STUDY PROTOCOL

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

NCT Number: NCT04773665

Version: 6.0

Date of Version: May 20, 2022

Study Sponsor:
VBI Vaccines Inc.
310 Hunt Club Road East
Ottawa, ON K1V 1C1
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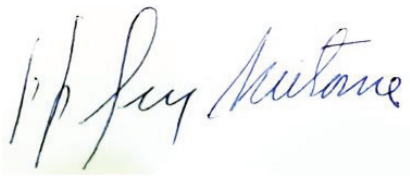
Sponsor Signatory:



June 19, 2022

Francisco Diaz-Mitoma — Date (dd/mm/yyyy)

Chief Medical Officer

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Statement of Compliance

By signing below, the Principal Investigator agrees to adhere to the protocol. Any change in the study must be reviewed by a formal protocol amendment procedure and the Principal Investigator will submit all changes, amendments and revisions to the appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Any change to the protocol that affects subject selection, safety, or changes in the conduct of the trial will require written approval from the IRB/IEC before implementing the change.

The Principal Investigator also agrees to conduct the study in accordance with

All applicable Laws and Regulations

The International Conference on Harmonization guidelines on Good Clinical Practice (ICH GCP), copies of which have been provided to the principal investigator.

The Principal Investigator also thereby agrees that the IRB/IEC will approve all subject informed consent form templates before the study is initiated. The investigator will obtain informed consent and document this process for all participants enrolled in this study.

Principal Investigator	Signature	Date (dd/mmm/yyyy)

STUDY SYNOPSIS

Title	A Phase 1a/1b Randomized, Observer-Blind, Placebo-Controlled 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.
Finished Product	VBI-2902a and VBI-2905a are investigational vaccine candidates that use enveloped virus-like particle (eVLP) expression of modified versions of two different variants of the SARS-CoV-2 spike (S) glycoprotein and are designed to induce neutralizing antibody and cell-mediated immune responses against the SARS-CoV-2 spike protein. VBI-2902a expresses the spike protein of SARS-CoV-2 Wuhan isolate (the first virus variant isolated in 2019 in Wuhan, China), while VBI-2905a expresses the spike protein of SARS-CoV-2 variant Beta (B.1.351 variant, first isolated in 2020 in South Africa). The Phase 1a portion of this study tests one- and two-dose regimens of VBI-2902a with 5 µg S protein content and aluminum phosphate (alum) adjuvant or placebo delivered by intramuscular (IM) injection. The Phase 1b portion of the study tests a one-dose regimen of VBI-2905a with 5 µg S protein content and alum adjuvant or placebo delivered by IM injection in participants previously vaccinated with an authorized mRNA COVID-19 vaccine. The placebo in both phases contains saline solution.
Active Ingredients	The active ingredient in Phase 1a is the S protein based on SARS-CoV-2 isolate Wuhan- Hu-1 at a dose of 5 µg formulated with alum adjuvant. The active ingredient in Phase 1b is the S protein based on SARS-CoV-2 variant Beta (B.1.351, S. Africa) at a dose of 5 µg formulated with alum adjuvant.
Purpose	The Phase 1a portion of the study evaluates the safety, tolerability and immunogenicity of one- and two-dose regimens of VBI-2902a at a 5 µg dose level of Wuhan isolate S protein as compared to placebo, in healthy adults 18-54 years of age with no history of SARS-CoV-2 infection or COVID-19 vaccinations. The Phase 1b portion of the study evaluates the safety, tolerability and immunogenicity of a one dose regimen of VBI-2905a at a 5 µg dose level of S protein based on variant Beta (B.1.351), in healthy adults 18-54 years of age and no history of clinical or laboratory diagnosis of SARS-CoV-2 infection or COVID-19 illness.
Objectives	<u>Phase 1a:</u> The primary objective is 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. The secondary objective is 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. <u>Phase 1b:</u> The primary objective is 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 (age 18-54 years) who had been previously vaccinated with mRNA vaccines.

	The secondary objective is to evaluate the immunogenicity of a one-dose regimen of VBI-2905a at a 5 µg dose level of S protein in healthy adults (age 18-54 years) who had been previously vaccinated with mRNA vaccines.
Study Design	The trial is a phase 1a/1b, randomized, observer-blind, placebo-controlled study. Phase 1a 60 healthy adults, age 18-54 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 will be enrolled into the Phase 1a part of the study to evaluate the safety, tolerability and immunogenicity of a one- dose or two-dose regimen of VBI-2902a at a dose level of 5 µg of S protein or placebo. Participants will be randomized at a 2:1 ratio to VBI-2902a or placebo: • 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 (AEs) 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. Study participants will continue with study visits as planned up to 12 months of follow up after the first dose of study vaccine. Phase 1b 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 will receive VBI-2905a at a dose of 5 µg of S protein at Day 1 • Group G5 - 27 participants will receive placebo at Day 1 See below for a schematic Study Design and descriptions of study groups.

	The DSMB will review blinded post-vaccination safety data 7 days after each vaccination (reactogenicity, AEs and safety laboratory assessments). In Phase 1b, the DSMB will review blinded Day 7 safety data after the first 10 participants in groups G4 and G5 have received the first dose. Only after the DSMB confirms that safety is acceptable and that stopping rules were not met will the enrollment in the respective study group continue to its completion. The SSC will review unblinded immunogenicity data 7 days and 28 days after the first vaccination (Groups G4 and G5). Schedule of Events During the study, there will be a total of 9 visits (Phase 1a and Phase 1b), including the screening visit and 12 months of follow up (see Table 1, and Table 2 below). During the screening visit, participants will provide informed consent, provide samples for SARS-CoV-2 testing (PCR and/or rapid antigen test and for viral variant testing / sequencing) and safety laboratory testing (hematology, biochemistry, urinalysis), provide history of previous COVID-19 vaccination, including type of vaccine and dates of vaccination, and will be evaluated against study inclusion and exclusion criteria to confirm study eligibility. The eligible participants will proceed to Day 1 to be randomized and receive the study vaccine or placebo. Participants will be contacted by phone 3 days after each vaccination for a safety follow up call. Diary cards will be distributed to study participants at vaccination visits to record body temperature, local and systemic reactions from day of the vaccination(s) and the next 6 days. Serious AEs (SAEs) and medically-attended AEs (MAAEs) will be recorded throughout the study. In Phase 1a, participants will visit the study site for dose administration, safety assessments and blood sample collection on Days 1 and 28 and for safety assessments and blood sample collection on Days 7, 35, 56, 112, 224 and 336. In Phase 1b, participants will visit the study site for dose administration, safety assessments and blood sample collection on Day 1 (prior to vaccine administration), and for safety assessments and blood sample collection on Days 7, 14, 28, 56, 84, 168 and 336. Study participants will be tested for SARS-CoV-2 infection by PCR or rapid antigen test and surveyed for signs and symptoms of COVID-19 illness throughout the study. Duplicate nasopharyngeal swab samples will be retained for storage and potential sequencing of viral RNA should samples test positive for SARS- CoV-2 infection. Participants will be followed until the study completion on Day 336. If a subject is lost to follow-up, every effort will be made by the study center personnel to contact the subject and to determine the reason for discontinuation. Measures taken to follow-up will be documented.
COVID-19 Surveillance	Surveillance for COVID-19 symptoms will be conducted throughout the study. If a participant experiences any of the symptoms listed below, he or she is instructed to contact the study site immediately and participate in an in-person or telehealth visit as soon as possible, optimally within 3 days of symptom onset (and at the latest 4

	days after symptom resolution). To confirm the diagnosis, SARS-CoV-2 test (PCR/ or rapid antigen test) should be performed as soon as possible. During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with solicited systemic events (i.e., fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. Participants may utilize a diary card to record any symptoms. In Phase 1b, nasopharyngeal swabs samples for SARS-CoV-2 testing will be collected in duplicate with one sample to be used for the PCR/ or rapid antigen test and the second sample stored (frozen) for possible sequencing of viral RNA if SARS-CoV-2 virus is detected. Clinical Criteria for COVID-19 (CDC- COVID-19 Interim Case Definition, Aug. 5, 2020): In the absence of a more likely diagnosis, at least two of the following symptoms: • 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)
Study Continuation Criteria	Safety criteria for study continuation Early DSMB reviews of post-vaccination safety data and stopping rules will be implemented for safety and protection of study participants (see Protection of Participants, below). In Phase 1a, the second vaccination will proceed only after the DSMB has confirmed that the vaccine safety and tolerability is acceptable and that stopping rules were not met through 7 days after the first dose. In Phase 1b, DSMB will review blinded Day 7 safety data after the first 10 participants in groups G4 and G5 have received their dose. 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. For details on timing of DSMB reviews, please see Figure 1 below.

	Stopping rules - study vaccinations will stop if 2 or more participants receiving VBI-2902a or VBI-2905a meet stopping rules criteria 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. Immunogenicity criteria for study continuation Neutralizing antibody (nAb) titers, determined by pseudovirus microneutralization assay and plaque-reduction neutralization test (PRNT) on serum collected at Day 28 (4 weeks after the first vaccination) and Day 56 (4 weeks after the second vaccination) will be used as the primary determinant for immunogenicity, and will determine whether the study will proceed to Phase 1b. Additional immunological endpoints, described below, will also be considered as secondary endpoints. Geometric mean nAb titers and binding antibodies to spike protein and its receptor binding domain (RBD) in one-dose and two-dose groups in Phase 1a at Days 1, 7, 28, 35 and 56 will be compared against a panel of COVID-19 convalescent sera as well as a WHO International Standard of high titer pooled COVID-19 convalescent sera. A non-inferior GMT nAb titer against the GMT of the panel of COVID-19 convalescent sera (tested against the original Wuhan strain PNA for phase 1a participants and against the B.1.351 variant PNA in phase 1b) in subjects receiving 2 doses of VBI-2902a will justify proceeding to Phase 1b; comparison of the nAb GMT against the WHO reference standard will be used to aid benchmarking against other COVID-19 vaccine candidates. Day 28 antibodies to RBD and T-cell endpoints will be considered if Day 56 nAb results do not allow a clear determination of equivalence or superiority to the convalescent sera neutralizing antibody GMTs. If responses are inferior to that of the panel of convalescent serum, neither VBI-2902a nor VBI-2905a will undergo further testing at the proposed dose levels and dose regimens. In Phase 1b the percentage with a 4- fold or greater increase in nAb titers following vaccination will be determined, as this represents a meaningful boosting of immunity. The group sizes will allow determination of at least two-fold differences in nAb titers at a power of 80% with an alpha error of 0.05. Safety and tolerability will be evaluated in the total of ~67 participants who will receive at least one dose of VBI2902a or VBI- 2905a and in ~47 participants who will receive placebo. If no safety signals are detected and immunogenicity is demonstrated, further clinical development will be considered. Further clinical development may not be considered if nAb titers are not equivalent to or superior to that of the panel of COVID-19 convalescent serum. The safety, tolerability and percentage of subjects with 4-fold or greater increases in neutralizing antibody titers at Days 28 and 56 will be used to determine whether further clinical development of a one-dose vaccination regimen is justified.
Duration of Study	The total study duration for each vaccinated subject (assuming a screening period of 28 days) is 364 days
Subject Selection and Sample Size	Approximately 60 participants will be enrolled in Phase 1a and 54participants in Phase 1b.

	Participants in Phase 1a will be randomized at 2:1 to VBI-2902a or placebo. Participants in Phase 1b 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 nAb titers with 80% power and an alpha error of 0.05.
Study Vaccine Doses and Mode of Administration	Study vaccines will be administered intramuscularly as per study vaccination schedule by trained personnel at the study centers. Participants will remain at the study center for 60 minutes after vaccination and will be evaluated by study center personnel for AEs before discharge. The participants, site investigators and study site personnel performing outcome measurement and the sponsor will be blinded to vaccine allocation.
Study Population	<u>Inclusion Criteria</u> To be eligible for the study, each participant must satisfy ALL of the following criteria: 1. Healthy female and male participants 18 -54 years of age. 2. If female: a. is of childbearing potential and must have a negative pregnancy test prior to study vaccinations and agree to use an effective method of birth control as deemed appropriate by the investigator (e.g., hormonal contraceptive, barrier contraceptive with additional spermicide, or an intrauterine device) beginning >30 days prior to the first study vaccine administration and continuing until the end of the study. OR b. is not of childbearing potential, defined as postmenopausal (12 months with no menses without an alternative medical cause) or surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy). 3. Phase 1b, groups G4 and 5: previously received a full course (2 doses) of an authorized S protein mRNA COVID-19 vaccine (e.g. COVID-19 vaccines produced by Pfizer/BioNTech or Moderna) at least 4 months prior to enrollment (1 month is defined as 28 days). 4. Sign an informed consent document indicating understanding of the purpose of and procedures required for the study and willingness to participate in the study. <u>Exclusion Criteria</u> Participants with any of the following criteria will be excluded: 1. History of clinical or laboratory diagnosis of COVID-19 or SARS-CoV-2 infection

	2. **Phase 1b, groups G4 and G5**: Previous receipt of an experimental or authorized SARS-CoV-2 (COVID-19) vaccines other than an S-protein mRNA vaccine. 3. **Phase 1a:** Previous receipt of an experimental or authorized SARS-CoV-2 (COVID-19) vaccine. 4. Positive PCR or rapid antigen test for SARS-CoV-2 at screening. 5. Individuals with chronic medical conditions, including any of the following: a. Diabetes mellitus Type 1 or Type 2 b. Chronic pulmonary disease (e.g., COPD or Asthma) c. Hypertension (e.g., SBP >140 mmHg or DBP >90 mmHg) d. Chronic kidney disease (e.g., GFR <60 mL/min/1.73 m^2) e. Chronic liver disease f. Obesity (e.g., BMI >30 kg/m^2) 6. Any history of cancer requiring chemotherapy or radiation within 5 years. 7. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study. 8. Lack of participant's capacity (mental, social, behavioral), in the investigator's judgement, to provide informed consent for participation in the study. 9. Known or suspected impairment of immunological function, including but not limited to autoimmune diseases: a. <u>autoimmune diseases</u> (e.g. multiple sclerosis, type 1 diabetes, myasthenia gravis, Crohn disease and other inflammatory bowel diseases, celiac disease, systemic lupus erythematosus, scleroderma, including diffuse systemic form and CREST syndrome, systemic sclerosis, dermatomyositis polymyositis, rheumatoid arthritis, juvenile idiopathic arthritis, autoimmune thyroiditis - including Hashimoto thyroiditis, Grave's or Basedow's disease, immune thrombocytopenic purpura, autoimmune hemolytic anemia, autoimmune hepatitis, psoriasis, vitiligo, vasculitis, Guillain- Barré syndrome, Transverse myelitis, Addison's disease, Bell's Palsy and Alopecia Areata); b. <u>secondary immunodeficiency disorders</u> (e.g., Acquired Immunodeficiency Syndrome caused by Human Immunodeficiency Virus infection (HIV/AIDS), solid organ transplant, splenectomy); c. <u>primary immunodeficiency disorders</u> (e.g., common variable immune deficiency (CVID), Defective phagocytic cell function and neutropenia syndromes, complement deficiency). 10. History of allergic reactions or anaphylactic reaction to any vaccine component. 11. Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV). 12. Pregnant or breastfeeding or plans to conceive from 2 weeks before the study until the end of study. 13. Clinically significant abnormal physical examination, vital signs, or clinically significant abnormal values for hematology, serum chemistry or urinalysis at screening as determined by the investigator.

