STATISTICAL ANALYSIS PLAN

Official Title: A Phase 1a/1b Study to Evaluate the Safety, Tolerability, and Immunogenicity of the COVID-19 (SARS- CoV-2) Vaccine Candidates VBI-2902a and VBI-2905a in Healthy Adults

Protocol Identifying Number: VBI-2902a-CT01

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Final Statistical Analysis Plan (SAP)

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REVISION HISTORY

Version/Date	Version name	Section	Changes implemented
1.0 05OCT2022	Draft Version	Global	Due to a major protocol amendment (Protocol V6.0, May 20, 20220), Phase 1b portion of the study was modified to remove study group G6. Enrollment of participants who have not been previously vaccinated with licensed COVID-19 vaccine, study group G6 was removed from the Protocol. Immunogenicity analysis was modified to exclude immunogenicity measurements first time after the participants receive a licensed (non-study) COVID-19 vaccines or tested positive SARS-CoV-2 infection or develop COVID-19 illness during the study.

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LIST OF ABBREVIATIONS

AE	Adverse event
AEs	Adverse events
AEC	All enrolled cohort
ADR	Adverse drug reaction
ATC	Anatomical Therapeutic Chemical Classification System
BRDD	Biologic and Radiopharmaceutical Drugs Directorate, Health Canada
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic case report form
FAS	Full Analysis Set
GMT	Geometric Mean titer
ICH	International conference on harmonisation
ITT	Intent-to-treat
MAAE	Medically-Attended Adverse Events
MedDRA	Medical dictionary for regulatory activities
PRNT	Plaque-reduction neutralization test
RBD	Receptor-binding Domain
S	Spike protein of SARS-CoV-2
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Safety cohort
SOA	Schedule of assessments
SSC	Study steering committee
SUSAR	Suspected, unexpected serious adverse reaction
SVR	Sustained virologic response
TEAE	Treatment emergent adverse event
TFL	Table figure and listing
VBI	VBI Vaccines Inc.

US	United States
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide detailed descriptions of the statistical methods, data derivations and data displays for study protocol VBI-2902a-CT01, "A Phase 1a/1b Study to Evaluate the Safety, Tolerability, and Immunogenicity of the COVID-19 (SARS- CoV-2) Vaccine Candidates VBI-2902a and VBI-2905a in Healthy Adults", Version 6.0 dated 20 May 2022. The table of contents and templates for the Tables, Figures and Listings (TFLs) will be produced in a separate document.

The preparation of this SAP has been based on International Conference on Harmonisation (ICH) E3 and E9 guidelines.

All data analyses and generation of TFLs will be performed using SAS 9.3® or higher.

2 STUDY OBJECTIVES AND ENDPOINTS

Phase 1a	
Primary Objectives:	**Primary Endpoints:**
To evaluate the safety and tolerability of VBI-2902a containing 5 µg of S protein in one- or two-dose regimens in previously unvaccinated healthy adults of 18-54 years of age.	• Rate and severity of local and systemic solicited adverse events (AEs) during 7 days after each study vaccination • Rate and severity of unsolicited AEs during 28 days after each study vaccination • Rate and severity of medically-attended adverse events (MAAEs) during 28 days after each study vaccination • Rate of serious adverse events (SAEs) at during 28 days after each study vaccination • AEs leading to discontinuation of study vaccination • AEs leading to study discontinuation • Rate and severity of laboratory abnormalities (hematology, biochemistry, urinalysis) during 28 days after each study vaccination
Secondary Objective:	**Secondary Endpoints:**
To evaluate the immunogenicity of VBI-2902a containing 5 µg of S protein in one- or two-dose regimens in previously unvaccinated healthy adults of 18-54 years of age.	• Rate and severity of unsolicited AEs throughout the study • Rate and severity of medically-attended adverse events (MAAEs) throughout the study • Rate of serious adverse events (SAEs) throughout the study • Rate and severity of laboratory abnormalities (hematology, biochemistry, urinalysis) throughout the study • GMT and the geometric mean fold increase in serum antibody titer post-vaccination over Day 1 (baseline) at Days 7, 28, 35, 56, 112,

	224 and 336 (Phase 1a, groups G1, G2 and G3); ○ Neutralizing activity against spike protein-expressing pseudovirus, and/or PRNT neutralizing activity against wild-type SARS-CoV-2 virus and other variants of concern ○ RBD Antibody titers against wild-type variant spike protein measured by ELISA
Exploratory Objectives	**Exploratory Endpoints**
	• Geometric mean number of IFN-γ-positive cells per 10^6 PBMCs by ELISPOT assay post-vaccination over Day 1 (baseline) at Days 7, 28, 35, 56 and 336 (groups G1, G2 and G3) • GMT of serum IgG subclass responses against spike protein by ELISA post-vaccination over Day 1 (baseline) responses at Days 7, 28, 35, 56, 112, 224 and 336 (groups G1, G2 and G3)
Phase 1b	
Primary Objective:	**Endpoints:**
To evaluate the safety and tolerability of a one-dose regimen of VBI-2905a at a 5 µg dose level of S protein in healthy adults (18-54 years) who had been previously vaccinated with mRNA vaccines (groups G4 and G5).	• Rate and severity of local and systemic solicited adverse events (AEs) during 7 days after each study vaccination • Rate and severity of unsolicited AEs during 28 days after each study vaccination • Rate and severity of medically-attended adverse events (MAAEs) during 28 days after each study vaccination • Rate of serious adverse events (SAEs) at during 28 days after each study vaccination • AEs leading to discontinuation of study vaccination • AEs leading to study discontinuation • Rate and severity of laboratory abnormalities (hematology, biochemistry, urinalysis) during 28 days after each study vaccination
Secondary Objective:	**Endpoints:**
To evaluate the immunogenicity of a one-dose regimen of VBI-2905a at a 5 µg dose level of S protein in healthy adults (18-54 years) who had been previously vaccinated with mRNA vaccines (groups G4 and G5).	• Rate and severity of unsolicited AEs throughout the study • Rate and severity of medically-attended adverse events (MAAEs) throughout the study

