3. INVESTIGATIONAL PLAN

3.1. Study Design

This is a phase 1/2 open-label study assessing the safety, reactogenicity, and immunogenicity of saRNA COVID-19 boost vaccines in participants that have been previously vaccinated against or previously infected with COVID-19. Participants enrolled will include individuals previously vaccinated against COVID-19 or previously infected with COVID-19 > 3 months prior to enrollment. Previously unvaccinated/vaccinated status and previously uninfected/infected status will be established by medical history and by SARS-CoV-2 serology assessed in the prescreening visit.

The phase 1 study is a single arm, open-label study. The phase 2 is a randomized open-label study. For the phase 2 study, laboratory analyses of immunogenicity assessments will be performed blind to participants' vaccine treatment on study. In all study phases, SARS-CoV-2 serological status will be assessed in a prescreening visit.

Participants will be ≥ 18 years of age who are healthy or have medically-stable chronic diseases. The treatment regime is described in the sections that follow. The study schema is shown in Figure 1.

Phase 1

In the phase 1 study, up to 60 previously vaccinated/infected participants will be enrolled in 6 separate cohorts to receive a single vaccine boost consisting of either the AAHI-SC2 or AAHI-SC3 vaccine. Dosing schedule, mode of administration, and dosage for phase 1 are indicated in Table 4.

Table 4: Phase 1 Previously Vaccinated/Infected Dosing Schedule

Phase	Cohort	Participants	Va cine	Dosing Schedule	Dosage
PHASE 1	1A	10	AAHI-SC2	Day 1	25 µg IM
	1B	10	AAHI-SC2	Day 1	50 µg IM
	1C	10	AAHI-SC2	Day 1	70 µg IM
	2A	10	AAHI-SC3	Day 1	25 µg IM
	2B	10	AAHI-SC3	Day 1	50 µg IM
	2C	10	AAHI-SC3	Day 1	85 µg IM

Safety will be assessed for all participants and will include monitoring of vital signs, and incidence and severity of AEs. Blood samples will be collected for hematology and chemistry analyses and urine samples will be collected for urinalysis. Toxicities will be graded using the

Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007).

For each cohort in phase 1, after all 10 participants have completed the toxicity assessment period, the SRC will review safety results to determine if the event warrants stopping the trial, modifying the trial, or continuing without modification.

Solicited local and systemic reactogenicity AEs will be collected using diaries for 7 days following study intervention (ie, administration of vaccine). Unsolicited AEs will be recorded in a diary from time of vaccination until 30 days after study intervention. Medically attended adverse events (MAAEs) and SAEs will be recorded for 6 months after study intervention (related MAAEs and SAEs will be recorded at any time).

Immunogenicity analyses will be conducted by collecting serum and PBMC samples from individual participants before and after vaccinations to test for humoral- and cell-mediated immune responses. Neutralizing antibodies will be assessed.

Phase 2

In the phase 2 study, up to 120 previously vaccinated/infected additional participants will be enrolled. Participants in phase 2 will be randomized 1:1:1:1 to receive Janssen or Pfizer-BioNTech vaccine (control arm), the AAHI SC2 vaccine (experimental arm 1), or the AAHI-SC3 vaccine (experimental arms 2 and 3). Dose levels for the AAHI-SC2 and AAHI-SC3 vaccines will be as determined in the phase 1 study. Randomization will be stratified by age (18 to 55 years or > 55 years), by previous infection (previously infected or not), and by HIV status (positive or negative). Treatment arms are shown in Table 5.

Table 5: Phase 2 Previously Vaccinated/Infected Dosing Schedule

Treatment Arm	Participants	Vaccine	Dosing schedule	Dosage
Control arm	30	EUA or approved vaccine	Day 1	Per prescribing information
Experimental arm 1	30	AAHI-SC2	Day 1	TBD: As determined in phase 1 study
Experimental arm 2	30	AAHI-SC3	Day 1	TBD: As determined in phase 1 study
Experimental arm 3	30	AAHI-SC3	Day 1 and day 29	TBD: As determined in phase 1 study

In addition to dosing visits described above, all participants in all phases of the study will have follow up study visits for data collection.

The SRC will provide ongoing safety review in the phase 2 study. If a possible safety signal is detected, the SRC will determine if the event warrants stopping the trial, modifying the trial, or continuing without modification.

Solicited local and systemic reactogenicity AEs will be collected using diaries for 7 days following study intervention (ie, administration of vaccine). Unsolicited AEs will be recorded in

a diary from time of vaccination until 30 days after study intervention. MAAEs and SAEs will be recorded for 6 months after study intervention (related MAAEs and SAEs will be recorded at any time).