	14. Any laboratory test abnormality that would be considered of Grade 1 severity or above (as per FDA grading guidelines) and is considered as clinically significant by the investigator. Grade 2 severity or above is exclusionary, regardless of clinical assessment. 15. Has received blood products or immunoglobulin within 90 days of enrollment or is likely to require blood products during the study period. 16. Chronic administration (defined as more than 14 days in total) of immune-suppressive or other immune-modifying drug within sixmonths prior to the product dose (for corticosteroids, this is defined as prednisone ≥20 mg/day or equivalent). Inhaled and topical steroids are allowed. 17. Immunization with attenuated vaccines (e.g., MMR) within 4 weeks prior to enrollment. 18. Immunization with inactivated vaccines (e.g., influenza) within 2 weeks prior to enrolment. 19. Participation in another clinical study within 30 days. 20. Any skin abnormality or tattoo that would limit post-vaccination injection site assessment. 21. Family members of study site personnel.
Safety and Immunogenicity Assessments	Safety Assessments Safety and tolerability will be evaluated throughout the study by collecting solicited local (injection site) and systemic AEs (reactogenicity) for 7 days post-vaccination, unsolicited AEs for 28 days postvaccination and medically attended AEs (MAAEs) and serious AEs (SAEs) throughout the study. Participants will also be monitored by physical examinations, vital signs, and safety laboratory testing (hematology, serum chemistry, urinalysis). See Table 1, and Table 2 , Schedules of Events, for details. The safety population includes all participants who received at least one dose of the study vaccine. The baseline values for all laboratory evaluations and vital signs will be defined as the last evaluation done before the administration of the study vaccine on Day 1. Safety will be evaluated by examining the incidence and severity of AEs, and changes in clinical laboratory test values, physical examination results and vital sign measurements from the screening phase through study completion across study groups. Immunogenicity Assessments 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 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 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-γ ELISPOT-positive cells per 10^6 PBMCs. Immunogenicity results will be presented descriptively as point estimates and 95% confidence intervals (CIs), which will be tabulated by study group. Exploratory immunogenicity endpoints may include 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. The immunogenicity population will include all participants who receive the prescribed study vaccine or placebo and underwent at least one immunogenicity assessment after vaccination.

The total amount of blood to be drawn for clinical laboratory tests, and immunology evaluations is approximately 15-20 mL for initial (pre-vaccination) blood draw, and approximately 55-60 mL for subsequent blood draws.

Protection of Participants Informed Consent
The study protocol, informed consent form, and other study related documentation will be reviewed and approved by the local research ethics board (REB).
Written informed consent will be obtained after participants have read the approved informed consent form, have had adequate opportunity to discuss the study with an investigator or a qualified designee and before the initiation of any study related procedures.

Data Safety Monitoring Board (DSMB)
While the trial is ongoing, to allow regular review of the accumulated safety data, a DSMB will be established to perform early review of blinded post-vaccination safety data 7 and 28 days after each vaccination (solicited and unsolicited AEs and safety labs), and regularly thereafter through study termination. Second vaccinations will only be administered after the DSMB confirmation that safety after the first dose is acceptable and that stopping rules have not been met. The DSMB may recommend to continue, pause, modify, or suspend the further enrollment to the study.

Stopping Rules
The 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

- Grade 4 local (injection site) or systemic solicited AE within 7 days after any study injection
- 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 DSMB recommend unblinding of individual cases, data from placebo recipients will not contribute to the stopping rules. Study randomization and further vaccinations of all participants will stop if 2 or more participants receiving VBI-2902a or VBI-2905a meet stopping rules criteria 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. Surveillance of events that could represent enhanced COVID-19 Study participants will be tested (SARS-CoV-2 PCR or rapid antigen test) and surveyed for potential COVID-19 illness throughout the study. All confirmed cases will be reviewed contemporaneously by Medical Monitor, DSMB and the study sponsor. Pregnancy Testing For female participants of child-bearing potential, pregnancy testing will be performed immediately before each vaccination. A negative pregnancy test result will be required prior to the study vaccination. Follow-up Duration Participants will be followed a minimum of 12 months (assuming 28 days per month) after the Day 1 immunization with at least six-month follow-up safety assessments after last dose.
Endpoints	Primary Endpoints/Outcome Measures • 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) 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 Endpoints/Outcome Measures • 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 56 and 224 (Phase 1a) or Days 56 and 168 (Phase 1b): o Neutralizing activity against multiple variant spike protein-expressing pseudoviruses, and/or PRNT neutralizing activity

	against wild-type SARS-CoV-2 virus and the variant Beta (B.1.351) in all participants ○ RBD antibody titers against wild-type variant spike protein measured by ELISA • 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); Days 7, 14, 28, 56, 84, 168 and 336 (Phase 1b) ○ Neutralizing activity against multiple variant spike protein-expressing pseudoviruses, and/or PRNT neutralizing activity against multiple variants of SARS-CoV-2 virus and the variant Beta (B.1.351) in all participants. ○ RBD antibody titers against wild-type variant spike protein measured by ELISA <u>Exploratory Immunogenicity Endpoints/Outcome Measures</u> • Geometric mean number of IFN-γ -positive cells per 106 PBMCs by ELISPOT assay post-vaccination over Day 1 (baseline) at Days 7, 28, 35, 56 and 336 (Phase 1a); Days 7, 14, 28 and 336 (Phase1b) 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 (Phase 1a) or Days 7, 14, 28, 56, 84, 168 and 336 (Phase 1b)

Key Roles

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LIST OF ABBREVIATIONS

AE	adverse event
AEC	all enrolled cohort
ADR	adverse drug reaction
ALT	alanine aminotransferase
ALP	alkaline phosphatase
alum	aluminum phosphate
AST	aspartate aminotransferase
ATP	according-to-protocol
BMI	body mass index
BRDD	Biologic and Radiopharmaceutical Drugs Directorate, Health Canada
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
CMV	cytomegalovirus
CoV	coronavirus
CRO	clinical research organization
CVID	common variable immune deficiency
DBP	diastolic blood pressure
DSMB	Data Safety Monitoring Board
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
ELISPOT	enzyme-linked immunospot
EOS	end of study
ER	emergency room
eVLP	enveloped virus-like particle
EW	early withdrawal
FDA	Food and Drug Administration, United States
gB	glycoprotein B
GCP	good clinical practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GMT	geometric mean titer
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus

HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's brochure
ICH	International Council for Harmonisation
ICS	Intracellular cytokine staining
IM	intramuscular
IMC	immunogenicity cohort
IRT	interactive response technology
ITT	intent-to-treat
IV	intravenous
IWRS	interactive web response system
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East respiratory syndrome coronavirus
MLV	Moloney murine leukemia virus
MMR	measles, mumps, rubella vaccine
NA	not applicable
nAb	neutralizing antibody
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PPC	per-protocol cohort
PRNT	plaque-reduction neutralization test
PV	pharmacovigilance
RBD	receptor-binding domain
REB	research ethics board
REC	research ethics committee
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
SBP	systolic blood pressure
SC	safety cohort
SSC	study steering committee
SUSAR	suspected, unexpected serious adverse reaction
SVR	sustained virologic response
TEAE	treatment emergent adverse event
VBI	VBI Vaccines Inc.
VLP	virus-like particle
VSV	vesicular stomatitis virus

GLOSSARY OF TERMS

Adequate contraception	Adequate contraception is defined as a contraceptive method with a failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label, such as: • Abstinence from penile-vaginal intercourse • Oral contraceptives, either combined or progesterone alone, • Injectable progestogen, • Implants of etonogestrel or levonorgestrel, • Estrogen vaginal ring, • Percutaneous contraceptive patches, • Intrauterine device or intrauterine system, • Male partner sterilization prior to the female participant's entry into the study, and this male is the sole partner for that participant (information based on study personnel's review of the participant's health record or interview with the participant on her medical history) • Male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository) • Male condom combined with a female diaphragm, with or without a vaginal spermicide (foam, gel, film, cream, or suppository)
Adverse event	Any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product whether or not considered related to the medicinal product.
Adverse event following the immunization (AEFI)	Any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease.
Adverse event of special interest	An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted.

Adverse drug reaction	All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions
Blinding	A procedure in which at least one party to the study is kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the course of the study, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In a single-blind study, the investigator and/or staff are aware of the treatment assignment but the participant is not. In an observer-blind study neither the participant nor study personnel performing outcome measurement is aware of treatment assignment; an unblinded staff member prepares the study treatment but has no other role in the study.
CIOMS I	Council for International Organizations of Medical Sciences Reporting of Adverse Drug Reactions bases for ICH E2A and Canada
Eligible	Qualified for enrollment into the study because potential participant has strictly adhered to all inclusion/exclusion criteria.
Evaluable	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per-protocol cohort (PPC) analysis.
Investigational product **(Synonym of investigational medicinal product)**	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including a product with a marketing authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Investigator's brochure	Compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human participants.
Participant	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, as a recipient of the investigational product or placebo.
Randomization	The process of assigning trial participants to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.
Solicited adverse event	Adverse events to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the participant or an observer during a specified post-administration follow-up period.

Treatment	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant, identified by a unique number, according to the study randomization or treatment allocation.
Unexpected adverse drug reaction	An adverse reaction, the nature or severity of which is not consistent with applicable product information (e.g., Investigator's Brochure for unapproved investigational medicinal product).
Unsolicited adverse event	Any AE reported in addition to those solicited during the clinical study. Also, any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Version 1.0	18 November 2020
Version 2.0	14 December 2020
Version 2.1	16 December 2020
Version 3.0	04 January 2021
Version 3.1	04 February 2021
Version 3.2	18 March 2021
Version 4.0	24 June 2021
Version 4.1	20 July 2021
Version 5.0	10 August 2021
Version 6.0	20 May 2022

Version 6.0 (20 May 2022)

Rationale: A major protocol amendment was made to modify the Phase 1b study design to remove Group G6. Group G6 intended to enroll participants who were not vaccinated with any authorized or experimental COVID-19 vaccine into an open-label arm to receive two doses of VBI-2905a. Due to difficulty enrolling participants who have not been previously vaccinated with an authorized or experimental COVID-19 vaccine in Mexico (the location of the Group G6 study site), Group G6 is being removed from the protocol.

Version 5.0 (10 August 2021)

Rationale: A major protocol amendment was made to modify the Phase 1b study design and make a minor addition to the exclusion criteria in response to the Institutional Ethics and Scientific Committee reviews. The following changes were made:

- Group G7, the placebo arm in the two-dose regimen in participants who were not vaccinated previously, was removed. Text was modified to indicate that in this portion of the study (group G6), VBI-2905a administration will be open label, without a placebo group
- The number of participants in group G5 (placebo recipients) was increased from 9 to 27 to better characterize the kinetics of the longer-term antibody response post-mRNA vaccination and the comparisons with the active group
- The age range of participants in Phase 1b was changed from >18 years of age to 18-54 years of age to be consistent with the Phase 1a part of the study and to minimize the potential impact of age-dependent variability on assessments of immunogenicity.
- One additional exclusion criterion was added - the lack of participant's capacity (mental, social, behavioral) to provide informed consent
- Section 4.13, Immunogenicity Assessments, was modified to clarify how neutralizing antibody results will be assessed
- Section 6.1.7, Biological Sample Handling and Analysis, was modified to indicate that Nexelis will perform sequencing of SARS-CoV-2 in nasal/nasopharyngeal swab samples
- Pseudoneutralization assay (PNA) was added to the list of abbreviations

Version 4.1 (20 July 2021)

Rationale: A minor protocol amendment was made with the following changes:

- Replace references to Phase 1 and Phase 2 parts of the study with Phase 1a/1b throughout the Protocol. Due to study design changes made in the Protocol Amendment v4.0, designation of the study as a Phase 1a/1b more accurately reflects the early nature of this study
- Clarify that humoral and cell-mediated immunogenicity will be tested in all study participants (Tables 1, 2, and 3 and throughout the document)
- Deleted a duplicate line for assessment of concomitant medications (Tables 1, 2, and 3)

Version 4.0 (28 June 2021)

Rationale: A major protocol amendment was made to include unblinding of study groups after Day 56 in Phase 1 and Phase 2 and to revise the Phase 2 study design with the following changes:

- Modify eVLP to express S protein of South African variant B.1.351 (VBI-2905a) in place of S protein of Wuhan isolate (VBI-2902a)
- Modify the eVLP formulation for VBI-2905a to provide greater vaccine stability
- Change the number of study participants, modify eligibility criteria to Include healthy adults age ≥18 years with or without a history of prior COVID-19 vaccination, (mRNA vaccine only) and stratify randomization of the study based on the previous COVID-19 (mRNA) vaccination status
- Modify immunological assay sampling schedule for alignment with clinical trials of other vaccine candidates and to reduce the number blood draws for cell-mediated immunity assays
- Add immunological analysis of responses against SARS-CoV-2 variants
- Collect duplicate nasopharyngeal swabs at study visits and store one swab frozen for potential sequencing of viral RNA
- Change references to Health Canada to read “appropriate regulatory authorities” to reflect the addition of clinical sites in Mexico

These changes required extensive revisions throughout the protocol.

Version 3.1 (04 February 2021

Rationale: A minor protocol amendment of the 2902a phase 1/2 study was made for clarity and consistency in the following sections:

- Sections 5.1: exclusion criterion #15 related to immunization with inactivated vaccines (e.g., influenza)
- is changed from “within 1 week” to “within 2 weeks” prior to enrollment.
- Section 6.1: clarification on full physical exam and vital signs measurements was added Sections 7.1 and 7.5: description of study product and vaccine preparation is modified to clarify
- that for Phase 1 part of the study a single-vial of study vaccine will contain 5 µg /mL spike protein antigen and for Phase 2 part of the study a single-vial of study vaccine will contain 10 µg /mL.
- Table 1, Schedule of Events: a footnote regarding full physical examination at screening visit was updated with height measurement; a footnote is added to clarify that testing for cell-mediated immunity testing in Phase 2, Part 2.2 of the study will be performed in up to 10% of the study participants, at selected sites only.

