part to be subjects who have received primary vaccination only (Cohort 1) and subjects who have received primary plus 1 booster vaccination (Cohort 2)
Source of comparator vaccine changed from routine access to blinded trial vaccine
Randomization ratio changed from 3:1 to 1:1
Single-arm component mostly for safety analyses but also includes subset for humoral and cellular immunogenicity
Non-inferiority testing to be done in randomized component in both cohorts simultaneously, and if non-inferiority margin is met, then superiority testing to be done as well in the same cohort(s)
Comparison added between cohorts in Parts A and B

Change
Enrollment of a homologous primary vaccination cohort dropped
Number of prior booster vaccinations limited to 1
Inclusion relaxed to prior vaccination at least 3 months before screening (reduced from 6 months)
Exclusion limited to COVID-19 infection in last 3 months (reduced from 6 months)
Trial population to include 1000 subjects ≥65 years of age
Trial schedule: Visit 1 and day of vaccination combined (no need to allow time for routine access)
Safety data updated to be consistent with Topline Interim Clinical Study Report
T-cell data added to phase 2 results in Background section
Gate-keeping approach to multiplicity described
Seropositivity (≥2-fold and ≥4-fold increase) added as supportive analyses
Unblinding process added
COVID-19 resulting in critical illness added to severe COVID-19 as cases to be reviewed by DMC
Sites limited to Belgium, Denmark, and US
Clinical trial identifiers added
Editorial changes made for clarity and accuracy throughout

Appendix 8: Summary of Changes for Amendment#3 to the Clinical 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

Date of Edition 4.0: 09-Jun-2022

Rationale

The protocol Edition 4.0 has been created to implement changes to the previous edition.

Changes

Changes/ added terms are highlighted in **bold** letters in the text (see Table 7 below), deleted terms are marked using ~~strikethrough~~.

Table 7 Description of Changes from Edition 3.0 to Edition 4.0

Clinical Trial Protocol Edition 3.0, dated 01-Jun-2022 Previously written:	Clinical Trial Protocol Edition 4.0, dated 09-Jun-2022 Changed to:
1.3 Trial Synopsis **Exclusion Criteria** 9. Laboratory parameters (such as complete blood count, serum biochemistry including aspartate aminotransferase [AST], alanine amino transferase [ALT], alkaline phosphokinase [ALP], bilirubin, or creatinine values), pulse rate, blood pressure~~, or electrocardiogram (ECG)~~ outside normal range at screening and deemed clinically relevant by the investigator.	**1.3 Trial Synopsis** **Exclusion Criteria** 9. Laboratory parameters (such as complete blood count, serum biochemistry including aspartate aminotransferase [AST], alanine amino transferase [ALT], alkaline phosphokinase [ALP], bilirubin, or creatinine values), pulse rate, **or** blood pressure outside normal range at screening and deemed clinically relevant by the investigator.
1.4 Trial Schedule ~~ECG row, X in SCR column~~ Abbreviations:…~~ECG = electrocardiogram~~	**1.4 Trial Schedule** ECG row deleted, abbreviation deleted

Clinical Trial Protocol Edition 3.0, dated 01-Jun-2022 Previously written:	Clinical Trial Protocol Edition 4.0, dated 09-Jun-2022 Changed to:
8.4 Unscheduled Visit Clinically indicated additional visits may be necessary between scheduled visits. Unscheduled visits may be performed, e.g., to repeat laboratory testing or physical exams due to a new development. Examinations performed at unscheduled visits will be recorded in the source documents as well as in the respective eCRF sections for unscheduled visits.	**8.4 Unscheduled Visit** Clinically indicated additional **procedures or** visits may be necessary **at any time, including** between scheduled visits. Unscheduled visits may be performed, e.g., to repeat laboratory testing or physical exams due to a new development **or to perform any clinically indicated evaluation, such as an electrocardiogram (ECG)**. Examinations performed at unscheduled visits will be recorded in the source documents as well as in the respective eCRF sections for unscheduled visits.
~~**Appendix 3: Interpretation Support for Assessment of Screening ECGs**~~	Appendix deleted in its entirety.