Immunogenicity analyses will be conducted by collecting serum and PBMC samples from individual participants before and after vaccinations to test for humoral- and cell-mediated immune responses. Neutralizing antibodies will be assessed.

3.2. Number of Participants

Initially up to 180 participants will be enrolled in this study (60 participants in phase 1, and 120 participants in phase 2).

3.3. Duration of Study

3.3.1. Duration of Treatment

For most participants, treatment will be confined to study day 1 For participants in experimental arm 3 of the phase 2 study, treatment will occur on day 1 and day 29.

3.3.2. Duration of Follow-Up

Participants who receive study treatment will be f llowed by a health care professional until either death (by any cause) or for 1 year past first administration of vaccine.

3.3.3. End of Study

The end of study is defined as either the date of the last visit of the last participant to complete the post-treatment follow-up, or the date of receipt of the last data point from the last participant that is required for primary, and/or secondary analysis, as specified in the protocol statistical analysis plan (SAP), whichever is the later date.

3.4. Study Endpoints

3.4.1. Phase 1

3.4.1.1. Primary Endpoints

- Incidence of MAAEs and SAEs through 1 week post final vaccine administration
- Incidence of MAAEs and SAEs through 30 days post final vaccine administration
- Incidence of MAAEs and SAEs through 6 months post final vaccine administration
- Incidence and severity of solicited local reactogenicity AEs through 1 week after each vaccine administration
- Incidence and severity of solicited systemic reactogenicity AEs through 1 week after each vaccine administration
- Incidence and severity of unsolicited AEs through 1 week post final vaccine administration

- Incidence and severity of unsolicited AEs through 30 days post final vaccine administration
- Incidence of abnormal changes of laboratory safety examinations
- Changes in vital signs

3.4.1.2. Secondary Endpoints

Humoral Immunogenicity:

- GMT of S-specific and N-specific IgG antibodies against 2019 novel coronavirus tested by ELISA in serum
- GMT of neutralizing antibody

Cellular Immunogenicity:

- T cell activity against SARS-CoV-2 S protein and N protein as assayed by ELISpot

3.4.2. Phase 2

3.4.2.1. Primary Endpoints

Humoral Immunogenicity:

- GMT of S-specific and N-specific IgG antibodies against 2019 novel coronavirus tested by ELISA in serum
- GMT of neutralizing antibody

Cellular Immunogenicity:

- T cell activity against SARS-CoV-2 S protein and N protein as assayed by ELISpot

3.4.2.2. Secondary Endpoints

3.4.2.2.1. Safety

- Incidence of MAAEs and SAEs through 30 days post final vaccine administration
- Incidence of MAAEs and SAEs through 6 months post final vaccine administration
- Incidence and severity of solicited local reactogenicity AEs through 1 week after each vaccine administration
- Incidence and severity of solicited systemic reactogenicity AEs through 1 week after each vaccine administration
- Incidence and severity of unsolicited AEs through 30 days post final vaccine administration

4. PARTICIPANT ENROLLMENT AND WITHDRAWAL

4.1. Participant Eligibility

All admission criteria (inclusion and exclusion criteria) are numbered sequentially.

4.1.1. Inclusion Criteria

1. Healthy adults ≥ 18 years of age at time of enrollment.
2. Vaccinated with an EUA or approved vaccine against COVID-19 ≥ 3 months prior to enrollment on study or infection with COVID-19 ≥ 3 months prior to enrollment on study.
3. Able to understand and provide a signed informed consent that fulfills the relevant IRB or IEC guidelines.
4. Agrees to the collection of biospecimens (eg, NP swabs) and venous blood per protocol.
5. Ability to attend required study visits and return for adequate follow-up, as required by this protocol.
6. Temperature < 38°C.
7. Agreement to practice effective contraception for female participants of childbearing potential and non-sterile males. Female participants of childbearing potential must agree to use effective contraception whil on study until at least 1 month after the last dose of vaccine. Non-sterile male participants must agree to use a condom while on study until at least 1 month after the last dose of vaccine. Effective contraception includes surgical sterilization (eg, vasectomy, tubal ligation), two forms of barrier methods (eg, condom, diaphragm), IUDs, oral contraceptives, injectable contraceptives, patches, implants, and abstinence.
8. HIV-positive participants must have been on anti-retroviral therapy for ≥ 4 weeks and have HIV-1 viral load < 1,000 copies/mL at the time of enrollment.