Version 3.0 (04 January 2021)	
Rationale: A minor protocol amendment of the 2902a phase 1/2 study was made due to a limited supply of VBI-2902a vaccine at the time of study initiation. The phase 1 portion of the protocol is simplified to test only the 5µg dose level in one-dose or two-dose regimen in the 18 to 54 age cohort only. Phase 2 portion of the study will commence after DSMB review of Phase 1 Day 56 safety data and once the adequate supply of VBI-2902a vaccine is available**.**	
Synopsis: multiple sections Protocol: multiple sections	Wording to multiple sections was revised to reflect the new study design. Table 2, one of two (Part A) Schedule of Events, was deleted as only one Schedule of Events (formerly labeled as Part B and C) will now apply to all groups.
Rationale: In version 2.1, exclusion criterion #6 was deleted from the synopsis, but was inadvertently left in Section 5.1. This criterion is not needed as it is included in revised criterion#3.	
Protocol: Section 5.1 Inclusion and Exclusion criterion #6 (“History of or current Exclusion Criteria clinically significant medical illness . . .”) was deleted.	
Rationale: Some references to other sections within the document gave an incorrect section number.	
Protocol: Section 4.4 Early DSMB Study Review and Continuation Criteria, Section 5.2 Protection of Participants, Section 5.3 Follow-up Duration, Section 6 STUDY PROCEDURES AND INTERVENTIONS, Section 6.1.2 Sampling Schedule, Section 6.1.5 Recording of AEs, SAEs, and Potential Immune- Mediated Diseases, Section 7.7 Replacement Doses	References to other sections were corrected, as necessary, by incrementing the section number by one.
Version 2.1 (16 December 2020)	
Rationale: Additional DSMB safety reviews	
Synopsis: Study Design and Continuation and of Study Protocol: Design, Section 4.1; Fig.1 Study Design; Treatment Allocation, Section 4.8	Additional DSMB safety review at Day 35 data of group B1 prior to administration of the second dose in group B2 and DSMB safety review of Day 35 data of cohort B4 prior to administration of the second dose in group B5
Rationale: Revised Exclusion Criteria	
Synopsis: Study Population, Exclusion Criteria Protocol: Inclusion and Exclusion Criteria, section 5.1	Inclusion and exclusion criteria revised to clarify that only healthy participants with no chronic medical conditions are eligible for the study

Version 2.0 (14 December 2020)	
Rationale: Present the rationale for the clinical doses.	
Section 2.1 Background and Rationale	Paragraph added at the end of the section explaining the rationale for the clinical doses.
Rationale: Correct study duration.	
Synopsis Duration of Study and Section 4.5 Duration of Study	Study duration changed to 364 days from 360 days.
Rationale: Clarify what is meant by significant medical illness.	
Synopsis Study Population, and Section 5.1 Inclusion and Exclusion Criteria, Exclusion Criterion 3	Add the phrase "including respiratory conditions such as COPD or asthma" after "significant medical illness."
Rationale: Change exclusion criterion regarding pregnancy, breast feeding or plans to conceive.	
Synopsis Study Population, and Section 5.1 Inclusion and Exclusion Criteria, Exclusion Criterion 6	Duration covered by the exclusion criterion changed to "until the end of study" from "6 months after the last dose of study vaccine."
Rationale: Change definition of uncontrolled hypertension.	
Synopsis Study Population, and Section 5.1 Inclusion and Exclusion Criteria, Exclusion Criterion 17	Uncontrolled hypertension definition changed to "SBP ≥ 140 mmHg or an average DBP ≥ 90 mmHg" from "SBP ≥ 150 mmHg or an average DBP ≥ 95 mmHg."
Rationale: Correct reference to FDA guidelines for clinical laboratory abnormalities.	
Synopsis Study Population, and Section 5.1 Inclusion and Exclusion Criteria, Exclusion Criterion 22	Reference changed to "Table 8" from "Appendix 3.
Rationale: Correct amount of blood to be drawn to match protocol Section 6.1.2.	
Synopsis Safety and Immunogenicity Assessments	Amount of blood to be drawn changed to "15-20 mL for initial (pre-vaccination) blood draw, and approximately 55- 60 mL for subsequent blood draws" from "15-20 mL for initial (pre-vaccination) blood draw, and approximately 55-60 mL for subsequent blood draws."
Rationale: Clarify post-vaccination observation period.	
Table 1, Table 1 footnote 4, Table 2 footnote 4, Section 6.1 Detailed Description of Study Procedures and Section 7.10 Sixty Minutes Post-Immunization.	Post-vaccination observation period changed to 60 minutes from 30 minutes. Window changed to 10 minutes from 15 minutes in Section 7.10.
Rationale: Specification of dominant and non-dominant arm is not required.	
Section 6.1.3 Study Product Administration	References to dominant and non-dominant arm removed.

Rationale: Clarify that participants with symptoms consistent with COVID-19 should not be administered study vaccination.	
Section 7.11 Contraindications to Administration of the Product	Change text regarding minor illness such as mild diarrhea, mild upper respiratory infection to "any signs or symptoms consistent with COVID-19 illness (as described in the Section 4.2) should not receive the study vaccine."
Rationale: Clarify prohibited use of antipyretics and other medications during the study.	
Section 7. STUDY PRODUCT AND ADMINISTRATION	Section 7.14 text regarding antipyretic and other pain medications being permitted was deleted and a new section, section 7.15 Prohibited During the Study, added to clarify which medications and at what point during the study they are prohibited.
Rationale: Clarify that both dose levels of VBI-2902a contain the same amount of aluminum phosphate adjuvant.	
Section 7.1 Description of Study Product	Statement added to the third paragraph: "Doses as administered will include the same content of aluminum phosphate (0.33 mg aluminum)."
Rationale: Remove unnecessary text to clarify statement.	
Section 8.1 Safety Definitions	Text changed to "will be set as 7 days post vaccination" from "will be set as 168 hours (7 days) post vaccination."
Rationale: FDA guidance for grading of clinical laboratory abnormalities needed.	
Section 8.6 Assessment of Adverse Events	Table 8. FDA Guidance for Grading Clinical Laboratory Abnormalities added. Subsequent table numbers augmented by 1.
Rationale: Clarify definitions of analysis cohorts.	
Section 10.5 Analysis cohorts, Section 7.14 Concomitant Medications/Products/Vaccines That May Lead to the Elimination of a Participant from Per-Protocol Cohort (PPC) Analyses	Definitions of each of the four analysis cohorts added or clarified. List of abbreviations modified as necessary.

2 INTRODUCTION

2.1 Background and Rationale

The COVID-19 pandemic, caused by the SARS-CoV-2 novel coronavirus, continues to cause widespread illness, death and economic hardship worldwide. A safe and effective vaccine is urgently needed to combat SARS-CoV-2, and as a consequence, numerous vaccine development efforts, using a variety of approaches and technologies, are underway (World Health Organization 2021a). Ideally, an effective vaccine will provide protection against SARS-CoV-2 infection within a short timeframe, after one or two vaccine doses, and will induce immunity that is durable and efficacious in all recipients, including older adults and those with immunodeficiencies and other comorbidities.

Potent neutralizing antibodies (nAbs) directed against the spike proteins of the related coronaviruses SARS- CoV, MERS-CoV and SARS-CoV-2 have been isolated from sera of patients following infection, (Traggiai E 2004; Corti, D 2015; Chen X 2020). The majority of human nAbs against SARS-CoV specifically react with the spike protein receptor binding domain (RBD). However, several human monoclonal antibodies (mAbs) that can bind to epitopes outside of the RBD can also neutralize the virus (Coughlin MM 2012).

Several vaccine strategies against SARS-CoV and MERS-CoV have been focused on the S protein and tested extensively in pre-clinical studies (Zhou Y 2018) and showed potently neutralizing antibody (nAb) responses against S protected animals in challenge experiments. The majority of ongoing clinical trials of candidate vaccines against SARS-CoV-2 are directed against S or S subunits.

COVID-19 vaccines authorized for emergency use have been found to be highly effective against COVID-19 disease and spread of infection (Kyriakidis NC 2021). However, as SARS-CoV-2 infections continue to occur at high numbers, more easily transmitted virus variants have emerged and spread globally. Vaccines in use appear to provide protective immunity against variants, but protection can be weaker than what was observed against the original Wuhan strain. This has prompted efforts to modify vaccines to provide broader coverage against variants, particularly against those the World Health Organization (WHO) has identified as “variants of concern,” such as the B.1.351 or Beta variant that was first identified in South Africa (WHO 2021b).

Virus-like particles (VLPs) have been developed as an effective strategy for delivery of vaccine antigens (Roy P 2008). VLPs contain structural components of a virus particle, but are devoid of DNA or RNA, and thus are unable to replicate or cause disease. The immune system has been shown to react more strongly to a protein presented as part of a VLP than it does to the same protein alone (Kirchmeier M 2014). VLPs can be used to immunize against the parenteral virus from which they are derived or can be engineered to carry heterologous antigens to immunize against other infectious diseases. VLPs have been shown to be safe and highly effective for vaccination against infectious diseases such as hepatitis B and human papillomavirus (Tan M 2014).

Enveloped VLPs (eVLPs) are an innovative new class of synthetic vaccines that are designed to closely mimic the structure of enveloped viruses. They are comprised of a lipid bilayer and a protein core that is essentially of viral origin. It is possible to design eVLPs carrying several antigens that can activate both the cellular and humoral immune responses. eVLPs have the added advantage of being able to present surface proteins of enveloped viruses in their native form, associated with the eVLP lipid bilayer envelope, which can lead to a more effective response (Kirchmeier M 2014). The eVLP vaccine platform technology was initially developed by VBI Vaccines Inc. (VBI) for the VBI-1501 human cytomegalovirus (CMV) vaccine, which has been shown to be highly immunogenic in animal studies and in Phase 1 clinical testing. eVLPs are also undergoing Phase 1 testing by VBI for a vaccine candidate meant for therapeutic immunization against glioblastoma. VBI-2902a is an eVLP COVID-19 vaccine candidate that presents the S protein of SARS-CoV-2 embedded in the eVLP lipid monolayer. VBI-2902a is intended to elicit humoral and cellular immunity against the spike protein that protects against infection by SARS-CoV-2.

eVLPs are formed by expression of the Moloney murine leukemia virus (MLV) Gag protein in mammalian cells. The Gag protein is cleaved by cellular proteases to yield the viral matrix, capsid and nucleocapsid proteins. Capsid proteins spontaneously assemble into VLPs which acquire a lipid envelope as they are released from the cells. The eVLPs are not infectious because the viral pol gene, which is required for production of viral RNA, is not present in the cells used for vaccine manufacture. VBI-2902a eVLPs are produced in cells expressing a modified spike protein sequence that is stabilized in the prefusion conformation. The modified spike protein is expressed with a tail consisting of the transmembrane and cytoplasmic domains of the vesicular stomatitis virus (VSV) G glycoprotein, resulting in incorporation of membrane-anchored spike into the eVLP envelope. In comparison to recombinant spike protein produced in prokaryotic or insect cells, mammalian membrane-expressed spike protein is presented in a more native- like conformation due to fluidity afforded by the lipid bilayer as well as mammalian glycosylation. VBI- 2902a eVLPs are adsorbed to aluminum phosphate (Adju-Phos™), which serves as an immunological adjuvant and stabilizes the eVLP structure.

Studies in mice have demonstrated that immunization with VBI-2902a elicits high levels of antibodies that bind to the SARS-CoV-2 spike protein and neutralize virus infection of mammalian cells in vitro. In mice, nAb titers elicited by VBI-2902a were up to 64-fold higher than that of a pool of COVID-19 convalescent sera and 32-fold higher that that elicited by immunization with recombinant spike protein alone.

In an effort to broaden vaccine efficacy against newly emerged SARS-CoV-2 variants, VBI has developed a modified COVID-19 vaccine candidate termed VBI-2905a. The eVLP component of VBI-2905a is identical to the VBI-2902a eVLP except for the S protein sequence, which has been changed from the Wuhan sequence to the variant Beta (B.1.351) sequence. In mice, VBI-2905a performed similarly to VBI-2902a, stimulating a robust nAb response. However, while VBI-2902a stimulated a very strong response against the homologous Wuhan strain, but a weaker response against the heterologous variant Beta (B.1.351), VBI-2905a elicited a strong response against both variants. The formulation for VBI-2905a was modified to enhance vaccine stability and reduce aggregation by

replacing sucrose with L-arginine and NaCl, increasing the pH from 7.2 to 7.5 and increasing the aluminum phosphate concentration from 0.33 mg/mL to 0.66 mg/mL (aluminum content).

This clinical trial protocol has been designed to evaluate VBI-2902a in the Phase 1a part of the study and VBI-2905a in the Phase 1b part of the study

There is no previous experience with VBI-2902a or VBI-2905a in humans, but their eVLP structure is identical to that of VBI- 1501 other than that it expresses the SARS-CoV-2 spike protein in place of the CMV gB protein (Kirchmeier M 2014). VBI-1501 was shown to be safe, well-tolerated and immunogenic in a Phase 1 clinical study (clinicaltrials.gov No. NCT02826798). Safety of the eVLP vaccine platform was also demonstrated in an ongoing study of VBI-1901, a similar eVLP currently undergoing clinical study for therapeutic immunization against glioblastoma (clinicaltrials.gov No. NCT03382977). Aluminum phosphate, the other main component of VBI-2902a and VBI-2905a, has been used as an adjuvant in several licensed human vaccines and has an established record of safety and efficacy (Baylor NW 2002; Paneque-Quevedo AA 2013).

VBI-1501, a similar eVLP vaccine containing viral glycoprotein antigen, was studied at doses up to 2 µg of antigen. After administration of two doses of VBI-1501 with alum to adults age 18-40, partial responses were observed. A total of 88% of participants had a response with nAb detected in fibroblasts assay.

However, only a small fraction of participants had a response with nAb detected in epithelial cell assay. Similarly, the 2µg dose of SARS-CoV-2 spike protein in VBI-2902a is likely to be suboptimal dose for adults 18-54 years of age as well as in older adults (age >55) due to immune-senescence. Therefore, a higher antigen content of 5 or 10 µg per dose may be required to induce protective nAb responses after 2 doses of VBI-2902a. This antigen dose (5 or 10 µg) is comparable to other VLP vaccines, such as aluminum phosphate-adjuvanted hepatitis B vaccine (10 µg HBsAg, Recombivax). With regard to safety margins, pre- clinical toxicology studies in mice and rabbits showed no dose-limiting toxicity or other safety signals of concern with single-dose and repeat-dose (up to 4 doses) administration of up to 20 µg of the VBI-1501 eVLP vaccine (using the same eVLP platform and formulation with the same adjuvant).

3 OBJECTIVES

3.1 Phase 1a

The primary objective is 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.

The secondary objective is 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.

3.2 Phase 1b

The primary objective is 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 (age 18-54 years) who had been previously vaccinated with mRNA vaccines.

The secondary objective is to evaluate the immunogenicity of a one-dose regimen of VBI-2905a at a 5 μg dose level of S protein in healthy adults (age 18-54 years) who had been previously vaccinated with mRNA vaccines.

4 STUDY DESIGN

4.1 Design

Overview

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

Description of study parts and groups

A schematic of the study design is shown in Figure 1.

Phase 1a

60 healthy adults, age 18-54 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 will be enrolled into the Phase 1a part of the study to evaluate the safety, tolerability and immunogenicity of a one-dose or two-dose regimen of VBI-2902a at a dose level of 5 μg of S protein or placebo. Participants will be randomized at a 2:1 ratio to VBI-2902a or placebo:

- **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 (AEs) 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

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.

Participants who had been previously vaccinated with authorized mRNA COVID-19 vaccine(s) 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

In Phase 1b, the DSMB will review blinded Day 7 safety data after vaccination of the first 10 participants in groups G4 and G5 (previously vaccinated with mRNA COVID-19). 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). The study will be unblinded following DSMB and SSC review of safety and immunogenicity data collected through Day 56.Study participants will continue with study visits as planned up to 12 months of follow up after the first dose of study vaccine.

Schedule of Events

During the study, there will be a total of 9 visits (Phase 1a and Phase 1b, groups G4 and G5), including the screening visit and 12 months of follow up (see Table 1, and Table 2below).

During the screening visit participants will provide informed consent, provide samples for SARS-CoV-2 testing (PCR and/or rapid antigen test and for viral variant testing/sequencing) and safety laboratory testing (hematology, biochemistry, urinalysis), provide history of previous COVID-19 vaccination, including type of vaccine and dates of vaccination (Phase 1b), and will be evaluated against study inclusion and exclusion criteria to confirm study eligibility. Eligible participants will proceed to Day 1 to be randomized and receive the study vaccine or placebo.