Appendix 9: Summary of Changes for Amendment#4 to the Clinical 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

Date of Edition 5.0: 14-Jun-2022

Rationale

The protocol Edition 5.0 has been created to implement administrative corrections to the previous edition.

Changes

Page breaks were added to keep the appendices on separate pages.

Appendix 10: Summary of Changes for Amendment#5 to the Clinical 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

Date of Edition 6.0: 28-Jul-2022

Rationale

The protocol Edition 6.0 has been created to implement changes to the previous edition as requested by FDA.

Changes

Changes/added terms are highlighted in **bold** letters in the text (see Table 8 below), deleted terms are marked using ~~strikethrough~~.

Table 8 Description of Changes from Edition 5.0 to Edition 6.0

Clinical Trial Protocol Edition 5.0, dated 09-Jun-2022 Previously written:	Clinical Trial Protocol Edition 6.0, dated 28-Jul-2022 Changed to:
1.1 Abbreviations	**1.1 Abbreviations** **MAAE medically attended adverse event**
12.10 Trial Synopsis **Safety Endpoint Population-level Summaries** **Part A:** For all subjects receiving ABNCoV2 compared to those receiving Comirnaty, the percent who report the below~~:~~ **Parts A and B:** For all subjects receiving ABNCoV2, the percent who report the below~~:~~ • ~~Any s~~erious adverse events (SAEs) or adverse events of special interest (AESIs) assessed as related to trial vaccine during the trial period. • ~~Any~~ Grade 3 or higher adverse events (AEs) assessed as related to trial vaccine in the 8-day period starting with the day of vaccination. • ~~Any~~ SAE ~~or~~ AESI, regardless of relationship, during the active trial phase.	**12.10 Trial Synopsis** **Safety Endpoint Population-level Summaries** **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**.** **Safety endpoints:** • **S**erious adverse events (SAEs) or adverse events of special interest (AESIs) assessed as related to trial vaccine during the **entire** trial period**, 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

Clinical Trial Protocol Edition 5.0, dated 09-Jun-2022 Previously written:	Clinical Trial Protocol Edition 6.0, dated 28-Jul-2022 Changed to:
• ~~Any~~ SAEs ~~or~~ AESIs, regardless of relationship, during the entire trial period. • ~~Any~~ 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.	8-day period starting with the day of vaccination. • SAE**s,** AESI**s**, **or medically attended AEs (MAAEs),** regardless of relationship, during the active trial phase. • SAE**s**, AESI**s**, **or MAAEs,** regardless of relationship, during the entire trial period. • 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.
12.10 Trial Synopsis **Trial Population: Exclusion Criteria**	**12.10 Trial Synopsis** **Trial Population: Exclusion Criteria** **6. History of myocarditis or pericarditis.** (added, other subsequent criteria renumbered)
1.4 Trial Schedule	**1.4 Trial Schedule** **ECG**[b] (added at Screening) AE/SAE/AESI/**MAAE** recording Abbreviations:… **MAAE = medically attended adverse event;** [g] AESIs **and MAAEs** are not collected until vaccine has been received at visit 1. [h] During the follow-up period, data collection will be limited to SAEs, AESIs, **and MAAEs**, and any unsolicited AEs from the active trial period that are not yet resolved.
2.4.1 Risks	**2.4.1 Risks** **Myocarditis and pericarditis have so far not been observed in the phase 1 and phase 2 clinical development program of ABNCoV2. However, available data regarding myocarditis or pericarditis reported in individuals vaccinated with some licensed COVID-19 vaccines containing the S antigen strongly support a plausible causal relationship to the vaccines and have warranted inclusion of a warning statement and additional safety**