4.1.2. Exclusion Criteria

1. Serious adverse reaction to any vaccine, any unrelated medication or any component of the investigational vaccine, including a history of anaphylaxis and symptoms of a severe allergic reaction and history of allergies in the past.
2. Confirmed current COVID-19, SARS-CoV-2 infection in the last < 3 months, or PCR positive for SARS-CoV-2 at screening.
3. Vaccinated with an EUA or approved vaccine against COVID-19 in the last < 3 months.
4. Pregnant or breastfeeding women.
5. Any participants with a history of myocarditis or pericarditis.
6. Chronic lung disease (included COPD) as evidenced by one or more exacerbations requiring a course of steroids in the last year, or the requiring chronic low dose oral steroids to prevent exacerbations. Uncontrolled asthma, defined as requiring reliever

inhaler (short-acting beta agonist or ipratropium bromide) more than twice a week is also excluded.

7. Bone marrow or organ transplant recipient
8. Extreme obesity (defined as BMI of 40 kg/m^2 or higher).
9. Chronic kidney disease requiring dialysis.
10. History of liver disease.
11. Any disease associated with acute fever, or any infection.
12. Participants with acquired or hereditary immunodeficiencies other than well-controlled HIV are excluded from enrollment.
13. Current diagnosis of active tuberculosis.
14. History of hereditary, idiopathic or acquired angioed ma.
15. No spleen or functional asplenia.
16. Chronic use (more than 14 continuous days) of any medications that may be associated with impaired immune responsiveness including, but not limited to, systemic corticosteroids exceeding 10 mg/day of prednisone equivalent, allergy injections, immunoglobulin, interferon, or immunomodulators. The use of low dose topical, ophthalmic, inhaled and intranasal steroid preparations will be permitted.
17. According to the judgement of the investigator any medical, psychiatric, psychological, social, occupational or other conditions that could affect the participants ability to sign informed consent, provide safety assessment data or comply with the requirements of the study protocol.
18. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.

4.2. Strategies for Recruitment and Retention

Clinical study sites have been chosen based on their previous experience and infrastructure.

Site staff are responsible for ensuring that participants attend their regularly scheduled treatment visits.

4.3. Screen Failures

Participants who sign a screening informed consent form (ICF) but who do not meet all of the eligibility criteria will be considered screen failures. Data on screen failures will not be entered into the Electronic Data Capture (EDC) system for the purposes of the study. ICFs and screening source documents will be maintained as part of the study file with the eligibility failure reason clearly documented.

4.4. Withdrawal of Participants

A participant may voluntarily discontinue study participation at any time. At the Investigator's discretion, participants may be discontinued or withdrawn from the study at any time after discussion with the Investigator and Medical Monitor.

4.5. Treatment Discontinuation

Participant treatment must be discontinued if any of the following occur:

- Unacceptable toxicity/AE.
- Withdrawal of consent.
- Participant noncompliance.
- Pregnancy or currently nursing.
- Administrative decision by the Investigator or Sponsor.

Participants who are withdrawn from this study secondary to a laboratory toxicity or AE should be followed by the Investigator as outlined in Section 7.

4.6. Replacement of Participants

In phase 1, no participants who are vaccinated will be replaced. In phase 2, participants who are randomized to either the control or experimental arm will not be replaced.

4.7. Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the Investigators and the regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Death that is suspected to be related to the treatment regimen
- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

The study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the Sponsor, the IRB, and/or the South African Health Products Regulatory Authority (SAHPRA).

5. TREATMENT PROCEDURES

[redacted] [redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted] [redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted] [redacted]

[redacted]

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[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

5.1.5. Dosing and Administration

Participants will be administered vaccine in each study phase as described in Section 3.1. Participants will be monitored for 30 minutes after each administration for immediate adverse reactions (ARs), and appropriate personnel and therapies will be available to respond to any immediate AR.

Toxicity study stopping rules are detailed in Section 7.8.2.

5.1.6. Accountability of IP

The Investigator or designee(s) must maintain an inventory record of IP received, administered, returned, and discarded in the IP accountability record as detailed in the Pharmacy Manual. IP accountability records must be made available to the Sponsor or designated monitoring personnel for the purpose of conducting drug accountability.

Unused portions of IP are not to be stored or subsequently used and will need to be properly disposed of in accordance with institutional policy and procedure, and disposal must be recorded on the IP accountability record.

5.1.7. Management of Adverse Events and Individual Stopping Criteria

Participants will be monitored for 30 minutes after each administration for immediate adverse reactions ARs, and appropriate personnel and therapies will be available to respond to any immediate AR. Participants will also be monitored for adverse reactions throughout the study per the schedule of events listed in Table 10. Discussion of toxicities that may warrant stopping the study are detailed in Section 7.8.2.