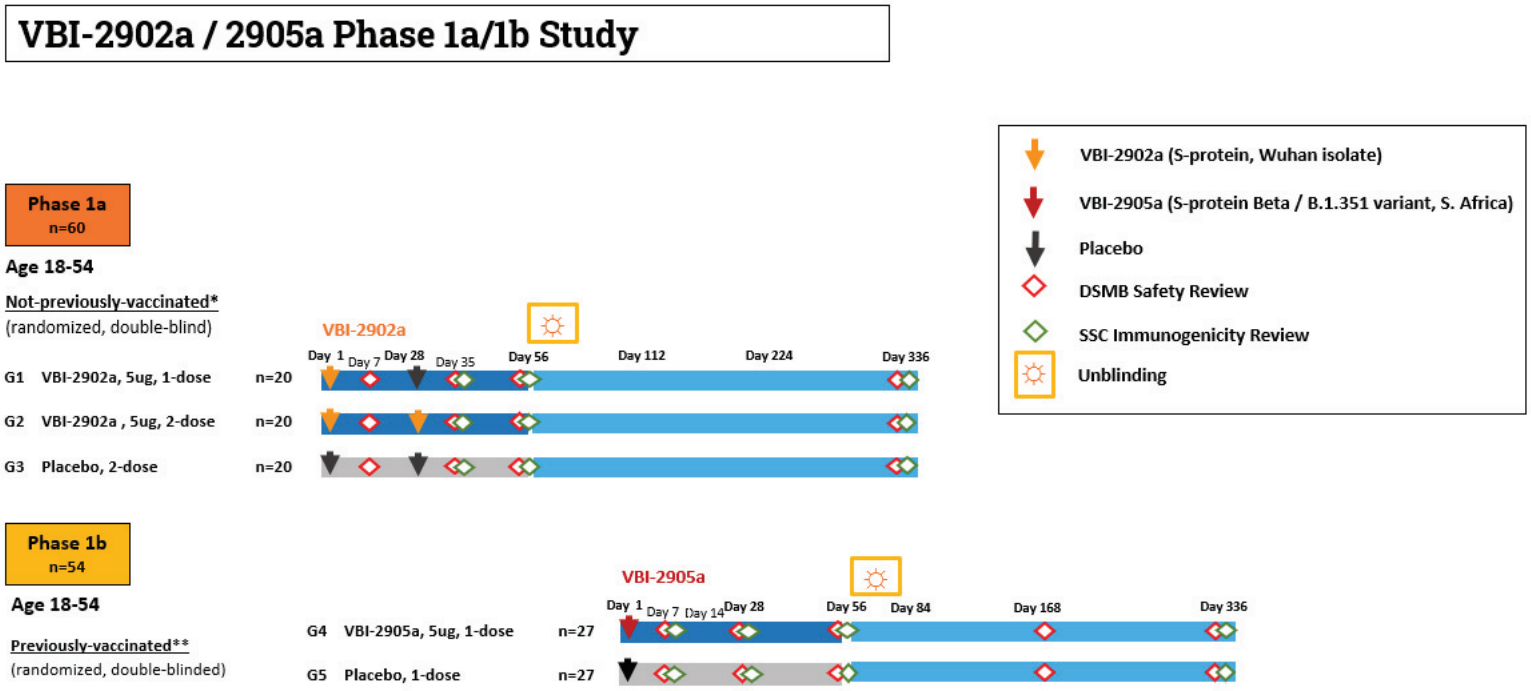
On the vaccination visits, participants will remain at the site for at least 60 minutes for an evaluation of AEs and vital signs. Participants will be contacted by phone 3 days after each vaccination for a safety follow up call. Diary cards will be distributed to study participants at vaccination visits to record body temperature, local and systemic reactions from day of the vaccination(s) and the next 6 days. Serious AEs (SAEs) and medically-attended AEs (MAAEs) will be recorded throughout the study.

In Phase 1a, participants will visit the study site for dose administration, safety assessments and blood sample collection on Days 1 and 28 (prior to study vaccination) and for safety assessments and blood sample collection on Days 7, 35, 56, 112, 224 and 336.

In Phase 1b, participants will visit the study site for dose administration, safety assessments and blood sample collection on Day 1 for safety assessments and blood sample collection on Days 7, 14, 28, 56, 84, 168 and 336. Study participants will be tested for SARS-CoV-2 infection by PCR or rapid antigen test and surveilled for signs and symptoms of COVID-19 illness throughout the study. Duplicate nasopharyngeal swab samples will be retained for storage and potential sequencing of viral RNA should samples test positive for SARS-CoV-2 infection.

Participants will be followed until the study completion on Day 336. If a subject is lost to follow-up, every effort will be made by the study center personnel to contact the subject and to determine the reason for discontinuation. Measures taken to follow-up will be documented.

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*

Table 1: Phase 1a Schedule of Events

Schedule of Events	Screening	Study Period									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	336
Study Month (28 days)	<-1	0	0.1	0.25	1	1.1	1.25	2	4	8	12
Visit Intervals (Days)	n/a	n/a	±1	+3	±3	±1	±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 tovaccination.
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 - solicitedAEs

Table 2: Phase 1b Schedule of Events

Schedule of Events	Screening		Study Period							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 tovaccination.
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 - solicitedAEs

4.2 COVID-19 Surveillance

Surveillance for COVID-19 symptoms will be conducted throughout the study. If a participant experiences any of the symptoms listed below, he or she is instructed to contact the study site immediately and participate in an in-person or telehealth visit as soon as possible, optimally within 3 days of symptom onset (and at the latest 4 days after symptom resolution). To confirm the diagnosis, SARS-CoV-2 test (PCR/ or rapid antigen test) should be performed as soon as possible. Participants who test positive for COVID-19 will be discontinued from further vaccination. During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with solicited systemic events (i.e., fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity.

Participants will be provided diary cards to record any symptoms.

In Phase 1b, nasopharyngeal swabs samples for SARS-CoV-2 testing will be collected in duplicate with one sample to be used for the PCR/ or rapid antigen test and the second sample stored (frozen) for possible sequencing of viral RNA if SARS-CoV-2 virus is detected.

Clinical Criteria for COVID-19 (CDC - COVID-19 Interim Case Definition, Aug. 5, 2020): In the absence of a more likely diagnosis, at least two of the following symptoms:

- 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)

4.3 Potential COVID-19 Illness Visit (Optimally Within 3 Days After Onset):

An unscheduled potential COVID-19 illness visit and unscheduled potential COVID-19 convalescent visit are required at any time during the study that COVID-19 is suspected.

This visit may be conducted as an in-person or telehealth visit; a telehealth visit involves the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing) remotely, thus allowing the participant and investigator to communicate on aspects of clinical care.

As a participant's COVID-19 illness may evolve over time, several contacts may be required to obtain the following information:

- Record any AEs,
- Record any concomitant medications received by the participant
- If the visit is conducted in person, obtain a nasopharyngeal swab for COVID-19 testing (collected by site staff. For Phase 1b only, collect swabs in duplicate with one swab being stored frozen for possible viral RNA sequencing).
- The participant should be encouraged to seek care or COVID-19 testing, if appropriate, from his or her usual provider.
- Collect COVID-19-related standard-of-care clinical and laboratory information.
- Schedule an appointment for the participant to return for the potential COVID-19 convalescent visit once recovered.

4.4 Early DSMB Study Review and Continuation Criteria

Safety criteria for study continuation

Early DSMB reviews of post-vaccination safety data and stopping rules will be implemented for safety and protection of study participants (see Section 5.2, Protection of Participants, below).

In Phase 1a, the second vaccination will proceed only after the DSMB has confirmed that the vaccine safety and tolerability is acceptable and that stopping rules were not met through 7 days after the first dose.

In Phase 1b, DSMB will review blinded Day 7 safety data after the first 10 participants in each group . 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.

For details on timing of DSMB reviews, please see Figure 1 above.

Stopping rules

Study vaccinations will stop if 2 or more participants receiving VBI-2902a or VBI-2905a meet the stopping rules criteria (defined in Section 10.7) unless the DSMB and study sponsor and site investigators review the safety data, and in consultation with the appropriate regulatory authorities, determine that the safety of study participants is not affected and that study vaccination may continue.

Immunogenicity criteria for study continuation

Neutralizing antibody (nAb) titers, determined by pseudovirus microneutralization assay and plaque- reduction neutralization test (PRNT) on serum collected at Day 28 (4 weeks after the first vaccination) and Day 56 (4 weeks after the second vaccination) will be used as the primary determinant for immunogenicity. Additional immunological endpoints, described below, will also be considered as secondary endpoints.

Geometric mean titers (GMT) of nAb and binding antibodies to the spike protein and its receptor binding domain (RBD) in one-dose and two-dose groups in Phase 1a at Days 1, 7, 28, 35 and 56 will be compared against a panel of COVID-19 convalescent sera as well as a WHO International Standard of high titer pooled COVID-19 convalescent sera. Day 28 antibodies to RBD and T-cell endpoints will be considered if Day 56 nAb results do not allow a clear determination of equivalence or superiority. If responses are inferior to that of the panel of convalescent serum in Phase 1a and Phase 1b, neither VBI-2902a nor VBI-2905a will undergo further testing at the proposed dose levels and dose regimens. In Phase 1b, the percentage of subjects with a 4-fold or greater increase in nAb titers will be determined, as this represents a meaningful boosting of immunity.

The group sizes will allow determination of at least two-fold differences in nAb titers at a power of 80% with an alpha error of 0.05. Safety and tolerability will be evaluated in the total of ~67participants who will receive at least one dose of VBI-2902a or VBI-2905a and in ~47 participants who will receive placebo. If no safety signals are detected and immunogenicity is demonstrated, further clinical development will be considered. Further clinical development may not be considered if optimal nAb titers are not equivalent to or superior to that of the panel of COVID- 19 convalescent serum. The safety, tolerability and percentage of subjects with 4-fold or greater increases in nAb titers at Days 28 and 56 will be used to determine whether further clinical development of a one-dose vaccination regimen is justified.

4.5 Duration of Study

The total study duration for each vaccinated subject (assuming a screening period of 28 days) is 364 days.

4.6 Subject Selection and Sample Size

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 will be randomized at 1:1 to receive one dose of VBI-2905a or placebo.

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 nAb titers with 80% power and an alpha error of 0.05.

4.7 Study Vaccine Doses and Mode of Administration

During the screening visit participants will provide informed consent. Participants will remain at the study center for 60 minutes after vaccination and will be evaluated by study center personnel for AEs before discharge. The participants, site investigators and study site personnel performing outcome measurement and the sponsor will be blinded to vaccine allocation. Study vaccine will be administered by qualified unblinded study center staff.

4.8 Treatment Allocation

Phase 1a

In Phase 1a, VBI-2902a at a dose of 5 µg will be administered to participants 18-54 years of age. An Independent Data Safety Monitoring Board (DSMB) will perform an early review of blinded post-vaccination safety data at Day 7 after the first vaccination (reactogenicity, AEs and safety labs). The second vaccination will be given only if the DSMB confirms that early 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. Enrollment in Phase 1b will commence once the DSMB confirms that safety data through Day 56 is acceptable and that stopping rules were not met.

The 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 inclusive of Day 35, i.e., 35 days after the first (7 days after the second) vaccination, as well as Day 56, i.e., 56 days after the first (28 days after the second) vaccination from Phase 1a. Based on the pre-specified criteria for primary and secondary safety and immunogenicity endpoints, the Phase 1b dose and regimen of VBI- 2905a may be modified.

Phase 1b

Phase 1b will evaluate the safety, tolerability and immunogenicity of a one-dose regimen of VBI-2905a at a dose level of 5 µg of S protein in healthy adults aged 18-54 years. DSMB will review blinded Day 7 safety data after the first 10 participants in each group have received their dose. 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 vaccination,. Study participants will continue with study visits as planned up to 12 months of follow up after the first dose of study vaccine.

4.9 Blinding

This study is an observer-blinded study. Both participants and the study center staff performing outcome measurement are blinded; vaccines will be administered by qualified unblinded study personnel who have no other role in the study.

4.10 Endpoints

Primary Endpoints/Outcome Measures

- 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) 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) at Day 56 and 28 days after each study vaccination

Secondary Endpoints/Outcome Measures

- 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 56 and 224 (Phase 1a) or Days 56 and 168 (Phase 1b):
    - Neutralizing activity against multiple variant spike protein-expressing pseudovirus, and/or PRNTneutralizing activity against wild-type SARS-CoV-2 virus and the variant Beta (B.1.351) in all participants
    - RBD antibody titers against wild-type variant spike protein measured by ELISA

- 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); Days 7, 14, 28, 56, 84, 168 and 336 (Phase 1b)
    - Neutralizing activity against multiple variant spike protein-expressing pseudoviruses, and/or PRNT neutralizing activity against multiple variants of SARS-CoV-2 virus and the variant (B.1.351) in all participants
    - RBD antibody titers against wild-type variant spike protein measured by ELISA

Exploratory Immunogenicity Endpoints/Outcome Measures

- Geometric mean number of IFN-γ-positive cells per 106 PBMCs by ELISPOT assay post-vaccination over Day 1 (baseline) at Days 7, 28, 35, 56 and 336 (Phase 1a); Days 7, 14, 28 and 336 (Phase 1b)

4.11 Data Collection

This study will be conducted in compliance with ICH CGP guidelines. This study will use electronic data collection (to collect data directly from the investigational site using eCRFs). The Investigator is responsible for ensuring that all sections of each eCRF are completed promptly and correctly. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained. Study monitors will perform source document verification to identify inconsistencies between the eCRFs and source documents. Discrepancies will be resolved in accordance with the principles of GCP.

4.12 Safety Monitoring

Safety and tolerability will be evaluated throughout the study by collecting solicited local (injection site) and systemic AEs (reactogenicity) for 7 days post-vaccination, unsolicited AEs for 28 days postvaccination and medically-attended AEs (MAAEs) and serious AEs (SAEs) throughout the study. Participants will also be monitored by physical examinations, vital signs, and safety laboratory testing (hematology, serum chemistry, urinalysis). See Table 1, and Table 2 Schedules of Events, for details.

The safety population includes all participants who received at least one dose of the study vaccine. The baseline values for all laboratory evaluations and vital signs will be defined as the last evaluation done before the administration of the study vaccine on Day 1. Safety will be evaluated by examining the incidence and type of AEs, and changes in clinical laboratory test values, physical examination results and vital sign measurements from the screening phase through study completion across study groups.

4.13 Immunogenicity Assessments

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 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-γ ELISPOT-positive cells per 10^6 PBMCs.

A non-inferior GMT nAb titer against the GMT of the panel of COVID-19 convalescent sera (tested against the original Wuhan strain PNA for Phase 1a participants and against the B.1.351 beta variant PNA in Phase 1b) in subjects receiving 2 doses of VBI-2902a will justify proceeding with further clinical development; comparison of the nAb GMT against the WHO reference standard will be used to aid benchmarking against other COVID-19 vaccine candidates.

Similarly, the immunogenicity of VBI-2905a booster in previously vaccinated will be assessed in G4 participants by comparing it to G5 participants. A four-fold increase in the post-boost neutralizing antibody titer in the beta variant PNA will be consider as a confirmatory benchmark to advance clinical development of the 2905a vaccine candidate. If the results are not confirmatory, then the analysis of the RBD ELISA and IgG and T cell data will be undertaken by the SSC to make a decision to further the development of 2905a.

Immunogenicity results will be presented descriptively as point estimates and 95% confidence intervals (CIs), which will be tabulated by study group. Exploratory immunogenicity endpoints may include GMTs against variants of concern, as well as 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.

The immunogenicity population will include all participants who receive the prescribed study vaccine or placebo and underwent at least one immunogenicity assessment after vaccination.

The Study Steering Committee (SSC), comprised of representatives from the study sponsor (not involved in study operations) and external vaccine experts, will review unblinded immunogenicity data7 days and 28 days after the first vaccinations (Phase 1a and Phase 1b)). The study will be unblinded following DSMB review of safety data collected through Day 56. Study participants will continue with study visits as planned up to 12 months of follow up after the first dose of study vaccine.

5 STUDY POPULATION

The study will enroll approximately 114 participants at study centers in Canada. Adherence to inclusion and exclusion criteria is essential to ensure safety to participants and precise comparison of control and treatment groups. Deviations from inclusion and exclusion criteria are not allowed because they could jeopardize the scientific integrity of the study, regulatory acceptability or participant safety.

Inclusion and exclusion criteria for specific parts of the study are defined below.