Clinical Trial Protocol Edition 5.0, dated 09-Jun-2022 Previously written:	Clinical Trial Protocol Edition 6.0, dated 28-Jul-2022 Changed to:
	information about these events in EUA Fact Sheets and labeling of those approved vaccines.
5.3 Safety Endpoints The endpoints include the frequency and percentage of subjects who report the following: • SAEs or adverse events of special interest (AESIs) assessed as related to trial vaccine during the trial period, 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 ~~or~~ AESIs, regardless of relationship, during the active trial phase. • SAEs ~~or~~ AESIs, regardless of relationship, during the entire trial period ~~(active trial phase and follow-up)~~. • 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.	**5.3 Safety Endpoints** The endpoints include the frequency and percentage of subjects who report the following: • SAEs or adverse events of special interest (AESIs) assessed as related to trial vaccine during the **entire** trial period, 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. • **Medically attended AEs (MAAEs), regardless of relationship, during the active trial phase.** • **MAAEs assessed as related to trial vaccine during the entire trial period.** • 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.
8.3 Follow-up Phase **…** the core procedures from the active phase are repeated, including collection of AESIs and SAEs…	**8.3 Follow-up Phase** **…** the core procedures from the active phase are repeated, including collection of **MAAEs,** AESIs**,** and SAEs…
9.1 Production, Packaging and Labeling	**9.1 Production, Packaging and Labeling** Link to US prescribing information for Comirnaty updated

Clinical Trial Protocol Edition 5.0, dated 09-Jun-2022 Previously written:	Clinical Trial Protocol Edition 6.0, dated 28-Jul-2022 Changed to:
9.2 Shipment, Storage, and Handling ABNCoV2 ~~and Comirnaty~~ vaccine~~s~~ ~~are~~ shipped and stored at -20°C (±5°C).	**9.2 Shipment, Storage, and Handling** ABNCoV2 vaccine **is** shipped and stored at -20°C (±5°C). **Comirnaty vaccine is shipped and stored according to package leaflet instructions. For further details see the pharmacy manual.**
11 Safety and Reactogenicity Safety will be monitored in both Part A and Part B by collection of medical history at baseline…	**11 Safety and Reactogenicity** Safety will be monitored in both Part A and Part B by collection of medical history **and performance of an electrocardiogram (ECG)** at baseline…
11.1.5 SAEs ~~and~~ AESIs	**11.1.5 SAEs, AESIs, and MAAEs**
	MAAEs are defined as adverse events 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.
11.7 Unsolicited AEs SAEs ~~and~~ AESIs will be collected throughout the entire trial…	**11.7 Unsolicited AEs** SAEs**,** AESIs**, and MAAEs** will be collected throughout the entire trial…
11.9 Adverse Events of Special Interest	**11.9 Adverse Events of Special Interest** **11.9.1 General AESI Definitions** **…For timelines for reporting and follow-up of AESIs, see section 11.13.1. The same timelines and reporting processes as for SAEs are applicable.**
11.9 Adverse Events of Special Interest	**11.9 Adverse Events of Special Interest** **11.9.2 Myocarditis and Pericarditis** (entire section was added)

Clinical Trial Protocol Edition 5.0, dated 09-Jun-2022 Previously written:	Clinical Trial Protocol Edition 6.0, dated 28-Jul-2022 Changed to:
11.12 Cardiac Assessment	**11.12 Cardiac Assessment** **A standard 12-lead ECG will be required at screening. An ECG may be performed at any other visit if clinically indicated. The investigator will assess the clinical significance for abnormal ECGs.** (section added, subsequent sections renumbered)
11.14 Reporting	**11.14 Reporting** **11.14.2 Reporting of MAAEs** **All MAAEs will be collected for the trial duration, including the follow-up period. MAAEs must be entered in the eCRF within 24 hours of awareness by the investigators. If an MAAE is considered serious or meets criteria for an AESI, reporting procedures in Section 11.14.1 are to be followed.** (section was added, subsequent section renumbered)
13.3.2 Stopping Rules	**13.3.2 Stopping Rules** **…** • **Any case of myocarditis or pericarditis in temporal association to the administration of trial vaccine** **…** **A DMC meeting should be convened within 48 hours after the sponsor receives the relevant safety information.**
Appendix 3	**Appendix 3: Myocarditis and Pericarditis Scale, Brighton Collaboration** **Table 4 Myocarditis Case Definition for Surveillance of Adverse Events after Vaccination** (appendix and table added, subsequent appendices renumbered)
Appendix 4	**Appendix 4: Adverse Event Follow-up Questionnaire — Inflammatory Cardiac Disorders** (appendix added, subsequent appendices renumbered)

Appendix 11: Summary of Changes for Amendment#6 to the Clinical 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

Date of Edition 7.0: 15-Feb-2023

Rationale

The protocol Edition 7.0 has been created to implement changes to the previous edition as requested by EMA.