6. STUDY PROCEDURES AND EVALUATIONS

All required study procedures and evaluations are to be conducted as outlined in this protocol. In the event of a deviation from the protocol due to an emergency, accident, or mistake, the Investigator or designee must notify the Sponsor as soon as possible.

All laboratory assessments and evaluations will be performed locally. Procedures and evaluations to be performed are detailed in the schedules of events shown in Table 10.

6.1. Prescreening Assessments

If possible, the prescreening visit should occur on the same day as and immediately prior to the screening visit. The assessments to be performed in the prescreening visit include:

- Study introduction and written informed consent for prescreening obtained prior to performing any study assessments or procedures
- Blood draw for SARS-CoV-2 testing
- Blood draw for HIV testing

SARS-CoV-2 and HIV testing will use rapid testing assays.

6.2. Baseline/Screening Assessments

The following procedures and evaluations are to be performed at baseline/screening:

- Study introduction and written informed consent obtained prior to performing any study assessments or procedures (screening visit and/or protocol amendments that affect study assessments or participant treatment).
- Inclusion/exclusion
- Demographics and complete medical history, including current symptoms and COVID-19-related symptoms
- Tuberculosis screening
- History of COVID-19
- Confirmation of contraceptive measures
- Physical exam
- Vital signs
- Concomitant medications
- Blood draw and urine collection for clinical laboratories
- Biospecimen collection for SARS-CoV-2 testing
- Pregnancy test (serum [β-human chorionic gonadotropin] or urine): The pregnancy test result will be confirmed as negative immediately prior to vaccine administration. A positive pregnancy test occurring while the participant is participating in the study is considered an immediately reportable event.

6.3. Safety Assessments

All participants will be monitored for AEs during the study. Assessment of AEs will include the following parameters:

- All MAAEs and SAEs for 6 months after last vaccine administration (related MAAEs and SAEs at any time)
- Solicited local and systemic AEs via diary for 7 days after each vaccine administration (applicable to the phase 1 and phase 2 studies)
- Unsolicited AEs via diary from first dose of study treatment until 30 days after last vaccination (applicable to the phase 1 and phase 2 studies)
- Vital signs
- Body weight
- Physical examinations
- Hematology: CBC with differential
- Chemistry panel: Collection of whole blood for complete metabolic panel (CMP)
- Urinalysis: protein, glucose, and RBCs
- Pregnancy test.

6.3.1. Solicited Local and Systemic Adverse Events

Solicited AEs will be captured at study visits and by a diary distributed to participants. Thermometers and rulers will be provided to participants for evaluating AEs. Text and/or phone reminders to complete the solicited AE diary may be provided to participants.

Solicited local AEs to be asses ed include redness, firmness, swelling, pain or itching at the injection site, medication taken for pain after IM administration, tingling/numbness, and bleeding or bruising at the injection site after IM administration. Solicited systemic AEs to be assessed include chills, nausea, vomiting, diarrhea, headache, fatigue, myalgia, abdominal discomfort/pain, joint pain, and fever. The solicited AE diary may be either electronic diary (eDiary) or a paper diary, as available. A sample diary for collecting solicited AEs is provided in Appendix 1.

6.3.2. Unsolicited Adverse Events

Unsolicited AEs will be captured at study visits and by a diary distributed to participants. Diaries for unsolicited AEs will be reviewed at all study visits until 30 days after the last dose of vaccine. A sample diary for the recording of unsolicited events is provided in Appendix 2.

6.4. Follow-Up for Disease History

Participants will be followed for self-reported SARS-CoV-2 exposure, symptoms of COVID-19 disease, and any outside test results for SARS-CoV-2 infection at study visits. Participants with symptoms of COVID-19 should be encouraged to seek testing and care, if appropriate, from their usual provider.

6.5. Clinical Laboratory Procedures and Evaluations

A list of the laboratory assessments that will be conducted during the study is provided in Table 9.

Table 9: Laboratory Assessments

Chemistry[a]	**Hematology**[b]	**Urinalysis**
Albumin	WBC	Protein
ALP	RBC	Glucose
ALT	Platelets	Presence of RBCs
AST	Hemoglobin	
Calcium	Hematocrit	
Chloride	Basophils	
Creatinine	Eosinophils	
Glucose	Lymphocytes	
Phosphorus	Monocytes	
Potassium	Neutrophils	
Sodium		
Blood urea nitrogen (BUN) or urea[c]		
Uric acid		

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; CRP, C-reactive protein; IL-6, interleukin-6; RBC, red blood cells; TNF-α, tumor necrosis factor alpha; WBC, white blood cells.