	• Rate of serious adverse events (SAEs) throughout the study • Rate and severity of laboratory abnormalities (hematology, biochemistry, urinalysis) throughout the study • GMT and the geometric mean fold increase in serum antibody titer post-vaccination over Day 1 (baseline) at Days 7, 14, 28, 56, 84, 168 and 336 Phase 1b) o Neutralizing activity against spike protein-expressing pseudovirus, and/or PRNT neutralizing activity against wild-type SARS-CoV-2 virus, variant Beta (B1.351) and other variants of concern o RBD Antibody titers against wild-type variant spike protein measured by ELISA
Exploratory Objectives	**Exploratory Endpoints**
	• Geometric mean number of IFN-γ-positive cells per 10^6 PBMCs by ELISPOT assay post-vaccination over Day 1 (baseline) at Days 7, 14, 28and 336 • GMT of serum IgG subclass responses against spike protein by ELISA post-vaccination over Day 1 (baseline) responses at Days 7, 14, 28, 56, 84, 168 and 336

This SAP will detail assessments associated with the Final and the Study Steering Committee (SSC). There is a separate DSMB SAP.

3 STUDY DESIGN

Overview

The trial will be a phase 1a/1b study, randomized, observer-blind, placebo-controlled.

Description of study parts and groups

Phase 1a

Phase 1a of the study will evaluate the safety, tolerability and immunogenicity of a one-dose or two-dose regimen of the VBI-2902a at the low dose level of 5 µg of S protein or placebo in 60 healthy adults 18 to 54 years of age with no previous clinical or laboratory diagnosis of COVID-19 or SARS-CoV-2 infection and not previously received an experimental or authorized COVID-19 vaccine. Participants will be randomized to three cohorts at a 1:1:1 ratio (2:1 ratio to VBI-2902a or placebo [saline]):

- **Group G1 –** 20 participants will receive VBI-2902a at a dose of 5 µg of S protein at Day 1 and placebo at Day 28.

- **Group G2 –** 20 participants will receive VBI-2902a at a dose of 5 µg of S protein at Days 1 and 28.
- **Group G3 –** 20 participants will receive placebo at Days 1 and 28.

An Independent Data Safety Monitoring Board (DSMB) will review blinded safety data (reactogenicity, adverse events and safety laboratory assessments) at Day 7 after the first vaccination. The second vaccination will only be given if the DSMB confirms that Day 7 safety is acceptable and that stopping rules were not met. The DSMB will further review blinded post-vaccination safety through Day 35, 7 days after the second vaccination and through Day 56, 28 days after the second vaccination. A Study Steering Committee (SSC), comprised of representatives from the study sponsor (not involved in study operations) and external vaccine experts, will review unblinded immunogenicity data 7 days and 28 days after the second vaccination. The study will be unblinded following DSMB review of safety data collected through Day 56.

Phase 1b

Phase 1b of the study will evaluate the safety, tolerability and immunogenicity of a one-dose regimen of VBI-2905a at a 5 µg dose level of S protein in healthy adults (18-54 years) who had been previously vaccinated with mRNA vaccines.

The DSMB will perform an early review of blinded post-vaccination safety data at Day 7 (reactogenicity, AEs and safety laboratory assessments). DSMB will review blinded Day 7 safety data after the first 10 participants in groups G4 and G5 (previously vaccinated). Only after the DSMB confirms that safety is acceptable and that stopping rules were not met will the enrollment in the respective study groups continue to its completion.

The SSC will review unblinded immunogenicity data 7 days and 28 days after the first vaccinations (Groups G4 and G5).

A total of 54 healthy adults, age 18-54 years, with no history of clinical or laboratory diagnosis of SARS-CoV- 2 infection or COVID-19 illness, will be enrolled in the Phase 1b part of the study. All participants in Phase 1b will have been previously vaccinated with an authorized mRNA COVID-19 vaccine, including the second dose administered at least 4 months prior to enrollment. Participants will be randomized at a 1:1 ratio to receive, in a blinded fashion, one dose of VBI-2905a or placebo:

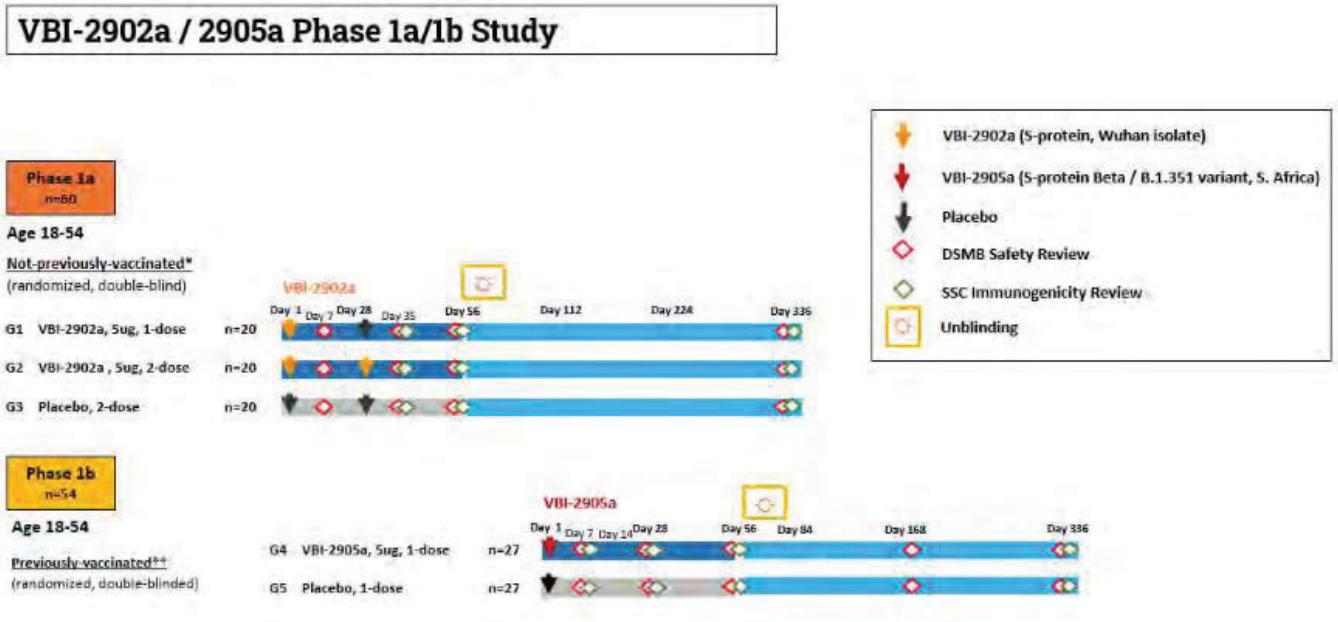
- **Group G4** – 27 participants who had previously received a full course (2 doses) of an authorized S protein mRNA COVID-19 vaccines, with the second dose administered at least 4 months prior to the enrollment into the study, will receive VBI-2905a at a dose of 5 µg of S protein at Day 1.
- **Group G5** – 27 participants who had previously received a full course of an authorized S protein mRNA COVID-19 vaccines at least 4 months prior to the enrollment into the study, will receive placebo at Day 1.

3.1 General Study Design

A study schematic is presented in Figure 1.

Figure 1: Clinical Trial Design

Figure 1: Clinical Trial Design



* *Not previously vaccinated with any licensed or experimental COVID-19 vaccine and no history of clinical or laboratory diagnosis of SARS-CoV-2 infection or COVID-19 illness*

** *Received a full course of an authorized mRNA COVID-19 vaccine at least 4 months prior to the study and no history of clinical or laboratory diagnosis of SARS-CoV-2 infection or COVID-19 illness*

3.2 Randomization and Study Treatments

Randomization of subjects will vary based on which phase and part of the study is currently enrolling. Description of the randomization allocations & treatment arms is outlined in the description of the study design above.

3.3 Sample Size and Power

A total of approximately 60 participants will be enrolled in Phase 1a and approximately 54 participants in Phase 1b. Participants in Phase 1a will be randomized at 2:1 to VBI-2902a or placebo. Participants in Phase 1b who have been previously vaccinated with COVID-19 mRNA vaccine will be randomized at 1:1 to receive one dose of VBI-2905a (group G4) or placebo (group G5) at Day 1

The Phase 1a and phase 1b parts of the study are being conducted at clinical sites in Canada. For the Phase 1b part of the study, the sites will only enroll participants who have previously received mRNA COVID-19 vaccines.

With ~10% drop-out rate it is estimated that at least 56 participants will complete Phase 1a and 48 participants will complete Phase 1b. The sample size per active group will allow for the detection of at least a two-fold difference in neutralizing antibody (nAb) titers with 80% power and an alpha error of 0.05.

4 ANALYSIS COHORTS

4.1 All-Enrolled-Cohort (AEC)

The All-Enrolled-Cohort will include all screened participants who provide informed consent and screening or baseline assessments, regardless of the subject's randomization and treatment status in the study.
Summary of analysis of population and disposition will be based on AEC

4.2 Intent-To-Treat Cohort (ITT)

The Intent-To-Treat cohort includes all participants in the AEC who were randomized. Participants will be analyzed as randomized.

Summary of protocol deviations, demographics and baseline characteristics will be based on ITT cohort.

4.3 Safety-Cohort (SC)

The Safety-Cohort will include all participants in the AEC who receive a study vaccination. Participants will be analyzed as vaccinated, i.e., a subject will be assigned according to the vaccination received.

Summary of all safety (AEs, lab, vital sign, physical examination), medical history, prior and concomitant medication will be based on SC.

4.4 Full Analysis Set (FAS)

The FAS will include all participants in the AEC who received at least one dose of the study vaccine and provided at least one evaluable immunogenicity sample both at baseline and after baseline.

Subjects who received a treatment other than that to which they were randomized, but for whom the treatment received can be unequivocally confirmed, will be analyzed as treated, provided they have no other deviations that compromise their data.