Changes

Changes/added terms are highlighted in **bold** letters in the text (see Table 9 below), deleted terms are marked using ~~strikethrough~~.

Table 9 Description of Changes from Edition 6.0 to Edition 7.0

Clinical Trial Protocol Edition 6.0, dated 28-Jul-2022 Previously written:	Clinical Trial Protocol Edition 7.0, dated 15-Feb-2023 Changed to:
1.1 Abbreviations	**1.1 Abbreviations** (added) **SAR: serious adverse reaction**
1.2 Definitions • "completed vaccination regimen" defined as: Completed vaccination regimen with a locally authorized SARS-CoV-2 vaccine. "Completed" includes full primary vaccination as described in the labeling of the initial vaccine, ~~but~~ also includes any mix/match series of 2 doses…	**1.2 Definitions** "completed **primary** vaccination regimen" defined as: 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… "**completed primary plus boost vaccination**" added: **Completed primary plus boost vaccination with locally authorized SARS-CoV-2 vaccine(s). "Completed primary plus boost vaccination" includes full primary**

Clinical Trial Protocol Edition 6.0, dated 28-Jul-2022 Previously written:	Clinical Trial Protocol Edition 7.0, dated 15-Feb-2023 Changed to:
	vaccination as described above 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. "**end of study/study completion**" added: **The final date on which data are collected (i.e., the last subject's last visit or scheduled assessment).**
1.3 Protocol Synopsis, Sites and Countries **Part A:** ~~X~~ sites in Belgium and Denmark **Part B:** ~~Y~~ sites in the United States ~~and Denmark~~	**1.3 Protocol Synopsis, Sites and Countries** **Part A: 13** sites in Belgium and Denmark **Part B: 45** sites in the United States
1.3 Protocol Synopsis, Sample Size The immunogenicity subset in Part B will consist of approximately 250 subjects in each cohort. This subset sample size is based on feasibility alone.	**1.3 Protocol Synopsis, Sample Size** 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**.
1.3 Protocol Synopsis, Trial Population: **Inclusion Criteria** 2. Documented, previous ~~administration of~~ locally authorized SARS-CoV-2 vaccine(s) ~~for primary vaccination only~~ or ~~for~~ primary plus 1 boost vaccination, with last vaccination at least 3 months before screening… **Exclusion Criteria** 16. History of any vaccinations or plan to receive any vaccinations with a~~n inactivated~~ vaccine within 14 days prior to or after trial vaccination.	**1.3 Protocol Synopsis, Trial Population:** **Inclusion Criteria** 2. Documented, previous **completion of a primary vaccination regimen with** locally authorized SARS-CoV-2 vaccine(s) or **completion of** primary plus 1 boost vaccination **(see definition of completed primary vaccination regimen and completed primary plus boost vaccination in Section 1.2)**, with last vaccination at least 3 months before screening… **Exclusion Criteria** 16. History of any vaccinations or plan to receive any vaccinations with a **non-live** vaccine within 14 days prior to or after trial vaccination. 23. **Known bleeding disorder that, in the opinion of the investigator, would contraindicate intramuscular injection.**