[a] A comprehensive metabolic panel (CMP) may be used to obtain chemistry assessments, provided all assessments listed above are included.

[b] A complete blood count (CBC) with differential may be used to obtain hematology assessments, provided all assessments listed above are included.

[c] BUN or urea should be assessed per institutional standards. Only one of the two tests is required.

6.6. Laboratory Procedures and Evaluations for Immunological Endpoints and Other Laboratory Procedures and Evaluations

Blood and other biospecimens (eg, NP swabs) will be collected at various times during this study, and shipped to the Immunity Bio laboratory. Any residual specimens collected and not shipped will be stored at the laboratory at the Wits VIDA clinic based at Chris Hani Baragwanath Academic Hospital within South Africa. If there are any extra samples remaining of shipment to the United States of America, these will be stored at ImmunityBio's laboratory in Torrey Pines, California. Samples will be stored for a maximum period of 15 years and participants will be requested to sign a separate, optional storage informed consent form in order to agree to sample storage

A brief summary of the laboratory procedures and evaluations to be performed with these samples is provided in the following sections.

6.6.1. Immunogenicity Assessments

6.6.1.1. Cellular and Humoral Response to SARS-CoV-2 Proteins

Whole blood samples for immunology analysis will be collected prior to vaccine administration and during follow-up visits as designated in the study schedule. Blood samples will be stored in a laboratory to be determined.

Binding antibody ELISAs will be used to assess anti-spike IgG antibodies. Validated cPass ELISA-based assays will be used to assess neutralizing antibodies against SARS-CoV-2. In the phase 2 randomized study, the laboratory analyses will be performed blind to participants' vaccine treatment on study.

6.6.2. SARS-CoV-2 Testing

Appropriate biospecimens (eg, NP swabs) will be collected for SARS-CoV-2 testing. A PCR-based test will be used to assess presence of virus.

6.6.3. HIV Testing

HIV testing will follow national guidelines. Two rapid tests will be performed. Indeterminate or discrepant results are resolved by ELISA testing at an accredited laboratory.

6.7. Study Schedule

The schedule of events are provided in Table 10.

6.7.1. Screening Procedures and Evaluations

Before performing any study procedures, the Investigator will obtain written informed consent from the participant. The Investigator will not undertake any measures specifically required for the clinical study until consent has been obtained. A participant that is consented and does not meet all entry criteria will be considered a screen failure.

6.7.1.1. Medical History

At screening, the participant's medical history should be taken as per institutional standards. Otherwise, only the following medical history should be recorded in the eCRF:

- Current symptoms
- Items listed in inclusion/exclusion
- Existing medical conditions.
- Medications/procedures related to existing conditions.
- History of any prior COVID-19 symptoms.
- Vaccination history

Table 10: Schedule of Events: Previously Vaccinated/Infected Participants

Study Period	**Prescreening[a]**	**Baseline/ Screening**	**Vaccine Administration and Initial Follow-Up**					**Extended Follow-Up**		
Study Day	**-5 to -1**	**-5 to -1**	**1**	**8**	**22**	**29**	**36**	**60**	**180**	**365**
Clinic visit number	**Prescreening**	**Screening**	**1**	**2**	**3**	**4**		**5**	**6**	**7**
Windows (Days)			**± 3**					**± 7**		**± 14**
General Assessments										
Informed consent	X	X								
Inclusion/ exclusion		X								
Demographics		X								
Medical history		X								
Tuberculosis screening [b]		X								
COVID-19 history of disease [c]		X	X	X	X	X		X	X	X
Confirm contraceptive measures		X	X			X				
Physical exam: height, weight [d]		X	X	X	X	X				
Vital signs [e]		X	X	X	X	X				
Concomitant medications		X	X	X	X	X		X	X	
Participant training on AE diaries			X							
Issue diaries for solicited AEs (phase 1 and 2 only) [f]			X			X				
Review and collect solicited AE diary (phase 1 and 2 only) [f]				X				X		
Issue diaries for unsolicited AEs			X							
Review unsolicited AE diary				X	X	X				
Collect unsolicited AE diary								X		