5.1 Inclusion and Exclusion Criteria

Inclusion Criteria

To be eligible for the study, each participant must satisfy ALL of the following criteria:

1. Healthy female and male participants 18-54 years of age
2. If female:
    a. is of childbearing potential and must have a negative pregnancy test prior to study vaccinations and agree to use an effective method of birth control as deemed appropriate by the investigator (e.g., hormonal contraceptive, barrier contraceptive with additional spermicide, or an intrauterine device) beginning >30 days prior to the first study vaccine administration and continuing until the end of the study.

    OR

    b. is not of childbearing potential, defined as postmenopausal (12 months with no menses without an alternative medical cause) or surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy).
3. Phase 1b: previously received a full course (2 doses) of an authorized S protein mRNA COVID-19 vaccine (e.g. COVID-19 vaccines produced by Pfizer/BioNTech or Moderna) at least 4 months prior to enrollment (1 month is defined as 28 days).
4. Sign an informed consent document indicating understanding of the purpose of and procedures required for the study and willingness to participate in the study.

Exclusion Criteria

Participants with any of the following criteria will be excluded:

1. History of clinical or laboratory diagnosis of COVID-19 or SARS-CoV-2 infection
2. **Phase 1b**: Previous receipt of an experimental or authorized SARS-CoV-2 (COVID-19) vaccine other than an S protein mRNA vaccine.
3. **Phase 1a:** Previous receipt of an experimental or authorized SARS-CoV-2 (COVID-19) vaccine.
4. Positive PCR or rapid antigen test for SARS-CoV-2 at screening.
5. Individuals with chronic medical conditions, including any of the following:
    a. Diabetes mellitus Type 1 or Type 2
    b. Chronic pulmonary disease (e.g., COPD or Asthma)
    c. Hypertension (e.g., SBP >140 mmHg or DBP >90 mmHg)
    d. Chronic kidney disease (e.g., GFR <60 mL/min/1.73 m^2)
    e. Chronic liver disease
    f. Obesity (e.g., BMI >30 kg/m^2)
6. Any history of cancer requiring chemotherapy or radiation within 5 years.

7. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.
8. The lack of participant's capacity (mental, social, behavioral), in the investigator's judgement, to provide informed consent for participation in the study
9. Known or suspected impairment of immunological function, including but not limited to autoimmune diseases:
    a. autoimmune diseases (e.g. multiple sclerosis, type 1 diabetes, myasthenia gravis, Crohn disease and other inflammatory bowel diseases, celiac disease, systemic lupus erythematosus, scleroderma, including diffuse systemic form and CREST syndrome, systemic sclerosis, dermatomyositis polymyositis, rheumatoid arthritis, juvenile idiopathic arthritis, autoimmune thyroiditis -including Hashimoto thyroiditis, Grave's or Basedow's disease, immune thrombocytopenic purpura, autoimmune hemolytic anemia, autoimmune hepatitis, psoriasis, vitiligo, vasculitis, Guillain-Barré syndrome, Transverse myelitis, Addison's disease, Bell's Palsy and Alopecia Areata);
    b. secondary immunodeficiency disorders (e.g., Acquired Immunodeficiency Syndrome caused by Human Immunodeficiency Virus infection (HIV/AIDS), solid organ transplant, splenectomy);
    c. primary immunodeficiency disorders (e.g., common variable immune deficiency (CVID), Defective phagocytic cell function and neutropenia syndromes, complement deficiency).
10. History of allergic reactions or anaphylactic reaction to any vaccine component.
11. Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).
12. Pregnant or breastfeeding or plans to conceive from 2 weeks before the study until the end of study.
13. Clinically significant abnormal physical examination, vital signs, or clinically significant abnormal values for hematology, serum chemistry or urinalysis at screening as determined by the investigator.
14. Any laboratory test abnormality that would be considered of Grade 1 severity or above (as per FDA grading guidelines) and is considered as clinically significant by the investigator. Grade 2 severity or above is exclusionary, regardless of clinical assessment.
15. Has received blood products or immunoglobulin within 90 days of enrollment or is likely to require blood products during the study period.
16. Chronic administration (defined as more than 14 days in total) of immune-suppressive or

other immune-modifying drug within six months prior to the product dose (for corticosteroids, this is defined as prednisone ≥20 mg/day or equivalent). Inhaled and topical steroids are allowed.

17. Immunization with attenuated vaccines (e.g., MMR) within 4 weeks prior to enrollment.
18. Immunization with inactivated vaccines (e.g., influenza) within 2 weeks prior to enrollment.
19. Participation in another clinical study within 30 days.
20. Any skin abnormality or tattoo that would limit post-vaccination injection site assessment.
21. Family members of study site personnel.

5.2 Protection of Participants

Informed Consent:

Each local research ethics board (REB) or research ethics committee (REC) will review and approve the study protocol, informed consent form and other study-related documentation.

Written informed consent will be obtained after participants have read the approved informed consent form and have had adequate opportunity to discuss the study with an investigator or a qualified designee and before the initiation of any study related procedures.

Data Safety Monitoring Board (DSMB):

While the trial is ongoing, to allow regular review of the accumulated safety data, a DSMB will be established to perform early review of blinded post-vaccination safety data at 7 and 28 days after each vaccination (solicited and unsolicited AEs and safety labs) and regularly thereafter through study termination. Second vaccinations will only be administered after the DSMB confirmation that safety after the first dose is acceptable and that stopping rules have not been met. The DSMB may recommend to continue, pause, modify, or suspend the further enrollment to the study. Stopping rules can be found in Section 10.7.

5.3 Follow-up Duration

Participants will be followed a minimum of 12 months (assuming 28 days per month) after the Day 1 immunization with at least six months follow-up safety assessments after final dose or early withdrawal (EW) (see Section 8).

6 STUDY PROCEDURES AND INTERVENTIONS

An overall table of study treatments is provided in Table 3 below. The schedule of events is located in Section 4, Table 1, and Table 2above.

Table 3: Overall Summary of Study Treatments

Part	Group	Treatment name	Dose (µg)	Alum	Participant age (years)	Total participants
Phase 1a	G1	VBI-2902a	5	Yes	18-54	20
	G2	VBI-2902a	5	Yes	18-54	20
	G3	Placebo	None	No	18-54	20
Phase 1b	G4	VBI-2905a	5	Yes	18-54	27
	G5	Placebo	None	No	18-54	27
	Total					114

6.1 Detailed Description of Study Procedures

Informed consent:

The signed informed consent must be obtained before study participation.

6.1.1 Check inclusion and exclusion criteria:

Verification of ongoing eligibility to be completed by the investigator or qualified designee prior to vaccine administration.

6.1.2 Collect demographic data:

Record demographic data such as date of birth, gender, height, weight, and ethnicity in the participant's eCRF.

6.1.3 Medical history:

Obtain the participant's medical history by interview and/or review of the participant's medical records and record any pre-existing conditions or signs and/or symptoms present in a participant prior to the first study injection in the eCRF. Information collected will include participant's COVID-19 vaccination status, including date of last vaccination and type of vaccine, if vaccinated.

6.1.4 Physical examination:

Perform a full physical examination at the screening visit or at Day 1 prior to injection; history-directed physical examination can be completed at subsequent visits. Full physical examination should include vital signs: weight, height, blood pressure, pulse rate and respiratory rate.

If the investigator determines that the participant's health on the day of injection temporarily precludes injection, the visit will be rescheduled. Collected information needs to be recorded in the eCRF.

Treatment of any abnormality observed during this examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

6.1.5 Vital Signs:

Vital signs (body temperature, blood pressure, heart rate, respiration rate) will be measured pre-vaccination and 60 minutes (+10 minutes window) post-vaccination.

6.1.6 Check contraindications, warnings and precautions to injection:

Contraindications, warnings and precautions to injection must be checked at the beginning of each injection visit on Days 1 and 28.

6.1.7 Pregnancy test:

Urine pregnancy tests must be confirmed negative at screening and prior to study vaccine administration.

6.1.8 Assess pre-injection body temperature:

The body temperature of all participants needs to be measured using the study supplied thermometer prior to any study product administration. The preferred route for this study is oral and the participant should be instructed to refrain from eating or drinking 60 minutes prior to obtaining the temperature. If the participant has a fever (defined as temperature ≥38.0°C/100.4°F oral) on the day of injection, the injection visit will be rescheduled within the allowed interval for this visit.

6.1.9 Telemedicine or home visits:

Due to the ongoing COVID-19 outbreak, growing emergency measures are being put in place to limit the spread of the outbreak, including government and institutional restrictions. These restrictions may affect how the study is conducted during this time. Possible changes, which could impact study visits include, for example, use of available technology for remote

monitoring/data collection, “virtual” study visits, electronic completion/transmission of study- related questionnaires, and/or any other changes (telephone, email or text message contact, alternative location for assessment, including local laboratories or home visits) deemed necessary until the pandemic and associated government/institutional restrictions are lifted. Some blood samples may be drawn using local lab services, and the sponsor may arrange home visits if site visits cannot occur.

6.1.10 Study group and treatment number allocation:

Participants in Phase 1a and Phase 1b will be randomized using a stratified permuted block randomization. In Phase 1a, participants aged 18 – 54 will be randomized 2:1 to receive VBI-2902a or placebo. In Phase 1b subjects aged 18-54 will be randomized 1:1 to receive VBI-2905a or placebo.

For the Phase 1b part of the study, the sites will only enroll participants who have previously received mRNA COVID-19 vaccines.

Figure 1 describes the enrollment and safety evaluation by regimen, age group, and dose-level.

6.1.11 Sampling

Serology:

- Hepatitis B surface antigen
- Hepatitis B core antibody
- Hepatitis C antibody
- Human immunodeficiency virus antibody

Hematology:

- Hemoglobin
- Hematocrit
- RBC count
- MCV
- MCH
- MCHC
- Platelet count
- WBC count
- Total neutrophils (Abs) Eosinophils (Abs)
- Monocytes (Abs)
- Basophils (Abs)
- Lymphocytes (Abs)

Chemistry:

- Creatinine
- GFR
- Total bilirubin
- AST
- ALT
- GGT
- ALP

Other:

- Urinalysis
- Urine pregnancy test (β-hCG)
- Nasopharyngeal swab for SARS-CoV-2 virus by PCR or rapid antigen test
- Nasopharyngeal swab for SARS-CoV-2 RNA sequencing/variant determination

6.1.12 Sampling Schedule

See Table 1, and Table 2Section 4 for the schedules of events.

Blood samples for human immunodeficiency virus (HIV), hepatitis B and hepatitis C: approximately 10 mL is taken at the screening visit. A positive test is exclusionary.

Nasal/nasopharyngeal swab for SARS-CoV-2 virus by PCR or rapid antigen test and viral sequencing: Nasopharyngeal swabs are taken at the screening visit and all subsequent visits. In Phase 1b, two swabs will be taken, one for SARS-CoV-2 virus testing and one to be stored frozen for potential sequencing at a later time point. A positive test at screening is exclusionary. Timepoints are as follows:

- Phase 1a: Days 1, 7, 28, 35, 56, 112, 224 and 336
- Phase 1b: Days 1, 7, 14, 28, 56, 84, 168 and 336

Blood samples for hematology/ biochemistry: approximately 6 mL of blood will be taken at the screening visit and all subsequent visits. Timepoints are as follows:

- Phase 1a: Days 1, 7, 28, 35, 56, 112, 224 and 336
- Phase 1b: Days 1, 7, 28, 56, 84, 168 and 336

Blood samples for humoral immune responses: approximately 10 mL of blood will be taken at day 1 and all subsequent visits. Timepoints are as follows:

- Phase 1a: Days 1, 7, 28, 35, 56, 112, 224 and 336
- Phase 1b: Days 1, 7, 14, 28, 56, 84, 168 and 336

Blood samples for cell-mediated immune responses: approximately 40 mL of blood will be taken at day 1 and all subsequent visits. Timepoints are as follows:

- Phase 1a: Days 1, 7, 28, 35, 56, 112, 224 and 336
- Phase 1b: Days 1, 7, 14, 28 and 336

Urine samples for urinalysis: screening and all subsequent visits. Timepoints are as follows:

- Phase 1a: Screening and Days 1, 7, 28, 35, 56, 112, 224 and 336
- Phase 1b: Screening and Days 1, 7, 14, 28, 56, 84, 168 and 336

Urine samples for pregnancy test: screening and day of vaccination. Timepoints are as follows:

- Phase 1a: Screening and Days 1 and 28
- Phase 1b: Screening and Day 1

The total amount of blood to be drawn for clinical laboratory tests and immunology evaluations is approximately 15-20 mL for screening and subsequent blood draws that do not include blood samples for cell-mediated immune responses and approximately 55-60 mL for subsequent blood draws that do include blood samples for cell-mediated immune responses.

6.1.13 Study Product Administration

After completing all prerequisite procedures prior to injection, one dose of study vaccine/placebo will be administered IM in the deltoid of either the right or left arm. The second injection in two-dose groups will be administered IM in the deltoid of the opposite arm. Reasons for participant refusal for site rotation will be documented in the eCRF. If the investigator or qualified designee determines that the participant's health on the day of administration temporarily precludes administration, the visit will be rescheduled within the allowed interval for this visit (N/A for Day 1; +/-3 days for Day 28).

Participants will be observed for 60 minutes following the administration of their injection.

Appropriate medical treatment will be readily available in case of anaphylaxis.

6.1.14 Check and Record Concomitant Medication/Injection and Intercurrent Medical Conditions

Concomitant medication/injection must be checked and recorded in the eCRF. Intercurrent medical conditions must be checked and recorded in the eCRF.

6.1.15 Recording of AEs, SAEs, and Potential Immune-Mediated Diseases

The participants will be instructed to contact the investigator/study personnel immediately should they manifest any signs or symptoms they perceive as serious (see Section 8).

At the vaccination visit, 7-day diary cards will be provided to the participant. The participant will record body temperature (oral) and any local/systemic adverse events (AEs)

(i.e., on the day of injection and during the next 6 days). The study center will contact the participant at 3 days (+/- 1 day) post-vaccination to assess participant status and to remind the participant to complete the diary cards. The participant will be instructed to return the completed diary card to the investigator/study personnel at the next study visit.

Any unreturned diary cards will be sought from the participant through telephone call(s) or any other convenient procedure. The investigator/study personnel will transcribe the collected information into the eCRF in English.

Diary cards are considered source documents.

6.1.16 Study Conclusion

The investigator will:

Review data collected to ensure accuracy and completeness Complete the Study Conclusion page in the eCRF.

The study will conclude at Day 336 (EOS). If the investigator deems appropriate to extend the participant's follow-up for medical reasons this will be discussed by the investigator with the participant.

6.1.17 Biological Sample Handling and Analysis

Samples will not be labeled with information that directly identifies the participant but will be coded with the identification number for the participant (participant number). Instructions on biological sample handling and shipping are provided in the laboratory manual.

Immune response analyses will be performed at the following laboratories: Neutralizing antibody by $PRNT_{90}$: National Research Council (Canada) Neutralizing antibody by pseudovirus microneutralization: Nexelis Spike protein and RBD ELISA: Nexelis

Cell-mediated immunity by ELISPOT and flow cytometry/ICS: VBI Sequencing of SARS-CoV-2-positive nasal/nasopharyngeal swabs will be conducted by Nexelis.

Leftover samples will not be used for research. However, additional testing on the samples may be performed for assay improvement or quality assurance related to SARS-CoV-2 vaccine development. If such testing is performed, it will be limited to immune response analyses to the SARS-CoV-2 vaccine but may be performed in additional laboratories. All samples will be destroyed or anonymized after final candidate licensure in North America. No genetic testing will be performed.