1.4 Trial Schedule AE/SAE/AESI/MAAE recording Blood collection for serum antibody titers, Part A Blood collection for serum antibody titers, Part B immunogenicity subset[j],	**1.4 Trial Schedule** AE/SAE/**SAR**/AESI/MAAE recording Blood collection for serum antibody titers **and nucleocapsid protein antibody testing**[i], Part A Blood collection for serum antibody titers **and nucleocapsid protein antibody testing**, Part B immunogenicity subset[k] (added abbreviation) **SAR = serious adverse reaction** (added footnote, subsequent footnote lettering changed) [i] Nucleocapsid protein antibody testing will be done only on samples collected at V1 and V3.
1.5 Responsibilities Project Leader [redacted] Medical Monitor [redacted] Trial Statistician [redacted]	**1.5 Responsibilities** Project Leader [redacted] **Medical Monitor ([redacted])** [redacted] Medical Monitor **(BN)** [redacted] Trial Statistician [redacted]

[redacted]	[redacted]
3.2 Trial Design, Part B Additionally, a subset of sites in the US will collect blood for serum and peripheral blood mononuclear cells (PBMCs) from approximately 500 subjects (250 from each cohort).	**3.2 Trial Design, Part B** Additionally, a subset of sites in the US will collect blood for serum and peripheral blood mononuclear cells (PBMCs) from approximately 500 subjects (**200 to** 250 from each cohort).
	3.3 End of Study / Study Completion (added) **Study completion is defined as the final date on which data are collected (i.e., the last subject's last visit or scheduled assessment).**
6.3 Inclusion of Older Subjects Sites will be instructed to pursue a target of ~~at least~~ 25% of enrollment to be subjects that are ≥65 years of age for Part A and ~~at least~~ 33% to be ≥65 years of age for Part B.	**6.3 Inclusion of Older Subjects** Sites will be instructed to pursue a target of 25% of enrollment to be subjects that are ≥65 years of age for Part A and 33% to be ≥65 years of age for Part B.
8.2.1 Visit 1 …of greatest importance is that collection of ~~immunogenicity~~ samples must always be performed prior to vaccine administration.	**8.2.1 Visit 1** …of greatest importance is that collection of samples **for serum antibody titers, PBMC testing, and nucleocapsid protein antibody testing** must always be performed prior to vaccine administration.
8.2.3 Visit 3 …and for serum antibody titers in Part A…	**8.2.3 Visit 3** …and for serum antibody titers **and nucleocapsid protein antibody testing** in Part A
8.4 Unscheduled Visit Unscheduled visits may be performed, e.g., to repeat laboratory testing or physical exams due to a new development, or to perform any clinically indicated evaluation,…	**8.4 Unscheduled Visit** Unscheduled visits may be performed, e.g., to repeat laboratory testing or physical exams due to a new development, **to do PCR testing for suspected COVID-19 infection,** or to perform any clinically indicated evaluation,…
	10.3 Nucleocapsid Protein Antibody Testing (added, subsequent section renumbered) **Serum samples also will be used to analyze nucleocapsid protein antibody titers as outlined in the trial procedure schedule in Section 1.4 (at Visits 1 and 3) in Part A and at selected investigational sites participating in the Part B immunogenicity subset. Samples for nucleocapsid protein antibody testing obtained at Visit 1 will be drawn prior to vaccination.**

11.1.5 ~~SAEs, SARs, AESIs, and MAAEs~~ An SAE is any untoward medical occurrence that:	**11.1.5 Serious Adverse Events, Serious Adverse Reactions, Adverse Events of Special Interest, and Medically Attended Adverse Events** An SAE is any untoward medical occurrence **or effect in a subject administered the trial vaccine** that **may or may not have a causal relationship with the study vaccine and that is serious, meaning that it**: (list follows) **Though SAEs, as specified above, include all serious events independent of whether they have a suspected causal relationship to the IMP or not, serious adverse reactions (SARs) are defined as a subset of SAEs that include all noxious and unintended responses to the IMP related to any dose administered that at any dose results in any of the serious outcomes listed above.**
11.4 Prohibited Medications • Vaccination with any licensed live vaccine within 30 days prior to or after trial vaccination or any licensed ~~inactivated or other non-replicating~~ vaccine within 14 days prior to or after trial vaccination.	**11.4 Prohibited Medications** • Vaccination with any licensed live vaccine within 30 days prior to or after trial vaccination or any licensed **non-live** vaccine within 14 days prior to or after trial vaccination.
11.8.1 Solicited Local AEs Injection site erythema, swelling, and induration will be assessed based on the longest diameter as measured by the subject in mm and recorded in the memory aid. Subjects are asked to document the solicited local AEs in the memory aid as described in Table 2 below. **Table 2 Grading of Local Symptoms**	**11.8.1 Solicited Local AEs** Injection site erythema, swelling, and induration will be assessed based on the longest diameter as measured by the subject in mm and recorded in the memory aid. Subjects are asked to document the solicited local AEs in the memory aid**. For injection site erythema, injection site swelling, and injection site induration, subjects are asked to record longest diameters; for injection site pruritus and injection site pain, subjects are asked to record level of severity** as described in Table 2 below. **Table 2 Grading of Local Symptoms** "Grading for Analysis" column added, with footnotes referencing FDA guidance