Study Period	**Prescreening[a]**	**Baseline/ Screening**	**Vaccine Administration and Initial Follow-Up**					**Extended Follow-Up**		
Study Day	**-5 to -1**	**-5 to -1**	**1**	**8**	**22**	**29**	**36**	**60**	**180**	**365**
Clinic visit number	**Prescreening**	**Screening**	**1**	**2**	**3**	**4**		**5**	**6**	**7**
Windows (Days)			**± 3**					**± 7**		**± 14**
In office AE collection			X	X	X	X		X		
Telephone follow-up							X[g]		X	X
Vaccine Administration: Phase 1										
Cohort 1A			AAHI-SC2 (25 µg)							
Cohort 1B			AAHI SC2 (50 µg)							
Cohort 1C			AAHI-SC2 (70 µg)							
Cohort 2A			AAHI-SC3 (25 µg)							
Cohort 2B			AAHI-SC3 (50 µg)							
Cohort 2C			AAHI-SC3 (85 µg)							
Vaccine Administration: Phase 2										
Experimental Arm 1			AAHI-SC2 (dose to be determined [TBD])							
Experimental Arm 2			AAHI-SC3 (dose TBD)							
Experimental Arm 3			AAHI-SC3 (dose TBD)			AAHI-SC3 (dose TBD)				
Control Arm			Janssen/Pfizer-BioNTech vaccine							
Laboratory Assessments										

Study Period	**Prescreening**[a]	**Baseline/ Screening**	**Vaccine Administration and Initial Follow-Up**					**Extended Follow-Up**		
Study Day	**-5 to -1**	**-5 to -1**	**1**	**8**	**22**	**29**	**36**	**60**	**180**	**365**
Clinic visit number	**Prescreening**	**Screening**	**1**	**2**	**3**	**4**		**5**	**6**	**7**
Windows (Days)			**± 3**					**± 7**		**± 14**
Chemistry panel [h]		X				X				
Hematology [i]		X				X				
Urinalysis [j]		X				X				
Biospecimens for SARS-CoV-2 [k]		X	X		X	X				
Collect whole blood for immunogenicity [l]			X	X	X			X		
Pregnancy test [m]		X	X			X				
Collect blood for SARS-CoV-2 serology	X									
HIV testing [n]	X									

[a] If possible, the prescreening visit should occur on the same day as and immed ately prior to the screening visit.
[b] A TB symptom screening questionnaire per local guidelines will be used If scr ening positive on questionnaire then sputum test and chest X-ray may be done to exclude the diagnosis of TB. If TB is excluded on these tests and the inv tigator onsiders that further TB testing is not clinically indicated then the potential participant may proceed with enrollment into the study. All potential participants suspected of aving or with proven TB will be linked into care at their local clinic.
[c] Potential exposure to SARS-CoV-2, symptoms of COVID-19, and outside testing results for SARS-CoV-2 infection will be collected at each assessment.
[d] Physical examination will be performed at screening and symptom-directed (targeted) physical examination at all other time points if indicated. Height required at baseline/screening visit only.
[e] Vital signs of temperature, heart rate, blood pressure, and respiratory rate will be assessed as indicated. Temperature will be documented at each visit and subsequently if clinically indicated.
[f] Solicited AE diaries will be issued on day 29 and collected on day 60 only for participants in experimental arm 3 of the phase 2 study.
[g] The telephone follow-up on day 36 is required only for participants in experimental arm3 of phase 2 that get a boost on day 29.
[h] See Table 9 for information on chemistry laboratory assessments.
[i] Hematology to include CBC with differential (5 part).
[j] Urinalysis testing will include at a minimum protein, glucose, and presence of red blood cells. Sample collection should occur prior to vaccine administration.
[k] Sample collection should occur prior to vaccine administration.
[l] On study days 1, sample collection should occur prior to vaccine administration. A lab manual will be provided to the sites with detailed guidance for serum and PBMC preparation, storage, and shipping. A day 1 aliquot should be stored for use, if needed, in diagnosis of suspected cases of thrombosis with thrombocytopenia syndrome.
[m] Testing should occur prior to vaccine administration. Pregnancy testing at day 29 applies to phase 2 arm 3
[n] HIV-positive participants must have been on anti-retroviral therapy for ≥ 4 weeks and have HIV-1 viral load < 1,000 copies/mL at the time of enrollment

6.7.2. Study Period(s)

Procedures and evaluations to be performed during visits should be performed with the site's standard-of-care protocol.

6.7.3. End-of-Study Procedures and Evaluations

End-of-study (EOS) is 1 year after the first vaccine injection. All participants receiving ≥ 1 dose of vaccine and discontinuing the study for any reason will complete a discontinuation visit approximately 30 days after they last received treatment. For participants who discontinue prior to study day 29, the discontinuation visit should include all assessments listed for Day 29 in Table 10. For participants who discontinue prior to day 60, the discontinuation visit should include all assessments listed for day 60. If a participant is unable to travel for the EOS visit, the participant will be required to visit his/her primary care provider for safety labs and a physical exam. Research staff will obtain records and follow up with a phone call.