Immunogenicity data will be censored (excluded) from immunogenicity analyses at all-time points following the first date of (1) administration of a non-study (licensed) COVID-19 vaccine OR (2) positive SARS-CoV-2 test OR (3) onset of COVID-19 illness

All Immunogenicity analyses will be based on FAS and PPS.

4.5 Per-Protocol-Cohort (PPC)

The PPC will include all participants in the FAS who:

- met all eligibility criteria
- received all study vaccinations according to the protocol
- have evaluable serum immunogenicity samples at baseline and at the time points of interest
- had no major protocol deviations (PD) leading to exclusion.

Immunogenicity data will be censored (excluded) from immunogenicity analyses at all timepoints following the first date of (1) administration of a non-study (licensed) COVID-19 vaccine OR (2) positive SARS-CoV-2 test OR (3) onset of COVID-19 illness

Immunogenicity data will be censored (excluded) from immunogenicity analyses at all-time points following the first date of (1) administration of a non-study (licensed) COVID-19 vaccine OR (2) positive SARS-CoV-2 test OR (3) onset of COVID-19 illness

All immunogenicity analyses will be based on FAS and PPC.

5 STATISTICAL CONSIDERATIONS AND ANALYSIS

5.1 General Guidance on Data Presentation

Unless otherwise specified, continuous variables will be summarized using descriptive statistics, including n, mean, standard deviation (SD), median, Q1 (1st Quartile), Q3 (3rd Quartile), min and max. Count variables will be summarized using frequency and percentage.

Min and max will have same decimal place as raw data; mean, median, Q1, and Q3 will have one additional decimal place; SD will have two additional decimal places. Percentage, and CV (Coefficient of Variation) (if presented), will be rounded to one decimal place.

For all statistical analyses, unless explicitly stated otherwise, percentages will utilize a denominator corresponding to the number of subjects within each treatment groups.
All summary tables will be presented by treatment groups. Listings will be presented to for all data collected in the CRF.

Generally, the DSMB outputs will be presented using actual treatment for the SC and will summarize the date from each study phase and treatment group separately. The DSMB will review blinded safety data and displays (reactogenicity, AEs and safety laboratory assessments) for treatment/age groupings within phases 1a and 1b. That being said, if deemed necessary, individual subjects may be unblinded per DSMB request. During Phase 1b of the study, the DSMB will review unblinded safety data and displays (reactogenicity, AEs and safety laboratory assessments). Details are outlined in the DSMB SAP.

5.2 Derived Variables

The below table provide the list of derived variables for Demographic duration derivation, baseline derivations and other important derivations applicable for this study.

Table 1 Formula for Derived Variables

Variables	Formula
Demographic and Baseline characteristics	
Age at signing of ICF (in years)	integer ((date of screening visit – date of birth + 1)/ 365.25)
Body mass index (BMI) (kg/m^2)	weight (kg)/[height (m)]^2
Derivation of Duration	
Study day at any visit	Date of interest – date of first dose of vaccination. One day is added if this difference is ≥ 0
Baseline Derivations	
Baseline	The baseline value is defined as the last non-missing observation prior to or on the date of the first vaccination dose on Day 1.
Change from baseline	Post baseline value – Baseline
Relative change from baseline	[(Post baseline value – Baseline)/Baseline]*100

5.3 Analysis Visit Windows

Analysis visit windows will be used for all visit-based assessments to map longitudinal observations to scheduled visits and thereby allow for by-visit analyses, since not all assessments are performed on the scheduled day. Unless otherwise specified, all longitudinal safety data analyses will be based on the analysis visit windows. The analysis visit windows will be calculated by bisecting the interval between adjacent scheduled visit days except for the first post-treatment visit, the phone call visits, and 2nd vaccination dose visit. These windows are provided for in Table 2:

Table 2 Visit Windows for Analysis

Nominal Visit	Lower Bound	Target	Upper Bound
V2 – Dose 1	1	1	1
Phone Call 1	2	3	4
V3	5	7	Day 28 Dosing Date - 1
V4 – Dose 2	Day 28 Dosing Date	28	Day 28 Dosing Date
Phone Call 2	Day 28 Dosing Date + 1	31	32
V5	33	35	46
V6	47	56	84
V7	85	112	168
V8	169	224	280
V9	281	336	

The actual assessment day will be mapped to the windows defined for each scheduled study visit with following rules:

- If more than one assessment falls within a visit window, the closest non-missing assessment to the scheduled day will be used in the analysis.
- If 2 non-missing assessment actual dates are equidistant from the target day, the later visit will be used in the analysis.
- For retest values of laboratory data, the retest value (the last valid observation assessed on the same visit day) will be chosen.

5.4 Handling of Missing or Incomplete Dates

Unless otherwise specified, missing data will not be imputed for the analyses.

Medications with partial or missing dates will be imputed as follows:

- **Missing or partial medication start date:**
  a. If only DAY is missing, the first day of the month will be assumed.
  b. If DAY and Month are both missing, the first day of the year will be assumed.
  c. If DAY, Month and Year are all missing, the date before the first dose date (Day 1) will be assumed.
- **Missing or partial medication stop date:**
  a. If only DAY is missing, the last day of the month will be assumed.
  b. If DAY and Month are both missing, the last day of the year will be assumed.

c. If DAY, Month and year are all missing, 'ongoing' status to stop date will be assigned.