11.8.2 Solicited General AEs Subjects are asked to document the solicited general AEs in the memory aid as described in Table 3 below. **Table 3 Grading of General Symptoms**	**11.8.2 Solicited General AEs** Subjects are asked to document the solicited general AEs in the memory aid**. Subjects are asked to record temperature and severity of symptoms** as described in Table 3 below. **Table 3 Grading of General Symptoms** "Grading for Analysis" column added, with footnotes referencing FDA guidance on grading of fever
11.9.1 General AESI Definitions For timelines for reporting and follow-up of AESIs, see Section ~~11.13.1~~.	**11.9.1 General AESI Definitions** **… Links to the Brighton Collaboration's case definitions for AESIs applicable for COVID-19 vaccine trials are provided in Appendix 3**. For timelines for reporting and follow-up of AESIs, see Section**11.14.1**.
11.9.2 Myocarditis and Pericarditis These definitions ~~are~~ provided in Appendix 3.	**11.9.2 Myocarditis and Pericarditis** **Reference to the publication of** these **case** definitions **is** provided in Appendix 3.
11.13 Pregnancyx …(see Section ~~11.13.2~~).	**11.13 Pregnancy** …(see Section **11.14.3**).
11.14.2 Reporting of MAAEs … reporting procedures in Section ~~11.13.1~~ are to be followed.	**11.14.2 Reporting of MAAEs** … reporting procedures in Section **11.14.1** are to be followed.
11.14.3 Reporting of Pregnancies … this must be reported to [redacted] within 24 hours of the investigator becoming aware of the event (Section ~~11.12~~). Any event during pregnancy fulfilling the criteria for an SAE or AESI will be reported to [redacted] (see Section ~~11.13.1~~).	**11.14.3 Reporting of Pregnancies** … this must be reported to [redacted] within 24 hours of the investigator becoming aware of the event (Section **11.13**). Any event during pregnancy fulfilling the criteria for an SAE or AESI will be reported to [redacted] (see Section **11.14.1**).
12.2.2 Sample Size Calculation, Part B The immunogenicity subset in Part B will consist of approximately 250 subjects in each cohort. This subset sample size is based on feasibility alone.	**12.2.2 Sample Size Calculation, Part B** The immunogenicity subset in Part B will consist of approximately 250 subjects in each cohort. This subset sample size is based on feasibility alone**, i.e., the number of participating sites and consenting subjects**.
12.3 Multiplicity 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	**12.3 Multiplicity** 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. ~~In the event that success criteria are met for both Cohort 1 and Cohort 2, VOCs will be tested sequentially in separate cohorts. If the numbers of evaluable subjects are similar in both cohorts, Cohort 1 will be tested first followed by Cohort 2 if the success criterion is met in at least one VOC in Cohort 1. If the numbers of evaluable subjects are different between the 2 cohorts, VOC will be tested in the cohort with the higher number of evaluable subjects, followed by the cohort with the smaller number of evaluable subjects provided the success criterion in the previous step is met by at least 1 VOC.~~ A Bonferroni adjustment will be used such that each VOC non-inferiority hypothesis will be tested at the α = level. For example, if 3 VOCs are tested, each test will be performed at the α = 0.0083 level such that success would require the lower confidence limit of a 98.3% CI to be at least 0.67.	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 α = $\frac{0.025}{number\ of\ VOCs\ tested}$ level. For example, if 3 VOCs are tested, each test will be performed at the α = 0.0083 level such that success would require the lower confidence limit 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 α = $\frac{0.0125}{number\ of\ VOCs\ tested}$ level so that the overall type I error rate will be no more than 5%.**
12.5 Analysis Populations The Immunogenicity Analysis Set for immunogenicity endpoints includes all subjects who are in the Safety Analysis Set, have at least a baseline and 1 post-vaccination neutralizing antibody titer result, ~~and~~ have not tested positive for SARS-CoV-2 infection within 2 weeks of trial vaccination.	**12.5 Analysis Populations** The Immunogenicity Analysis Set for immunogenicity endpoints includes all subjects who are in the Safety Analysis Set, have at least a baseline and 1 post-vaccination neutralizing antibody titer result, have not tested positive for SARS-CoV-2 infection, **and have not received a booster outside of the trial** within 2 weeks of trial vaccination.
12.6.1 Primary Estimand 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) and 2) Discontinuation from the trial due to AEs.	**12.6.1 Primary Estimand** The following are considered intercurrent events: 1) **A** positive test for SARS-CoV-2 infection prior to Visit 3 (12 to 16 days after vaccination)**, by either PCR or increase in nucleocapsid protein antibody titers indicative of infection,** and 2) Discontinuation from the trial due to AEs.
12.6.4 Subgroup Analyses The primary analysis will also be repeated for the following subgroups: age (<65 years and ≥65 years),…	**12.6.4 Subgroup Analyses** The primary analysis will also be repeated for the following subgroups: **prior vaccination regimen (per randomization strata in Section 12.1),** age (<65 years and ≥65 years),…