6.8. Concomitant Medications

All concomitant medications should be recorded in the participant's source documents and in the eCRF from the time of signature of the ICF until the EOS visit. The following concomitant medications are of special interest, and should be recorded until the EOS visit unless specified for a longer period below:

- Concomitant medications to manage SAEs attributed to COVID-19 and the study treatment from initiation of SAE until resolved (returned to baseline), recovered from sequelae, or death (due to the SAE).
- Concomitant medications given in supportive care for COVID-19 symptoms or treatment-related AEs including, but not limited to:
  - Analgesics

6.9. Participant Access to Study Medications at Close of Study

At the close of the study, a participant may be eligible to enroll in other open clinical trials. The investigational product will not be available to the participant once he/she has completed the EOS visit.

7. ADVERSE EVENT MONITORING AND REPORTING

AEs will be recorded and monitored and, when appropriate, reported to SAHPRA and others involved in an investigation (sponsors, IRBs, and investigators) in accordance with existing statutes. In addition, to assist in monitoring safety and making required reports, AEs will be categorized in accordance with the Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007). These scales are described in more detail in the following sections.

7.1. Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007)

The enrollment of healthy volunteers warrants a very low tolerance for risk. The Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007) will be used to assess the severity of clinical and laboratory abnormalities in healthy adult volunteers enrolled in this study. AEs will be graded according to the following tables from The Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007).

Table 11: Clinical Abnormalities: Local Reaction to Injectable Products

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	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	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	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

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Table 12: Clinical Abnormalities: Vital Signs

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

* Participant should be at rest for all vital sign measurements.
** Oral temperature; no recent hot or cold beverages or smoking.
*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.

Table 13: Clinical Abnormalities: Systemic

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 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800 gms/24 hours or requires o tpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interfere ce 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 a tivity	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
Systemic Illness	**Mild (Grade 1)**	**(Moderate(Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

Table 14: Laboratory Abnormalities: Serum

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 – 125 126 – 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
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	--

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
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 x ULN	> 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 s rve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference range 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 (125-12 mE/L) should be recorded as a grade 4 hyponatremia event if the participant had a new seizure associated with the low sodium value.
***ULN" is the upper limit of the normal range.

Table 15: Laboratory Abnormalities: Hematology

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
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.

Table 16: Laboratory Abnormalities: Urine

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.

7.2. Definition of Adverse Events

AEs and grading criteria listed below are consistent in definitions in 21 CFR 312.32.

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a participant during the study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the participant's health, including laboratory test values (as specified by the criteria b low), regardless of etiology. A diagnosis or syndrome should be recorded on the AE page of the case report form (CRF) rather than the individual signs or symptoms of the diagnosis or syndrom

An abnormal laboratory value is considered to be an AE if the abnormality:

- Results in discontinuation from the study;
- Requires treatment, modification/interruption of the study treatment dose, or any other therapeutic intervention; or
- Is judged to be of significant clinical importance.

Regardless of the severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as an SAE.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded as an AE. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as an AE.

An AE with medically-attended visits (either in person or telemedicine visit) that are not routine visits for physical examination or vaccination, such as visits for hospitalization, an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason, will be documented as a MAAE. MAAEs can also be SAEs and will follow the same serious adverse event criteria and collection guidelines noted in Section 7.3.

Duration and Frequency for Collecting AE and SAE Information

In the phase 1 and phase 2 studies, solicited AEs will be recorded by the investigator for 7 days after each dose . In the phase 1 and phase 2 studies, unsolicited AEs will be recorded from the time of first dose of study treatment until 30 days after study intervention. All MAAEs and SAEs will be recorded by the investigator from the time of first dose of study treatment until 6 months after study intervention. For MAAEs/SAEs that are considered related to study treatment, those events should be reported at any time regardless of vaccine administration date or end of study visit date.

7.3. Definition of Serious Adverse Events

AEs and grading criteria listed below are consistent in definitions in 21 CFR 312.32. AEs can be further divided into solicited AEs and unsolicited AEs. Solicited AEs are those for which the study team will specifically query the participant whether they occurred. Unsolicited AEs are those events that the participant report occurring without being queried about the specific event.