AEs with missing or incomplete onset dates will be counted as treatment emergent unless the event has a complete end date that occurs prior to the first vaccination dose OR month and year of AE onset or stop date indicate the AE occurs prior to the first vaccination dose.

Imputation rules for missing or partial AE start date are defined below:

If only day of AE start date is missing:

- If the AE start year and month are the same as that for the first dose date, and if the full (or partial) AE end date is not before the first dose date or AE end date is missing, then impute the AE start day as the day of first dose date;
- Otherwise, impute the AE start day as 15 of the month and compare with the AE end date if not missing. If the AE end date is before the imputed AE start date, set AE start date to AE end date.

If Day and Month of AE start date are missing:

- If AE start year = first dose year, and if the full (or partial) AE end date is not before the first dose date or AE end date is missing, then impute the AE start month and day as the month and day of first dose date;
- Otherwise, impute the AE start month as July and the day as 1 and compare with the AE end date if not missing. If the AE end date is before the imputed AE start date, set AE start date to AE end date.

There will be no imputation for completely missing or partial AE end dates. If the start date is completely missing for an AE, the AE is considered to be treatment-emergent unless the collection date is prior to the treatment start date.

5.5 DSMB Stopping Rules

5.5.1 Individual Level Rules

Stopping rules are proposed as conditions that would stop further vaccinations in an individual subject (at any dose level) if they experience any of the following events that are assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause:

- Fever >40.0°C (>104.0°F) for at least 1 daily measurement within 7 days after vaccination,
- Any grade 4 or life-threatening event within 7 days after any study injection, regardless of relationship to study vaccine,
- Clinically significant systemic reaction (i.e., angioedema, generalized urticaria) within 7 days after any study injection,
- SAE that is assessed by the investigator as possibly related, or for which there is no alternative, plausible, attributable cause.

Safety data will be monitored on an ongoing basis by the site investigators and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule. If the DSMB recommends unblinding of individual cases, data from placebo recipients will not contribute to the stopping rules.

5.5.2 Trial Level Rules

Study randomization and further vaccinations will stop if 2 or more participants receiving VBI-2902a meet stopping rules unless the DSMB and study sponsor and site investigators review the safety data, and in consultation with BRDD, determine that safety of study participants is not affected and that study vaccination may continue.

If any of these safety signals are met at any point during the study, the result of the discussions by the DSMB will be communicated by the Sponsor designate to the study centers and the regulatory authorities.

An investigator who identifies any safety concern (i.e., meeting of stopping rules or any other safety concern) should inform the Medical Director at the study CRO immediately, and further enrollment may be put on hold as a consequence.

Of note, no formal stopping rule will be applied for other safety data such as missed visits due to product-related AEs, Grade 2 AEs and AEs collected from Day 7 to Day 29 after injection. However, the DSMB will review these data, if available, in order to allow for an overall assessment of the benefit to risk.

6 STATISTICAL PLAN AND METHODS

A reduced subset of materials will be provided for the first DSMB while formal TLFs are created. The materials for the first DSMB will consist of Excel spreadsheets extracted from the clinical database. The spreadsheets will have variable labels as column headers and will be filtered to allow easy examination. Domains to be provided to the first DSMB include disposition, demographics, medical history, concomitant medications, adverse events, and laboratory results for blood chemistry, hematology, and urinalysis. Additionally, pivot tables counting adverse events by system organ class and preferred term and by system organ class, preferred term, and severity will be created for the following subsets of adverse events: local systemic solicited adverse events, unsolicited adverse events, serious adverse events, and adverse events leading to vaccine discontinuation.

6.1 Background Characteristics

6.1.1 Subject Disposition

A summary of subject disposition will be provided.

The count of subjects in the AEC will be presented along with subject who received the placebo. Additionally, there will be counts for subjects completing receiving vaccination #1, completing

vaccination #2, discontinuing from vaccination, the reasons for not completing the vaccination, completing the study, and the reasons for not completing the study.

6.1.2 Demographics and Baseline Characteristics

A summary of demographics and baseline characteristics will be provided. The demographics portion of the summary will include age, gender, race, ethnicity, baseline height, baseline body weight, and baseline BMI. Additionally, baseline lab results for hepatitis B, hepatitis C, and HIV will be presented.

6.1.3 Medical History

A summary of medical history will be provided. Any pre-existing conditions or signs/symptoms noted via interview or medical records prior to first study injection will be presented by system organ class using the Medical Dictionary for Regulatory Affairs® (MedDRA) Version 25.0.

6.1.4 Prior and Concomitant Medication

Each medication will be coded to a preferred term and an Anatomic Therapeutic Classification (ATC) code using the World Health Organization (WHO) Drug Dictionary. Prior medications are defined as medications that are stopped before the first vaccination dose. Concomitant medications are defined as those medications with a start date on or after the vaccination dose of study drug or the medications started before the dose and continued during the vaccination period . The number and percentage of subjects taking each prior or concomitant medication will be displayed by medication class (anatomical classification) and preferred term for each treatment group. Details for imputing missing or partial start and/or stop dates of medication are described in Section 5.4.

6.2 Extent of Exposure and Treatment compliance

A full course of study product administration consists of one or two doses of vaccine in each study vaccination period. A summary table detailing the total number of doses received will be presented by treatment compliance.