12.10 Timing of Analyses **12.10.1 ~~Follow-up and Trial Analyses~~** ~~If required, a follow-up analysis may be performed when all subjects have completed a specified period of follow-up.~~ ~~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.~~	**12.10 Timing of Analyses** **12.10.1 Primary Analyses** **The primary analysis for the trial will occur after all subjects have completed the 2 months of follow up. All planned immunogenicity and safety analyses will be performed. A data review meeting will take place once all data are entered into the database prior to database lock. 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. A full CSR will be written for this analysis.** **12.10.2Final Analyses** **The data collected at the 3 month and 6 month follow up visits will be analyzed at the end of the trial after the database lock. As limited immunogenicity and safety data are collected at these time points, a CSR addendum may be written in place of a full CSR.**
Appendix 3: ~~Myocarditis and Pericarditis Scale~~, Brighton Collaboration (prior case definition content deleted)	**Appendix 3: Case Definitions for COVID-19 Adverse Events of Special Interest,** Brighton Collaboration (Table 4 added, providing references to AESI case definitions)
Appendix 5: Signature Page **Sponsor Signature Page** [redacted]	**Appendix 5: Signature Page** **Sponsor Signature Page** [redacted]
Appendix 10: Summary of Changes for Amendment#5 to the Clinical Trial Protocol …(see ~~Table 7~~ below)…	**Appendix 10: Summary of Changes for Amendment#5 to the Clinical Trial Protocol** …(see **Table 8** below)…

Appendix 12: Summary of Changes for Amendment#7 to the Clinical 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

Date of Edition 8.0: 30-Jun-2023

Rationale

The protocol Edition 8.0 has been created to implement changes related to the analysis of nucleocapsid protein results.

Changes

Changes/added terms are highlighted in **bold** letters in the text (see Table 10 below), deleted terms are marked using ~~strikethrough~~. Additional minor editorial corrections were made.