Blood testing for HIV and hepatitis B and C, and nasal swab testing by SARS-CoV-2 PCR or rapid antigen test will be performed at each local study center using accredited laboratories.

6.1.18 Hematology and Biochemistry assessments

Hematology and biochemistry assessments, urinalysis and urine pregnancy testing will be performed at the laboratory associated with each study center, as per local practice.

7 STUDY PRODUCT AND ADMINISTRATION

7.1 Description of Study Product

In the Phase 1a part of the study, VBI-2902a study vaccine will be supplied as single-use vials for intramuscular injection. Each 2mL vial contains a total volume of 0.7 mL that takes into consideration a 40% overage to assure 0.5 mL is available to be withdrawn for injection. Vaccine vials (VBI-2902a) for Phase 1a will contain spike protein antigen at 5 µg/mL and aluminum content at 0.33 mg/mL

In the Phase 1b part of the study, VBI-2905a study vaccine will be supplied as single-use vials for intramuscular injection. Each 2mL vial contains a total volume of 0.7 mL that takes into consideration a 40% overage to assure 0.5 mL is available to be withdrawn for injection. Vaccine vials (VBI-2905a) for Phase 1b will contain spike protein antigen at 5 µg/mL and aluminum content at 0.66 mg/mL

Commercially available 0.9% sodium chloride will be used as placebo. Each 10mL vial will be used for single use/subject with 1mL administration volume.

7.2 Storage Conditions

Store study vaccines VBI-2902a and VBI-2905a at 2-8°C. Do not freeze. If the study vaccine is exposed to temperatures outside the specified temperature range, all relevant data will be sent to the sponsor to determine if the affected supplies can be used or will be replaced. The affected study vaccine must be quarantined and not used until further instruction from the sponsor is received.

Protect all vaccine formulations from light.

Store 0.9% sodium chloride at room temperature.

7.3 Labeling and Packaging

The individual vials will be supplied in fiberboard boxes. Each fiberboard box will contain vaccine vials (VBI-2902a or VBI-2905a) and will be labeled in both English and French for Canadian sites.

7.4 Shipment Conditions

Study vaccines are shipped at 2-8°C. See pharmacy manual for details of shipping and monitoring conditions.

7.5 Vaccine Preparation

In the Phase 1a part of the study, participants in the single dose group (G1) and the two-dose group G2) will be injected with 1.0 mL of vaccine using 2 vials of VBI-2902a.

In the Phase 1b part of the study, participants will be injected with 1.0 mL of vaccine using 2 vials of VBI-2905a.

Doses of VBI-2902a administered in Phase 1a will include aluminum phosphate with 0.33 mg aluminum content.

Doses of VBI-2905a administered in Phase 1b will include aluminum phosphate with 0.66 mg aluminum content. The rationale for the increased dose of aluminum in Phase 1b is for ensuring stability of VBI- 2905a. Similar Alum-containing VBI-1501A eVLP formulations were stable at 2-8°C for at least 48 months.

Study participants in the placebo groups (G3 and G5) will be injected with 1.0 mL of commercially available saline (0.9% sodium chloride).

7.6 Product Accountability

The investigator is responsible for ensuring that all study vaccines received at the center are inventoried and accounted for throughout the study. Center staff must not combine contents of the study vaccine containers.

Study vaccine must be handled in strict accordance with the protocol and the container label and will be stored in a limited access area under appropriate environmental conditions.

Study vaccine will be administered at the study center by qualified health personnel. Study vaccine will be supplied only to participants participating in the study. Study vaccine may not be relabeled or reassigned for use by other participants. The investigator agrees to ensure appropriate storage requirements and medicinal product accountability and to administer the study vaccine only at the centers agreed upon with the Sponsor.

7.7 Replacement Doses

Replacement vials will be available at each study center. Each of the three separate fiberboard boxes carries up to 10 vials of VBI-2902a, 10 vials of VBI-2905a or 10 vials 0.9% sodium chloride (placebo). If a vial is compromised, the study center is to follow instructions in Section 7.8 for disposal. Replacement vials can be removed from same box as the compromised vial originated.

7.8 Return of Unused Products

Following verification of product accountability, all used vials will be destroyed and documented as per study center policy. If a vial is compromised, such as unreadable label or presence of particles in the study product, the Sponsor should be notified immediately. The vial should be photographed and placed in a labelled container. The photographs and compromised vial should be returned to the Sponsor as outlined in the pharmacy manual. At the end of the study, all unused products will be returned to the Sponsor, as outlined in the pharmacy manual.

7.9 Dosage, Preparation and Administration of Study Products by the Study Staff

On the day study participants are dosed, vials will be removed from the refrigerator. The unblinded study staff will select the vials based on the randomization code selected for each study participant and the matching letter (A, B, or C, etc.) on the vial label. The vials will be transported to the administration site by unblinded health personnel. Study vaccine may remain out of refrigeration (23°C±4°C) for no more than 3 hours. Vaccine vials which are out of refrigeration for more than 3 hours on a vaccination administration day (i.e., Day 1 or 28) will be discarded. Vaccine vials not utilized on a vaccination administration day (i.e., Day 1 or 28) will be returned to the Sponsor (see Section 7.8).

The unblinded health personnel will thoroughly mix all study vaccines by swirling the vial for 30 seconds immediately before administration. After thorough mixing, the study vaccine will be either a white to off- white, opaque/milky solution or clear to slightly turbid with no visible particles. Saline placebo will not need to be mixed and will appear as a clear, colorless liquid. The study vaccine and placebo should be visually inspected for discoloration prior to administration. The study materials should not be used if the liquid in the vials appears discolored or contains visible particles. After visual inspection, the vaccine or placebo will be covered and immediately administered. The unblinded health personnel will have no other role in the study.

The first injection will be given in the deltoid of either the right or left arm using the IM route. Subsequent injections will be administered IM in the deltoid of the opposite arm. The aluminum-based Adju-Phos™ settles quickly, therefore, the study vaccine should be administered immediately after withdrawing the 1.0- mL dose of vaccine from the vial.

Vaccine dose preparation and administration will be performed by pharmacists and vaccine administrators who are aware of treatment assignments but will have no other role in the conduct of the trial. Once the injection is completed, only study staff who are unaware of treatment assignment will interact with the study participants and will be responsible for safety and all other evaluations in the study. Access to randomization code will be strictly controlled at the study pharmacy. The study participant will not be told whether the study product they receive is the active vaccine or placebo.

7.10 Sixty Minutes Post-Immunization

The following safety observation procedures will be performed immediately following immunization with the study vaccine for all participants:

Participants will remain in the clinic for at least 60 minutes post vaccination. The observation period will include an assessment of immediate solicited local and systemic reactions. Any unusual signs or symptoms reported during the initial 60 minutes of observation will prompt continued close monitoring. Based on their condition, participants may be asked to remain in the clinic for more than 60 minutes after the immunization (reason will be recorded in source data). All data (including assessment of solicited local and systemic reactions) will be recorded in the source document during and after the post-observation period. Refer to Section 8 for assessment of AEs and/or solicited local and systemic reactions.

During the injection visit, participants will be provided Diary Cards, a measurement device template (in mm) for measuring solicited local reactions (erythema [redness] and swelling), and an oral digital thermometer for recording daily temperature (in °C). The participants will be:

- Instructed how to examine swelling in the neck and axilla and record any unusual feeling and/or swelling in their Diary Cards.
- Requested to record their individual data in their Diary Cards, as described above.
- Advised that they will be asked about the occurrence of any symptoms or events requiring medical attention and the use of concomitant medication up to Day 336.
- Informed that they should bring their Diary Cards to the next visit after vaccination. The staff will review the Diary Cards entries with the participant.
- Advised on how to contact study personnel. Participants will be advised to immediately contact the investigator (or his/her designee), in the event of an SAE or change in health.
- Informed to notify their health care professional(s) (e.g., primary care physician) that they are participating in a clinical research study of a SARS-CoV-2 vaccine.

Measurement of vital signs (including blood pressure, heart rate, respiration, and oral temperature). Vital signs will be taken after 60 minutes (+ 10 minutes window) (with the participant in a seated position as per study center standard procedure. Any out-of-range

measurements will be assessed by the investigator (or his/her designee) and any further action will be determined upon his/her medical decision.

Discuss appointments (date and time) for the next planned visits to the study center. Also provide phone contact.

7.11 Contraindications to Administration of the Product

The following events constitute contraindications to administration of the study products at that point in time; if any of these events occur at the time scheduled for injection, the participant may be injected at a later date, within the time window specified in the protocol (+/-3 days for Day 28 administration), or withdrawn at the discretion of the investigator.

Acute disease and/or fever at the time of administration. Fever is defined as temperature ≥ 38.0°C /100.4°F oral.

Participants with any signs or symptoms consistent with COVID-19 illness (as described in the Section 4.2) should not receive the study vaccine.

7.12 Concomitant Medications/Products and Concomitant Administration

At each study visit, the investigator should obtain information from the participant about any medication/product/vaccine taken/received by the participant.

7.13 Recording of Concomitant Medications/Products of Concomitant Administration

The following concomitant medications/products/vaccines must be recorded in the eCRF if administered during the indicated recording period:

- All concomitant medications/products, except vitamins and dietary supplements, administered from injection up to study end.
- Any concomitant vaccination administered in the period starting from screening up to study end.
- Prophylactic medication (i.e., medication administered in the absence of ANY symptom and in anticipation of a reaction to the injection).

  For example, an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring [fever is defined as temperature ≥ 38°C oral]. Any concomitant medication/product/vaccine relevant to a Serious Adverse Event (SAE) or administered at any time during the study period for the treatment of an SAE.

7.14 Concomitant Medications/Products/Vaccines That May Lead to the Elimination of a Participant from Per-Protocol Cohort (PPC) Analyses

The use of the following concomitant medications/products/vaccines will not require withdrawal of the participant from the study but may determine a participant's evaluability in the PPC analysis:

- Any investigational or non-registered product (drug or vaccine) other than the study product(s) used during the study period.

- A vaccine not foreseen by the study protocol administered during the period starting from 28 days before injection and ending 28 days after injection. It should be noted that in case of a personal indication (such as tetanus vaccination after potential exposure) or an emergency mass vaccination for an unforeseen public health threat (e.g., a pandemic) is organized by the public health authorities, outside the routine immunization program, the time period described above can be reduced if necessary for that vaccine provided it is authorized by the appropriate regulatory authorities and used according to its Summary of Product Characteristics or Product Insert and according to the local governmental recommendations. The Sponsor is to be notified of any immunizations received; all vaccinations are to be captured in the participant's eCRF.
- Immunosuppressants or other immune-modifying drugs administered chronically (i.e., more than 14 days) during the study period (for corticosteroids, this will mean prednisone ≥ 20 mg/day, or equivalent).
- Receipt of inhaled/nebulized corticosteroids from 28 days prior to enrollment to Visit 5 (Day 56).
- Long-acting immune-modifying drug administered at any time during the study period (e.g., Infliximab).
- Immunoglobulins and/or any blood products administered during the study period.
- Receipt of blood/plasma products or immunoglobulins within 60 days before enrollment through conclusion of the study.

7.15 Prohibited During the Study

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis from that point onwards, and may require vaccinations to be discontinued in that participant; however, it is anticipated that the participant would not be withdrawn from the study. Medications should not be withheld if required for a participant's medical care.

- Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after each study vaccination. One exception to this is that seasonal and pandemic influenza vaccine can be given at least 14 days after, or at least 14 days prior to, the administration of study intervention.
- Receipt of chronic systemic treatment with known immunosuppressant medications, or radiotherapy, within 60 days before enrollment through conclusion of the study.
- Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment through conclusion of the study.
- Receipt of inhaled/nebulized corticosteroids from 28 days prior to enrollment through conclusion of the study.
- Receipt of blood/plasma products or immunoglobulins within 60 days before enrollment through conclusion of the study.

- Prophylactic use of antipyretics and other pain medication to prevent symptoms associated with study vaccination are not permitted. However, if a study participant is taking a medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

7.16 Permitted During the Study

- Medication other than that described as prohibited in Section 7.15 required for treatment of pre-existing stable conditions is permitted.
- Topical, or localized injections of corticosteroids (e.g., intra-articular or intra-bursal administration) are permitted.

7.17 Intercurrent Medical Conditions That May Lead to Elimination of a Participant from Per-Protocol Cohort (PPC) Analyses

At each study visit subsequent to the injection visit, it must be verified if the participant has experienced or is experiencing any intercurrent medical condition. If it is the case, the condition(s) must be recorded in the eCRF.

Participants may be eliminated from the Per-Protocol Cohort analysis for immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response or if they become diagnosed with an immunological disorder.

8 ADVERSE EVENT REPORTING

8.1 Safety Definitions

Adverse Event (AE):

Any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product whether or not related to the medicinal (investigational) product

Examples of an AE include but are not limited to:

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration even though they may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with product administration.
- Failure of expected pharmacological or biological action.
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of participant's previous therapeutic regimen).

Examples of an AE DO NOT include:

- Medical or surgical procedures not related to study procedures (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE/SAE.
- Situations where an untoward medical occurrence did not occur (e.g., social and/or convenience admission to a hospital, admission for routine examination).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Pre-existing conditions or signs and/or symptoms present in a participant prior to the first study injection. These events will be recorded in the medical history section of the eCRF.

If any of the solicited local or systemic reactions persist beyond Day 7, these will also be recorded as an AE. In this case, the AE start will be set as 7 days post vaccination. The participant will be requested to note when the AEs resolves and report this information to the investigator or clinic staff at the next visit at the study center or contact.

The clinical importance of AE will be determined based upon the investigator's judgment. The investigator must ensure that any sample obtained to follow-up an AE is properly labeled and stored. The investigator and others responsible for care of the participants should institute any supplementary investigations of significant AEs based on the clinical assessment of the likely causative factor. This may include seeking the opinion of a specialist in the field of the AE.

All AEs occurring within 28 days after vaccination must be recorded in the study source documents at the site or Diary Cards and reported in the "Adverse Event" screen in the participant's eCRF, irrespective of intensity or whether or not they are considered vaccination-related. Thereafter, from Day 28 through completion of the Day 336 visit, participants will need to record all AEs in their Diary Cards. Adverse events, pregnancy and SAEs will be monitored and recorded in the eCRF. Serious adverse events and pregnancy will be reported to Pharmacovigilance.

Treatment Emergent Adverse Event (TEAE)

TEAE is an event that emerges during treatment having been absent pre-treatment, or worsens relative to the pre-treatment state (ICH E9). The period of observation for collection of TEAEs extends from the time the participant receives the first dose of study drug through the last study visit.

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.

Serious Adverse Event (SAE)

During clinical investigations, adverse events may occur which, if suspected to be medicinal product related (adverse drug reactions), might be significant enough to lead to important changes in the way the medicinal product is developed (e.g., change in dose, population, needed monitoring, consent forms).

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning.

Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. An SAE is any untoward medical occurrence that *at any dose*:

- Results in death
- Is life-threatening

  Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.

- Requires hospitalization or prolongation of existing hospitalization

  Note: In general, hospitalization signifies that the participant has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an out-patient setting. Complications that occur during hospitalization are also considered AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

- Hospitalization for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an AE.

- Results in disability/incapacity

  Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza like illness, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital abnormality/birth defect in an offspring of a study participant Is another medically important event

Medical judgment should be exercised in deciding whether 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 participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also 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.

8.2 Solicited Local and Systemic Reactions

The intensity of the solicited local and systemic reactions will be graded as: (1) mild, (2) moderate, (3) severe, or (4) potentially life threatening (Table 4). Their causal relationship with the study vaccine will be assessed by the investigator (definitely not related, probably not related, possibly related, probably related or definitely related). The solicited local and systemic reactions will be measured and reported by each study participant from the time of study vaccine administration up to seven days post vaccination.