6.3 Safety Analyses

6.3.1 Adverse Events (AEs)

6.3.1.1 General Guidance on AEs

All AE related Tables and Listings will be analyzed using the SC. All adverse-events in the SC will be presented in listings. Only Treatment-Emergent Adverse Events (TEAEs) will be summarized in tables. TEAEs include: 1) AEs with an onset on or after the first vaccination dose and 2) AEs that worsen relative to the pre-treatment state. The period of observation for collection of TEAEs extends from the time the participant receives the first dose of vaccine through the last study visit.

Adverse events will be coded to the System Organ Class (SOC) and preferred term (PT) level using the Medical Dictionary for Regulatory Affairs (MedDRA dictionary).

TEAEs missing severity will be summarized as "missing" in summary tables.

The summary tables for unsolicited AEs will use the following algorithms for counting the subject:

- System Organ Class row: Subjects experiencing the same AE System Organ Class several times will only be counted once.
- Preferred term row: Subjects experiencing the same AE preferred term several times with different grades will only be counted once with the maximum grade.
- Any event row: Each subject with at least one adverse event will be counted only once at the maximum grade no matter how many events they have.

Unless otherwise stated, AEs will be ordered alphabetically by SOC and in descending order of frequency by PT.

The summary tables for the rate and severity of solicited AEs will be presented by the terms defined on the eCRF.

Other types of events collected are defined as follows:

1) Medically-Attended Adverse Events (MAAE) – A condition prompting emergency room visit, physician visit not related to a common disease/not a routine visit or an SAE not related to a common disease SAE.
2) Serious Adverse Event (SAE) – Any untoward medical occurrence that *at any dose* results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital abnormality/birth defect in an offspring of a study participant, or is another medically important event.

6.3.1.2 AE Summaries

An overview summary of TEAEs including:

1) Counts and percentages of subjects
    a. With any TEAE,
    b. With any local solicited AEs during 7 days of vaccination dosing,
    c. With any systemic solicited AEs during 7 days of vaccination dosing,
    d. With any unsolicited AEs within 28 days of each vaccination dose,
    e. With any unsolicited MAAEs at Day 56 and 28 days after each vaccination dose,
    f. With any unsolicited SAEs at Day 56 and 28 days after vaccination dose,
    g. With any unsolicited AEs leading to discontinuation of study vaccination,
    h. With any unsolicited AEs leading to study discontinuation,
    i. With any unsolicited AEs during the study,

j. With any unsolicited SAEs during the study.

will be presented stratified by treatment and age group.

For each type of AE noted in the overall summary point 2 except solicited AEs (2b and 2c), we will additionally produce summaries of the AEs by SOC and PT. Furthermore, summaries of event types 2d, and 2i will be presented for by SOC, PT, and severity (mild/moderate/severe/potentially life threatening).

Solicited AEs will be summarized separately for local AEs, systemic AEs, and fever >38 centigrade as collected on the solicited AEs eCRF pages. These summaries will be presented for each dose separately and cumulatively, will count the number of subjects experiencing at least one solicited AE, and will count the number of subjects experiencing at least one of each of the solicited AEs ordered per the solicited AEs eCRF pages.

Lastly, within the solicited AE by SOC/PT summary, 2-sided, alpha=0.05 Fisher's Exact tests will be performed to assess differences in rates of these adverse events between the treatment groups. No adjustment will be made to account for multiplicity of tests performed.

6.3.1.3 AE Listings

The following separate listings of AEs will be presented:

- All Unsolicited AEs
- All solicited AEs
- All SAEs
- All AEs leading to death
- All AEs leading to discontinuation of study vaccination
- All AEs leading to study discontinuation.

6.3.2 Clinical Laboratory Evaluation

6.3.2.1 Overall

An overall summary of laboratory abnormalities (hematology, biochemistry, and urinalysis) will be created for events taking place at Day 56 and 28 days after each study vaccination. This summary will present the counts and percentages of subjects experiencing each type and will further break down abnormalities by severity.

6.3.2.2 Hematology

A summary of hematology lab results for the absolute and change from baseline values will be presented by visit.

A listing for hematology results will be created together with the normal ranges and severity grades. Lab values that are below or above the normal ranges will be flagged.

6.3.2.3 Chemistry

Chemistry lab results will be presented in similar pattern to hematology.

6.3.2.4 Urinalysis

Urinalysis lab results will be presented in a similar pattern to hematology for all quantitative tests. For any qualitative tests being performed counts and percentages of normal vs. abnormal results will be presented.

6.3.2.5 SARS-CoV-2 Testing

Results of SARS-CoV-2 testing will be summarized using counts and percentages of positive vs. negative results by time point. COVID-19 symptom surveillance will also be summarized.

Clinical Criteria

In the absence of a more likely diagnosis, at least two of the following symptoms or signs:

- fever (measured or subjective)
- chills
- rigors
- myalgia
- headache
- sore throat
- nausea or vomiting
- diarrhea
- fatigue
- congestion or runny nose

Or any one of the following symptoms:

- cough
- shortness of breath
- difficulty breathing
- new olfactory disorder
- new taste disorder

Or severe respiratory illness with at least one of the following:

- Clinical or radiographic evidence of pneumonia
- Acute respiratory distress syndrome (ARDS)

6.3.3 Vital Signs

A summary of vital signs will be presented by visit & time point. Within each dosing visit, change from pre-dose vital signs will also be summarized. The counts of subjects presenting abnormal vital signs by visit and severity will be produced for fever >38 centigrade, tachycardia, bradycardia, and hypertension.