Table 10 Description of Changes from Edition 7.0 to Edition 8.0

Clinical Trial Protocol Edition 7.0, dated 15-Feb-2023 Previously written:	Clinical Trial Protocol Edition 8.0, dated 30-Jun-2023 Changed to:
1.1 Abbreviations	**1.1 Abbreviations** **CSR: clinical study report** **EUA: emergency use authorization** (spelled-out and/or abbreviated usage added/corrected in subsequent text)
1.4 Trial Schedule Table row "Blood collection for serum antibody titers and nucleocapsid protein antibody testing[i], Part A": X at FU2, FU3 [i] Nucleocapsid protein antibody testing will be done only on samples collected at V1 ~~and~~ V3.	**1.4 Trial Schedule** Table row "Blood collection for serum antibody titers and nucleocapsid protein antibody testing[i], Part A": X[i] at FU2, FU3 (footnote added) [i] Nucleocapsid protein antibody testing will be done only on samples collected at V1**,** V3**, FU2, and FU3**.
1.5 Responsibilities [redacted]	**1.5 Responsibilities** [redacted]

Clinical Trial Protocol Edition 7.0, dated 15-Feb-2023 Previously written:	Clinical Trial Protocol Edition 8.0, dated 30-Jun-2023 Changed to:
8.3 Follow-up Phase …but concomitant medications and other AEs are no longer recorded, and blood collection for serum antibody testing occurs only in Part A.	**8.3 Follow-up Phase** …but concomitant medications and other AEs are no longer recorded, and blood collection for serum antibody **and nucleocapsid protein** testing occurs only in Part A.
10.3 Nucleocapsid Protein Antibody Testing Serum samples also will be used to analyze nucleocapsid protein antibody titers as outlined in the trial procedure schedule in Section 1.4 ~~(~~at Visits 1 and 3~~)~~ in Part A and at selected investigational sites participating in the Part B immunogenicity subset.	**10.3 Nucleocapsid Protein Antibody Testing** Serum samples also will be used to analyze nucleocapsid protein antibody titers as outlined in the trial procedure schedule in Section 1.4 at Visits 1 and 3 **and Follow-up 2 and 3** in Part A and **at Visits 1 and 3** at selected investigational sites participating in the Part B immunogenicity subset.
12.6.1 Primary Estimand The following are considered intercurrent events: 1) A positive test for SARS-CoV-2 infection prior to Visit 3 (12 to 16 days after vaccination), by ~~either~~ PCR ~~or increase in nucleocapsid protein antibody titers indicative of infection~~, and	**12.6.1 Primary Estimand** The following are considered intercurrent events: 1) A positive test for SARS-CoV-2 infection prior to Visit 3 (12 to 16 days after vaccination), by PCR, and
12**.6.3 Sensitivity and Supportive Analyses**	**12.6.3 Sensitivity and Supportive Analyses** **Nucleocapsid protein test results will be used to perform additional sensitivity analyses of the primary endpoint. Test results that are indicative of SARS-CoV-2 infection will be used to exclude subjects from the analysis population as potential additional subjects experiencing the intercurrent event of COVID-19 infection prior to the 2 week timepoint.**

Clinical Trial Protocol Edition 7.0, dated 15-Feb-2023 Previously written:	Clinical Trial Protocol Edition 8.0, dated 30-Jun-2023 Changed to:
12.8 Exploratory Endpoints Geometric mean titers of neutralizing antibodies against the SARS-CoV-2 index virus and VOCs, along with their corresponding 95% CIs, will be summarized by time point and cohort for Part A to explore the kinetics of humoral responses over time. Results will be presented in both tabular and graphical format.	**12.8 Exploratory Endpoints** Geometric mean titers of neutralizing antibodies against the SARS-CoV-2 index virus and VOCs, along with their corresponding 95% CIs, will be summarized by time point and cohort for Part A to explore the kinetics of humoral responses over time. **Like for the primary analysis, COVID-19 infection is an intercurrent event for analyses of later time points due to its effect on humoral responses. Subjects with evidence of infection after the 2 week peak time point therefore will be removed from the Immunogenicity Analysis Set for these exploratory kinetic analyses. That is, not only will subjects with AEs of COVID-19 and positive PCR tests be removed, but additionally, due to the longer duration between follow-up visits and the possibility of asymptomatic COVID-19 infections, nucleocapsid protein testing will be used to remove subjects who have evidence of COVID-19 infection.** Results will be presented in both tabular and graphical format.