Any AE/SAEs, any signs, symptoms or diseases experienced by the participant following the signature of the informed consent but before administration of the vaccine will be recorded in source data as pre- dose events (as a part of participants' medical history).

For any unsolicited AEs greater than Grade 2 (moderate), the participant should inform the investigator within 48 hours of the time of the event. The investigator may request that the participant return to the clinic for evaluation. The investigator will document the review and follow-up of such events on the source document.

Any clinical laboratory test result that meets the criteria for an AE in the absence of appropriate and/or adequate clinical diagnosis should be reported as an AE, unless the result is considered normal or not clinically significant for the current trial participant population, as determined by the Investigator.

Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events

In absence of diagnosis, abnormal laboratory findings (e.g., clinical chemistry, hematology, urinalysis) or other abnormal assessments (e.g., physical examination findings) that the investigators judge to be clinically significant will be recorded as AE or SAE if they meet the definition of an AE or SAE. Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs. The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

8.3 Pregnancy Reporting

Participants who become pregnant during the study will be followed for safety. The investigator, or his/her qualified designee study center staff, will collect pregnancy information on any participant who becomes pregnant while participating in this study. The investigator or his/her qualified study center staff designee will record pregnancy information on the Pregnancy Report Form and submit it to the pharmacovigilance (PV) group at the study clinical research organization (CRO) within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to the Sponsor Safety Contact. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date.

While pregnancy itself is not considered an AE/SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or an SAE, and will be followed. A spontaneous abortion is always considered to be a SAE and will be reported. Furthermore, any SAE occurring as a result of a post-study pregnancy and considered reasonably related in time to receipt of the investigational product by the investigator, will be reported to the Sponsor Safety Contact. While the investigator is not obligated to actively seek this information from former study participants, he/she may learn of a pregnancy through spontaneous reporting. Information on pregnancies identified during the screening phase/prior to vaccine administration do not need to be collected; this information need not be communicated to the Sponsor.

The following events are considered SAEs related to pregnancy:

- spontaneous abortion (spontaneous pregnancy loss before 20 weeks gestation) or resulting in a fetus weighing less than 500 grams (Reproductive Care Program of Nova Scotia)
- ectopic and molar pregnancy
- stillbirth, defined as the complete expulsion or extraction from its mother after at least 20 weeks pregnancy, or after gaining a weight of 500 grams or more, of a fetus in which, after such expulsion or extraction, there is no breathing, beating of the heart, pulsation of the umbilical cord, or unmistakable movement of voluntary muscle.
- any early neonatal death (death of a liveborn infant within seven days of life)
- any congenital anomaly or birth defect identified in the offspring of a study participant at pregnancy, birth or later, regardless of whether fetus is alive or dead at birth

8.4 Detecting and Recording AEs and SAEs

Time period for detecting and recording adverse events and serious adverse events

All AEs starting after signing of the informed consent must be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered injection-related.

In order to avoid vague, ambiguous or colloquial expressions, the AE should be recorded in standard

medical terminology rather than the participant's own words. Whenever possible, the investigator should group together into a single term signs and symptoms which constitute a single diagnosis. Each AE is to be evaluated for duration, severity, seriousness and causal relationship to the investigational drug. The severity of the AE and its relationship to the test product will be assessed by the investigator. All participants who have an AE or SAE or have withdrawn early from the study due to an AE or SAE will be followed until resolution/stabilization as determined by the investigator or Sponsor or until the participant is lost to follow-up. All follow up data will be documented on the eCRF.

The time period for collecting and recording SAEs will begin at the first receipt of study vaccine/placebo and will end one year post first dose for each participant.

All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time of the first receipt of study vaccine/placebo. All SAEs will be collected and recorded from the time of the first receipt of study vaccine/placebo until the participant is discharged from the study.

In addition to the above-mentioned reporting requirements and in order to fulfill reporting obligations, SAEs that are related to study participation (i.e., protocol-mandated procedures, invasive tests, a change from existing therapy) will be collected and recorded from the time the participant consents to participate in the study until she/he is discharged from the study.

Post-Study adverse events and serious adverse events

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period (post Day 336). Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the investigational product/product, the investigator will promptly notify the PV Group at the study CRO or directly to the Sponsor in the event of study completion and study center closure.

8.5 Evaluation of Adverse Events and Serious Adverse Events

Active questioning to detect adverse events and serious adverse events

As a consistent method of collecting AEs, the participants should be asked a non-leading question such as:

'Have you acted differently or felt different in any way since receiving the product or since the last visit?'

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in the eCRF and participant diary (and completed SAE/pregnancy reporting form if required) and send it to the PV Group at the study CRO.

The investigator will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, laboratory tests, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

8.6 Assessment of Adverse Events

Each AE is to be evaluated for duration, severity (intensity), outcome, and causal relationship to the investigational drug.

The investigator will assess the maximum intensity that occurred over the duration of the event for all AEs (including SAEs) recorded during the study. The assessment will be based on participant reporting, the investigator's clinical judgment and FDA Guidance for industry (Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical studies, September 2007) and presented in Table 5, Table 6 and Table 7.

The intensity of each sign or symptom reported will be graded using the 4-point severity scale shown in Table 4.

Table 4: Severity Scale

Grade 1 (Mild)	No interference with daily activity
Grade 2 (Moderate)	Some interference with daily activity but not requiring medical intervention
Grade 3 (Severe)	Prevents daily activity and requires medical intervention
Grade 4 (Potentially life threatening)	Requiring Emergency Room (ER) visit or hospitalization

Table 5: Toxicity Grading Scale for Solicited Local Adverse Events

Solicited Local AE	Grade 1	Grade 2	Grade 3	Grade 4
Pain (pain without touching)	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness (pain when area is touched)	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Pruritus associated with injection See also skin: pruritus (itching - no skin lesions)	Itching localized to injection site AND relieved spontaneously or with <48 hours treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA
Erythema/Redness[a]	2.5–5 cm	5.1–10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling[b]	2.5–5 cm and does not interfere with activity	5.1–10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

Abbreviations: AE=adverse event; NA=not applicable

[a] In addition to grading the measured local reaction at the greatest single diameter, the measurement was recorded as a continuous variable.

[b] Induration/Swelling was evaluated and graded using the functional scale as well as the actual measurement. Source: (US Food and Drug Administration 2007)

Table 6: Toxicity Grading Scale for Solicited Systemic Adverse Events

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1-2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 - 3 loose stools or < 400 g/24 hours	4 - 5 stools or 400-800 g/24 hours	6 or more watery stools or >800 g/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Abbreviations: ER=emergency room; IV=intravenous Source: (US Food and Drug Administration 2007)

Table 7: Toxicity Grading Scale for Solicited Other Adverse Events

Vital Signs	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Fever[a] (°C) ** (°F) *	 38.0–38.4 100.4–101.1	 38.5–38.9 101.2–102.0	 39.0–40 102.1–104	 >40 >104
Tachycardia – beats/min	101–115	116–130	>130	ER visit or hospitalization for arrhythmia
Bradycardia – beats/min[b]	50–54	45–49	<45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141–150	151–155	>155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91–95	96–100	>100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85–89	80–84	<80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths/min	17–20	21–25	>25	Intubation

Abbreviations: ER=emergency room.
Note: Subject were at rest for all vital sign measurements

[a] Oral temperature; no recent hot or cold beverages or smoking
[b] When resting heart rate was between 60-100 beats per minute. Clinical judgment was used when characterizing bradycardia among some healthy subject populations, eg, conditioned athletes Source: (US Food and Drug Administration 2007)

Assessment of causality

The investigator must make the determination of relationship to the study vaccine for each AE/SAE. Solicited local reactions are assumed to be related to study drug. The investigator should decide whether, in his/her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational vaccine. If there is any valid reason, even if undetermined or untested, for suspecting a possible cause and effect relationship between the investigational vaccine and the occurrence of the AE,

then the AE should be considered “definitely”, “probably”, “possibly”, “unlikely”, or “unrelated”.

The investigator will review each event and assess its relationship to drug treatment using the criteria in Table 9.

Table 8: FDA Guidance for Grading Clinical Laboratory Abnormalities

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

Conversion factors to SI units will be provided to the clinical sites.

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	100 – 110 110 – 125	111 – 12 126 – 200	>125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1–10 xULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

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

***ULN is the upper limit of the normal range.

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

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

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

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

Table 9: Assessment Criteria

Term	Assessment Criteria	Description
Definitely	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenological (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon) • Re-challenge (response to drug re-administration) satisfactory, if necessary	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary.

Term	Assessment Criteria	Description
Probably	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Re-challenge not required	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfil this definition.
Possibly	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
Unrelated	• The adverse event is clearly not related to the investigational agent/procedure.	Another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.

Assessment of outcomes

The investigator will assess the outcome of all AEs (including SAEs) recorded during the study as:

- Ongoing
- Recovered/resolved
- Recovered/Resolved with sequelae
- Recovering/Improving
- Stabilized
- Unknown/Lost to Follow-up
- Fatal (SAE)

Medically attended visits

For each symptom the participant experiences, the participant will be asked if the participant received medical attention defined as hospitalization, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. This information will be recorded in the eCRF.

8.7 Reporting of Serious Adverse Events and Other Events

The Sponsor has a legal responsibility to promptly notify appropriate regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the Study Contact for Reporting SAEs is essential so that legal obligations and ethical responsibilities towards the safety of other participants are met. The purpose of the report is to fulfill specific regulatory and GCP requirements, regarding the product under investigation. All of these notifications will occur within 24 hours of the investigator becoming aware of the SAE.

For reporting of a SAE or pregnancy, the investigator shall use the designated SAE or pregnancy report form. Occurrence of any SAE/pregnancy must be reported immediately (within one working day) once the investigative study center has knowledge of the event.

If an SAE or pregnancy occurs to a participant during this study, the SAE report and relevant medical records should be sent (within 24 hours) to the contact listed below (Table 10).

Table 10: Timeframes for Submitting Serious Adverse Event and Other Event Reports

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	**Documents**	**Timeframe**	**Documents**
SAEs	24 hours*	SAE report	24 hours*	SAE report
Pregnancy	24 hours**	Pregnancy report form	24 hours*	Pregnancy report form

*Timeframe allowed after receipt or awareness of the information.

**Timeframe allowed after the diagnosis is established and known to the investigator

Contact information for reporting serious adverse events

Francisco Diaz-Mitoma, MD, PhD

Chief Medical Officer, VBI Vaccines Inc. Tel: 1.613.297.3304

Email: fdiazmitoma@vbivaccines.com

Completion and transmission of SAE reports

Once an investigator becomes aware that a SAE/ pregnancy has occurred in a study participant, the investigator (or qualified study center designee) must complete the information in the SAE/pregnancy report as thoroughly as possible with all available details of the event, WITHIN 24 HOURS. Even if the investigator does not have all information regarding a SAE, the report should still be completed within 24 hours and be appropriately documented in the eCRF. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS.

8.7.1 Unblinding

Blinding will be guaranteed by the preparation of the study vaccine by an unblinded pharmacist or other qualified study-site personnel with primary responsibility for study vaccine preparation. Participants will be randomly assigned to groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor and using the IWRS.

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual participant.

Data that may potentially unblind the study vaccine assignment (e.g., immunogenicity data, study vaccine accountability data, study vaccine allocation, biomarker, or other specific laboratory data) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

Each phase of the study will be unblinded after DSMB review of safety data collected through Day 56. Some key personnel of the sponsor, not involved in study operations, may be unblinded at the time of Study Steering Committee analysis. The investigator may in an emergency determine the identity of the intervention by contacting the IWRS. While the responsibility to break the intervention code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee if possible, to discuss the particular situation, before breaking the blind.

Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented in the IWRS and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

Participants who have had their intervention assignment unblinded should continue to return for scheduled evaluations. Participants should not be allowed to receive further study vaccinations and are only to be followed for safety evaluation visits.

8.7.2 Reporting of SAEs to Health Authorities and REC/REB

The study CRO will be responsible for reporting expedited and non-expedited SAEs that are deemed possibly related to study vaccine and unexpected (unexpected refers to events that do not appear in the package labeling or in the study vaccine IB) to regulatory authorities.

The investigator will be responsible for reporting all SAEs directly to the relevant ethical review body (REC/REB) as soon as possible, and will also provide the ethical review body with any safety reports prepared by the PV group at the study CRO.

All SAEs that are considered SUSAR should be reported to Regulatory Authorities by phone or by facsimile transmission as soon as possible but in no event later than seven calendar days for deaths and life- threatening adverse events and 15 calendar days for other SAEs after the Sponsor's initial receipt of the information; and should be followed to resolution, stabilization, or return to baseline regardless of conclusion of the study.

8.8 Follow-up of AEs and SAEs

Follow-up during the study

After the initial SAE report, the investigator is required to proactively follow each participant and provide additional relevant information by completing an SAE Reporting Form (Follow-up report) on the participant's condition to the PV group at the study CRO.

All SAEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the end of the study.

All AEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until Day 336 (EOS).

With the exception of medically attended adverse events (MAAEs), all AEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until Day 336 (EOS).

Follow-up after the participant is discharged from the study

The investigator will follow participants:

- with SAEs or participants withdrawn from the study as a result of an AE, until the event has resolved, subsided, stabilized, disappeared, or until the event is otherwise explained, or the participant is lost to follow-up.
- with MAAEs until the end of the study or the participants are lost to follow-up.
- with other non-serious AEs, until Day 336 (EOS) or they are lost to follow-up.

If the investigator receives additional relevant information on a previously reported SAE, he/she will provide this information to the PV Group at the study CRO (via 24/7 Safety Line) by completing a paper SAE Pregnancy Reporting Form, as applicable.

The PV Group or Medical Director at the study CRO may request that the investigator performs or arranges the conduct of additional clinical examinations/tests and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obliged to assist. In the event of a participant's death during participation in the study or during a recognized follow-up period, the PV Group at the study CRO will be provided with any available post-mortem findings, including histopathology.

8.9 Treatment of Adverse Events

Treatment of any AE is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of an AE should be recorded in the participant's *eCRF.*

Participant card

Study participants must be provided with the address and telephone number of the main contact for information about the clinical study.

The investigator (or qualified designee) must therefore provide a "participant card" to each participant. In an emergency situation this card serves to inform the responsible attending physician that the participant is in a clinical study and that relevant information may be obtained by contacting the investigator.

The participant card will indicate the following:

- Study name
- Study number
- Participant number
- Investigator's name and 24-hour contact telephone number
- Back-up phone number in case investigator is unavailable
- Enrollment date
- Expected study duration
- Any other information that is required to do an emergency breaking of the blind

Participants must be instructed to keep participant cards in their possession at all times.

9 PARTICIPANT COMPLETION AND WITHDRAWAL

9.1 Study Completion

A participant who returns for the End-of-Study Visit is considered to have completed the study.

9.2 Study Vaccine Discontinuation

In rare instances, it may be necessary for a participant to permanently discontinue study vaccination. Reasons for vaccine discontinuation may include the following:

- Non-serious AE / SAE
- Positive SARS-CoV-2 (PCR or rapid antigen test)
- Participant request
- Investigator request
- Pregnancy
- Protocol deviation (including no longer meeting all the inclusion criteria, or meeting 1 or more exclusion criteria)
- Other (specify)

Note that discontinuation of study intervention does not represent withdrawal from the study. If study vaccination is permanently discontinued, the participant will remain in the study to be evaluated for safety, immunogenicity, and efficacy.