6.3.4 Physical Examinations

A full physical examination will be conducted at the screening visit and history-directed physical examinations may be completed at subsequent visits. A summary of these findings will be presented by visit and body system.

6.4 Immunogenicity Analyses

Unblinded Immunogenicity analyses will be provided at day 35 and day 56 analyses

Immunogenicity analysis will censor the immunogenicity measurements first time after the participants receive a licensed (non-study) COVID-19 vaccines or tested positive SARS-CoV-2 infection or develop COVID-19 illness during the study

6.4.1 Immunogenicity Evaluations

Immunogenicity will be assessed by measuring serum nAB titers against wild-type SARS- CoV-2 virus (PRNT) and/or spike protein-expressing pseudovirus (microneutralization), serum binding antibody titers against spike protein and the spike protein receptor-binding domain (RBD), and peripheral blood mononuclear cell (PBMC) T cell responses against spike protein.

Testing will include assessment of responses against spike protein of the original SARS-CoV-2 isolate as well as spike protein of variant Beta (B.1.315) and other variants. In Phase 1a, time points for evaluation will be at Study Days 1, 7, 28, 35, 56, 112, 224 and 336. In Phase 1b, time points for evaluation for groups G4 and G5 will be at Study Days 1, 7, 14, 28, 56, 84, 168 and 336.

Neutralizing antibody and binding antibody results will be presented as the geometric mean titer (GMT) and the geometric mean fold increase in titer post-vaccination over baseline. T cell responses will be presented as the geometric mean number of IFN- ELISPOT-positive cells per 10^6 PBMCs.

Geometric mean nAb titers and antibodies to the receptor binding domain (RBD) for 5 µg and 10 µg dose groups at Day 1, 7, 28, 35 and 56 will be compared to each other and pooled COVID-19 convalescent serum to select the optimal dose of VBI-2902a in the age cohorts.

6.4.2 Analysis of Immunogenicity Endpoints

The immunogenicity endpoints are defined in Section 2.

- GMT and the geometric mean fold increase (GMFR) in serum antibody titer post-vaccination over Day 1 (baseline) at Days 7, 28, 35, 56, 112, 224 and 336 (Phase 1a, groups G1, G2 and G3); at Days 7, 14, 28, 56, 84, 168 and 336 (Phase 1b groups G4 and G5);
    - Neutralizing activity against multiple variant spike protein-expressing pseudovirus, and/or $PRNT_{90}$ neutralizing activity against wild-type SARS-CoV-2 virus and the variant Beta (B1.351) in all participants.
    - RBD Antibody titers against wild-type variant spike protein measured by ELISA.

Confidence intervals for the difference of geometric means will be included for the pairwise comparison of treatment groups.

The 95% CI for GMTs will be obtained within each group separately. The 95% CI for the mean of log-transformed titer/concentration will be first obtained assuming that log-transformed concentrations/titers are normally distributed with an unknown variance. The 95% CI for GMTs will be then obtained by exponential-transformation of the 95% CI for the mean of log-transformed titers using analysis of variance (ANOVA) model.

SAS® Code for comparing GMTs:

```
PROC MIXED DATA=<Data>; * specify and sub-select data set as applicable;
  *BY Agegrp;  * as applicable;
 CLASS trtpn; * other factors may be added, if applicable;
 MODEL AVAL = trtpn;   * AVAL=10**titer
  * add factors and options (e.g. ALPHA=.. Solutions) as applicable;
 LSMEANS trtpn / CL ALPHA=0.05 STDERR; * modify/adapt as applicable
 Ods output LSMEANS =_outmix;
 RUN;
 QUIT;
Data _outmix;
Set _outmix;
```

GMT= 10**(Estimate);

GMT_LCL = 10**(Lower);

GMT_UCL = 10**(Upper);

RUN;

The GMFR will be derived by using Analysis of Covariance (ANCOVA) to model the difference in the log of the titer values between post vaccination (Day 56) and baseline (Day 0), with treatment group as main effect and baseline titer as covariate. The GMFR will be compared between the treatment groups. Pair-wise comparisons between the treatments groups will be performed using two-sided, 95% confidence, based on the least-squares mean differences from the ANCOVA model.

SAS® Code for comparing GMFR:

PROC MIXED DATA=<Data> (analysis dataset);

class trtpn;

model diff= trtpn Base; * diff = log10Day56 – log10Day0.Base=log10Day0

Lsmeans trtpn/cl alpha=0.05;

Ods output LSMEANS =_outmix;

run;

Quit;

Data _outmix;

Set _outmix;

GMFR = 10**(Estimate);

GMFR_LCL = 10**(Lower);

GMFR_UCL = 10**(Upper);

Run;

6.4.3 Analysis of Exploratory Endpoints

The exploratory immunogenicity endpoints are defined in Section 2. Data will be presented by tables and listings.

Additional markers for T cell responses by ELISPOT and serum binding IgG subclasses as a marker of Th1 (IgG1 and IgG3) and Th2 (IgG4) dominated responses:

- Geometric mean number of IFN-γ-positive cells per 10^6 PBMCs by ELISPOT assay post-vaccination over Day 1 (baseline) at Days 7, 28, 35, and 336
- GMT of serum IgG subclass responses against spike protein by ELISA post- vaccination over Day 1 (baseline) responses at Days 7, 28, 35, 56, 112, 224 and 336

7 CHANGES FROM THE PLANNED ANALYSIS IN STUDY PROTOCOL

There are no changes to the analyses planned in the protocol. These analyses are subset to allow DSMB adjudication of the safety of VBI-2902a and VBI-2905a.

There will be unblinding in both Phase 1a and 1b of the study after Day 56, with an interim analysis conducted based on the Safety and Immunogenicity data , with a cutoff date at Day 56 (inclusive).

8 SCHEDULE OF EVENTS

Table 3: Phase 1a Schedule of Events

Schedule of Events	Screenin			Study							End-of Study Early D/C
Visit	1	2	Phone Call	3	4	Phone Call	5	6	7	8	9
Study Day	-28 to -1	1	3	7	28	31	35	56	112	224	33
Study Month (28 days)	<-	0	0.1	0.25	1	1.1	1.25	2	4	8	1
Visit Intervals (Days)	n/	n/a	±1	+3	±3	±1	±3	±3	±	±14	±1
Informed consent	●										
Inclusion/exclusion criteria	●	●									
Confirm ongoing eligibility			●	●	●	●	●	●	●	●	
Demographics	●										
Medical History / Prior Medications	●										
Full physical examination [1]	●										
Symptom-directed physical examination [2]		●		●	●		●	●	●	●	●
SARS CoV2 (PCR or Ag-rapid test, sequencing)	●	●		●	●		●	●	●	●	●
HIV, HBV, HCV serology (~10 mL)	●										
Hematology/ Biochemistry (~6 mL)	●	●		●	●		●	●	●	●	●
Urinalysis	●	●		●	●		●	●	●	●	●
Urine pregnancy test [3]	●	●			●						
Humoral immunogenicity (~10 mL)		●		●	●		●	●	●	●	●
Cell-mediated Immunogenicity (~40 mL)[4]		●		●	●		●	●			●
Randomization		●									
Concomitant medications		●	●	●	●	●	●	●	●	●	●
Study vaccination		●			●						
Post-vaccination observation (60 min)		●			●						
Vital Signs [5]		●			●						
AEs		●	●	●	●	●	●	●	●	●	●
COVID-19 signs and symptoms surveillance		●	●	●	●	●	●	●	●	●	●
Distribution of Diary Card [6]		●			●						

1. Complete physical examination including vital signs: weight, height, blood pressure, pulse rate and respiratory rate.
2. History directed physical examination prior to each vaccination and at every follow up visit.
3. Urine pregnancy test to be performed on women of child-bearing potential; a negative result must be obtained no more than 72 hours prior to vaccination.
4. Cell-mediated immunogenicity (PBMC T-cell responses) will be tested in all study participants.
5. Vital signs (body temperature, BP, HR, RR) will be collected pre-vaccination and 60 minutes (+10 minutes window) post-vaccination.
6. Diary cards will be provided to study participants at each vaccination visits to record reactogenicity - solicited AEs.

Table 4: Phase 1b Groups G4 and G5 (One Dose) Schedule of Events

Schedule of Events	Screening			Study						End-of Study Early D/C
Visit	1	2	Phone Call	3	4	5	6	7	8	9
Study Day	-28 to -1	1	3	7	14	28	56	84	168	336
Study Month (28 days)	<-1	0	0.1	0.25	0.5	1	2	3	6	12
Visit Intervals (Days)	n/a	n/a	±1	+3	+3	±3	±3	±7	±14	±14
Informed consent	•									
Inclusion/exclusion criteria	•	•								
Confirm ongoing eligibility			•	•	•	•	•	•	•	
Demographics	•									
Medical History / Prior Medications	•									
Full physical examination [1]	•									
Symptom-directed physical examination [2]		•		•	•	•	•	•	•	•
SARS CoV2 (PCR or Ag-rapid test, sequencing)	•	•		•	•	•	•	•	•	•
HIV, HBV, HCV serology (~10 mL)	•									
Hematology/ Biochemistry (~6 mL)	•	•		•		•	•	•	•	•
Urinalysis	•	•		•		•	•	•	•	•
Urine pregnancy test [3]	•	•								
Humoral immunogenicity (~10 mL)		•		•	•	•	•	•	•	•
Cell-mediated Immunogenicity (~40 mL)[4]		•		•	•	•				•
Randomization		•								
Concomitant medications		•	•	•	•	•	•	•	•	•
Study vaccination		•								
Post-vaccination observation (60 min)		•								
Vital Signs [5]		•								
AEs		•	•	•	•	•	•	•	•	•
COVID-19 signs and symptoms surveillance		•	•	•	•	•	•	•	•	•
Distribution of Diary Card [6]		•								

1. Complete physical examination including vital signs: weight, height, blood pressure, pulse rate and respiratory rate.

2. History directed physical examination prior to each vaccination and at every follow up visit.
3. Urine pregnancy test to be performed on women of child-bearing potential; a negative result must be obtained no more than 72 hours prior to vaccination.
4. Cell-mediated immunogenicity (PBMC T-cell responses) will be tested in all study participants.
5. Vital signs (body temperature, BP, HR, RR) will be collected pre-vaccination and 60 minutes (+10 minutes window) post-vaccination.
6. Diary cards will be provided to study participants at each vaccination visits to record reactogenicity - solicited AEs.