9.3 Study Discontinuation

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study may include the following:

- Refused further follow-up
- Lost to follow-up
- Death
- Study terminated by sponsor
- Non-serious AE / SAE
- Participant request
- Investigator request
- Protocol deviation.
- Other (specify)

If a participant does not return for a scheduled visit, every effort should be made to contact the participant. All attempts to contact the participant and information received during contact attempts must be documented in the participant's source document. In any circumstance, every effort should be made to document participant outcome, if possible.

Participants who are withdrawn because of SAEs/AEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigators will follow participants who are withdrawn as result of a SAE/AE until resolution of the event.

Withdrawals will not be replaced.

10 STATISTICAL METHODS

10.1 Outcome Measures

10.1.1 Primary Endpoints/Outcome Measures

Rate and severity of local and systemic solicited adverse events (AEs) during 7 days after each study vaccination

Rate and severity of unsolicited AEs at Study during 28 days after each study vaccinations

Rate and severity of medically attended adverse events (MAAEs) during 28 days after each study vaccinations

Rate of serious adverse events (SAEs) during 28 days after each study vaccinations AEs leading to discontinuation of study vaccination

AEs leading to study discontinuation

Rate and severity of laboratory abnormalities (hematology, biochemistry, urinalysis) at Day 56 and 28 days after each study vaccination

10.1.2 Secondary Endpoints/Outcome Measures

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 56 and 224 (Phase 1a) or Days 56 and 168 (Phase 1b):
  - Neutralizing activity against multiple variant spike protein-expressing pseudovirus, and/or PRNT neutralizing activity against wild-type SARS-CoV-2 virus and the variant Beta (B.1.351) in all participants
  - RBD antibody titers against wild-type variant spike protein measured by ELISA
- 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); Days 7, 14, 28, 56, 84, 168 and 336 (Phase 1b)
  - Neutralizing activity against multiple variant spike protein-expressing pseudoviruses, and/or PRNT neutralizing activity against multiple variants of SARS-CoV-2 virus and the variant (B.1.351) in all participants
  - RBD antibody titers against wild-type variant spike protein measured by ELISA

10.2 Determination of Sample Size

A total of approximately 60 participants will be enrolled in Phase 1a and approximately 54 participants in Phase 1b. The participants in Phase 1a will be randomized at 2:1 to VBI-2902a or placebo. Participants in Phase 1b will be randomized 1:1 to receive one dose of VBI-2905a or placebo.

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 nAb titers with 80% power and an alpha error of 0.05.

10.3 Immune Responses

Neutralizing antibody titers and binding antibody titers directed against the spike protein and its RBD region as well as cell-mediated immunity will be measured. This study is a first-in-humans study. Any immunogenicity results are intended to be exploratory and as such, no formal power calculation is reported.

10.4 Randomization

Treatment allocation for Phase 1a and Phase 1b will be done through an interactive response technology (IRT) system (interactive web response system, IWRS). Access to the IWRS will be through individual login and password. To enroll a new subject, the authorized staff at the site will be prompted to complete a randomization page including the subject's age, and other demographic information and to confirm individually the presence of all inclusion criteria, and the absence of all exclusion criteria. Upon confirmation that all inclusion criteria and no exclusion criteria are met the subject will be randomized. Blinded confirmation of the randomization will be sent by E-mail to the site and should be retained in the study files. The site pharmacy and/or unblinded study center staff will receive a notification for a unique subject randomization assignment, which must be filed in a locked area/computer folder not accessible by blinded study center staff. Specific instructions for use of the IWRS will be provided separately.

Randomization numbers will NOT be reused for any reason.

10.5 Analysis Cohorts

The All-Enrolled-Cohort (AEC) 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.

The Intent-To-Treat (ITT) cohort includes all participants in the AEC who were randomized.

The Safety-Cohort (SC) will include the 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.

The Immunogenicity Cohort (IMC) will include all participants from the AEC who received the prescribed study vaccine or placebo and underwent at least one immunogenicity assessment after vaccination.

The Per-Protocol-Cohort (PPC) for will include all participants who meet all eligibility criteria, for whom the administration route and site of vaccine was according to protocol, have evaluable serum immunogenicity samples at baseline and at the time points of interest, were SARS-CoV-2 negative at baseline and had no major protocol deviations (PD) leading to exclusion. A major PD leading to exclusion from the PPC is defined as a PD that is considered to have a significant impact on the immunogenicity results. These will be identified prior to unblinding and analysis and may include:

- participants enrolled who did not meet study entry criteria
- participants who did not receive the correct study vaccine
- participants who developed withdrawal criteria but were not withdrawn
- participants who received a prohibited concomitant medication

10.6 Statistical Analyses

Statistical analysis of data will be performed as described in the Statistical Analysis Plan.

10.6.1 Baseline Comparability

The baseline distribution of treatment groups will be assessed descriptively.

10.6.2 Safety Analysis

The safety analysis will be performed on all participants receiving at least one dose of the study vaccine/placebo (the safety population). Safety will be evaluated using the participants' recorded safety observations (Diary Cards), reports of AEs, SAEs, or pregnancy, reports of significant health events, physical examination findings, clinical laboratory results, vital signs, and concomitant medication use.

The local and general AEs/SAEs will be evaluated using FDA Guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical studies and causality assessment scale (see Sections 8.5 and 8.6).

The verbatim terms used in the eCRFs by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All eCRF-reported AEs with onset post-immunization will be included in the analysis. For each AE, the percentage of participants who

experienced at least one occurrence of the given event will be summarized by treatment group and age stratum.

Special attention will be given to those participants who died, who discontinued study due to an AE, or who experienced a severe or a serious adverse event (e.g., summaries, listings, and narrative preparation may be provided, as appropriate) or experience an allergic or allergic-like reaction.

An aggregate event "Any" will be defined as the maximal severity of the combined events "Local" and "General".

Fisher's Exact Test will be used to assess differences in rates of solicited adverse events between treatment groups. All statistical tests performed will be 2-sided with Type I error of 5%. No adjustments will be made for multiplicity of tests performed.

In addition, all safety data will be analyzed descriptively. All of the information captured on the participants' Diary Cards will be presented by participant in the data listings.

Descriptive statistics for selected laboratory parameters will be presented by treatment group.

10.6.3 Planned Interim Report

A planned interim report will be based on immunological testing and summary safety assessment up to and including Day 56, following unblinding of the study.

10.7 Safety Monitoring and Study Stopping 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.

Study randomization and further vaccinations will stop if 2 or more participants receiving VBI-2902a or VBI-2905a meet stopping rules unless the DSMB and study sponsor and site investigators review the safety data, and in consultation with the appropriate regulatory authorities, 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.

10.7.1 Safety Evaluation

Safety and tolerability endpoints (solicited local and systemic reactions, AEs/SAEs, physical examination findings, clinical laboratory results, and vital signs) will be tabulated. Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

Participants will be monitored throughout the study for adverse reactions to the study formulations and/or procedures. The participants will be instructed to inform the study physician and/or study staff of any AEs that may occur at any time during the study. Periodically during the study, after the participant has had an opportunity to spontaneously mention any problems, the investigator or qualified designated study center staff may inquire about how the participant is feeling.

All AEs and SAEs will be followed until they are resolved (return to normal or baseline values), unless: 1) they are judged by the investigator to be no longer clinically significant, 2) the investigator attributes the AE/SAEs to a cause other than the study drug or assesses them as chronic or stable, or 3) the participant is lost-to follow-up. Supplemental measurements and/or evaluations may be necessary to fully investigate the nature and/or causality of an AE or SAE. This may include laboratory tests, diagnostic procedures or consultation with other healthcare professionals. If the participant dies, any post-mortem findings (including histopathology) must be provided to the Sponsor or designee. In addition, the designated Medical Monitor may request blood tests, diagnostic imaging studies or specialist physician consultations in order to further evaluate any AE or abnormality considered to be potentially clinically significant.

The following information regarding each AE will be obtained: date of onset and resolution (duration), intensity, whether the event was serious, any required treatment or action taken, outcome, relationship to the investigational vaccine, and whether the AE caused withdrawal from the study.

Standard clinical parameters have been identified for evaluating the safety of a biologic/vaccine product including standardized methods for local and systemic vaccine reactions classified by severity within predefined categories, repeated vital signs and physical examinations, 12 month follow-up (assuming 28 days per month) for adverse events (at least six months after Dose 3) and concomitant medication changes, monitoring of clinical chemistries (liver and renal function), urinalysis, and hematology as clinically indicated.

The DSMB will perform safety evaluations using blinded data. In cases that require further safety assessment, the DSMB can request to be unblinded as to participant treatment group. The DSMB will be comprised of five individuals in total, including four physicians familiar in the conduct of vaccine-related clinical trials and safety measures, as well as a biostatistician, who are not otherwise involved in the conduct of the project. The DSMB will review safety data from this study, while taking into account any other findings that could have an impact on the safety of the participants, and will determine whether there is a safety signal or not.

10.7.1.1 Outcome of the Safety Evaluation

A safety evaluation of data from Phase 1a through Day 56 will be performed before initiating Phase 1b. If **no safety signal** is observed, the favorable outcome of the safety evaluation will be documented and provided in writing, authorizing the investigator to start injection of participants in the next part of the study.

If a **safety signal** is observed during the safety evaluation or if the investigator reports any of the holding rules, the DSMB chair is responsible for the urgent communication and escalation of the concern to the Sponsor who will decide during an *ad hoc* meeting whether to suspend, modify or continue the conduct of the study on all groups or on selected groups. The decision of the Sponsor will be documented and provided in writing to the investigators regarding the further conduct of the study, process of suspension of injection and/or study modification

In the event that a safety signal is observed, the Sponsor might decide to cancel injection of all groups or selected groups.

In this case, for impacted groups:

- Participants who are already injected will continue all visits as planned.
- Participants who signed an informed consent but have not received any study product will be informed that their study participation will be stopped.

11 REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with all regulatory requirements. The study will be conducted in accordance with the latest version of the Declaration of Helsinki, GCP, ICH regulatory guidelines, and requirements regarding ethical committee review, informed consent, and other statutes and regulations regarding the protection of the rights and welfare of participants participating in the study.

The protocol, including the informed consent document and all recruiting materials, will be submitted by the investigator to the local REC /REB for review and approval. These RECs/REBs are constituted in conformance with regulations of the appropriate regulatory authorities. A copy of the REC's/REB's letter of approval for the study will be kept at the study center along with a copy of the informed consent form approved by the REC/REB for the study.

No changes will be made to the protocol without REC/REB approval, except where necessary to eliminate apparent immediate hazards to participants.

Participants will be able to withdraw their consents to participate at any time without giving a reason and with assurance that their care will not be affected in any way. The investigators may withdraw a participant if, in the investigator's clinical judgment, it is in the best interest of the participant or if the participant is unable to comply with study requirements.

11.1 Benefits/Potential Risks

A complete description of the potential risks and benefits can be found in the informed consent document and IB.

11.2 Informed Consent Process and Documentation

The investigator or designate will be responsible for presenting a full description of the research project including risks/benefits and how personal health information may be used and disclosed in research. A written informed consent/authorization will then be obtained from the participant prior to the screening procedures and injection. The investigator or designate will also be responsible for maintaining up-to- date records of the consent forms and providing a copy to the participant.

Participants will be encouraged and will have ample opportunity to have their questions answered before and after consenting to participate.

11.3 Modification of the Protocol

No modifications of the protocol may be made by study personnel without consultation with the Sponsor and the investigator. Any protocol amendment will be submitted to the local REC/REB and investigators at all study centers will submit any protocol amendments to the REC/REB at each center for approval.

11.4 Interruption of the Trial

Stopping rules and early termination criteria are described in Section 10.7 Safety Monitoring and Study Stopping Rules.

11.5 Confidentiality of Data and Access to Participant Records

Confidentiality will be maintained within legal limits in the review of medical records and consent forms, which may contain the identity of the participant. Such records will be coded only with the participant‘s initials and study number.

12 MONITORING

The study will be monitored by the study CRO according to GCP. Monitors will follow the CRO SOP for clinical trial monitoring.

The monitor will ensure that all participants have been enrolled according to the protocol and that informed consent has been obtained prior to any study procedure. Monitors will review the study files, the participant files, source documents, eCRFs, any SAE forms, as well as the product logs and laboratory records to ensure that the study is being conducted according to the protocol and GCP. All eCRFs will be reviewed by the monitor.

The study will be monitored once the first participant has been enrolled, during the study at appropriate intervals, and after the last participant has completed the study. The monitoring visit schedule will be determined by the monitor and investigator based on the frequency of enrollments and follow-up visits.

12.1 Auditing

Audits or inspections may be made by the REC/REB to ensure that the study has been conducted in accordance with the protocol, appropriate regulatory authority regulations, and ICH/GCP. Audits may also be performed by appropriate regulatory authorities, at their discretion.

12.2 Archiving

The investigators will retain all source documents and study records at the study center, including consent forms and copies of case report forms for 25 years after completion of the study.

12.3 Stipends for Participation

Participants will be provided a stipend according to local practice to compensate for their time and travel required for each visit to the study center.

12.4 Adverse Event Compensation and Insurance

In the occurrence of an adverse event, the participant will be evaluated and treated by the investigators in accordance with local regulations. No additional form of compensation is available.

12.5 Publication Policy

Study result manuscripts will be prepared by the Principal Investigator and reviewed by all co-investigators and the Sponsor and submitted to peer-reviewed journals and scientific meetings within 24 months of the last study visit. The Sponsor reserves the right to review any manuscript or abstract 45 days prior to submission. The Sponsor will also be responsible for all study-related press releases, with opportunity for the Principal Investigator and all co-investigators to review prior to release.

13 ADMINISTRATIVE MATTERS

To comply with ICH GCP administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality and publications must be fulfilled.

13.1 Data Entry instructions

Data entry will be done by the Qualified site designee. Clinical data management will be performed at the study CRO following CRO SOP standards and data cleaning procedures and under the supervision of the Data Manager.

While completed eCRFs are reviewed by the study CRO at the study center, omissions or inconsistencies detected by eCRF review may necessitate clarification or correction of omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data.

The investigator will be provided with a CD-ROM of the final version of the data generated at the investigational study center once the database is archived and the study report is complete and approved by all parties.

13.2 Monitoring

The study CRO verifies that, amongst others, the:

- Data are authentic, accurate, and complete.
- Safety and rights of participants are being protected.
- Study is conducted in accordance with the currently approved protocol, any other study agreements, GCP and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

The investigator must ensure provision of reasonable time, space and qualified personnel for monitoring visits.

Direct access to all study-center related and source data is mandatory for the purpose of monitoring review.

Upon completion or premature discontinuation of the study, the monitor will conduct study center closure activities with the investigator or study center staff, as appropriate, in accordance with applicable regulations and GCP.

13.3 Record Retention

Following closure of the study, the investigator must maintain all center study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible, when needed (e.g., audit or inspection), and must be available for review in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re- generating a hard copy, if required. Furthermore, the investigator must ensure that an acceptable back- up of the reproductions exists and that there is an acceptable quality control procedure in place for making these reproductions.

The investigator/institution should seek the written approval of the Sponsor before proceeding with the disposal of these records after the indicated time period for record retention. The minimum retention time will meet the strictest standard applicable to a particular study center, as dictated by ICH GCP, any institutional requirements, or applicable laws or regulations; otherwise, the minimum retention period will default to 25 years.

The investigator/institution must notify the Sponsor of any changes in the archival arrangements, including, but not limited to archival at an off- study center facility, transfer of ownership of the records in the event the investigator leaves the study center.

13.4 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

13.5 Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on a publicly available clinical trial register before enrollment of participants begins.

13.6 Provision of Study Results to Investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report. The investigators will have access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a study center or other mutually agreeable location.

The investigators are encouraged to share the summary results with the study participants, as appropriate.

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