An SAE is any AE that suggests a significant hazard or AE, whether or not considered to be related to study treatment. An SAE fulfills one or more of the following criteria:

- Results in death.
- Is life-threatening (ie, in the opinion of the Investigator, the participant is at immediate risk of death from the AE as it occurred).
- Requires in-subject hospitalization or prolongation of existing hospitalization (hospitalization is defined as an in-subject admission, regardless of length of stay).
- Results in persistent or significant disability or incapacity (a substantial disruption of the participant's ability to conduct normal life functions).
- Results in a congenital abnormality or birth defect.
- Is an important medical event that may jeopardize the participant or may require medical intervention to prevent one of the outcomes listed above. Important medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalization, or disability, but may jeopardize the participant or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

7.4. Evaluation of Adverse Events

A qualified Investigator will evaluate all AEs and report their seriousness, severity/intensity, relationship to the study treatment, duration, action taken, and participant outcome.

7.4.1. Severity/Intensity

The severity/intensity of AEs and SAEs will be graded based upon the participant's symptoms in accordance with the Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007).

AEs that are not defined in the Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007) should be evaluated for severity/intensity according to the following scale:

- Grade 1 = Mild: transient or mild discomfort, no limitation in activity; no medical intervention/therapy required.
- Grade 2 = Moderate: mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required.
- Grade 3 = Severe: marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization possible.
- Grade 4 = Life threatening: extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.
- Grade 5 = Death: the event results in death.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria under Section 7.3. An AE of severe intensity may not be considered serious. Seriousness, not severity, serves as a guide for defining regulatory obligations.

7.4.2. Relationship to the Investigational Product

The relationship between the administration of study treatment and the occurrence of an AE/SAE will be determined, as defined below:

- Not suspected/Not related The temporal relationship of the AE or SAE to the study drug administration makes a causal relationship unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the obse ved event.
- Suspected/Related: The temporal relationship of the AE or SAE to the study drug administration makes a causal relationship possible, probable, or definite; and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

7.4.3. Duration of Adverse Events

The Investigator will provide a record of the start date and stop dates for all AEs and SAEs.

An AE start date should be entered as the first date the participant experiences any signs or symptoms. If a later diagnosis is made, the date the symptom started is the start date rather than the date of the diagnosis.

For SAEs, the start date should be entered as the date the event first met serious criteria (see Section 7.3 for definitions).

AEs and SAEs should have an end date that corresponds to the resolution of the event. SAEs will be followed until satisfactory resolution or until the site Investigator deems the event to be chronic or the adherence to be stable.

Please see the study-specific CRF data entry completion guidelines and SAE report completion guidelines for further instructions for capturing the start and stop dates of AEs and SAEs.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity. AEs characterized as intermittent require documentation of the onset and duration of each episode.

For 30 days after the last dose, at each study visit, the Investigator will inquire about the occurrence of AE/SAEs since the last visit or follow-up. From 30 days after the last dose to 6 months after the last dose, at each study visit, the Investigator will inquire about the occurrence of SAEs since the last visit or follow-up. Events will be followed for outcome information until resolution or stabilization.

7.4.4. Outcome

The Investigator will report the outcome of the event for AEs and SAEs. AEs will be followed for 30 days after the participant's last dose of study treatment. Grade 3 or 4 AEs will be followed until resolution or stabilization. All SAEs that have not resolved upon discontinuation of the participant's participation in the study must be followed until recovered, recovered with sequelae, not recovered (death due to other cause), death (due to the SAE), lost to follow-up, or otherwise explained.

7.5. Reporting Procedures

The Investigator is required to ensure that the data on the AE and SAE report forms are accurate and consistent.

7.5.1. Reporting Procedures for Adverse Events

Any AE (as defined in Section 7.2) should be reported as an AE on the AE page of the CRF and in the participant's source documents.

Any medical condition that is present at the study participant's screening visit will be considered as baseline and not reported as an AE; however, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

7.5.2. Reporting Procedures for Serious Adverse Events

SAEs will be recorded on the study-specific SAE Report Form, the AE page of the CRF, and in the participant's source documents. All SAEs must be reported to Sponsor Drug Safety within 24 hours of the Investigator's knowledge of the event by email, fax, or other appropriate method using the SAE Report Form. This instruction pertains to initial SAE reports as well as any follow-up reports.

SAE Reporting Information:

Email: SAE.Reporting@Nantbio.com

Fax: (800) 853-3497

The Investigator will ensure that the data in the SAE report forms are accurate, and consistent with the evaluations described in Section 7.4 above. The SAE report should provide a detailed description of the SAE and include summaries of hospital records and other relevant documents, which must be de-identified. The Investigator will report the action taken with study treatment as a result of any SAE and report if concomitant and/or additional treatments were given for the event. All SAEs that have not resolved upon discontinuation of the participant's participation in the study must be followed until recovered, recovered with sequelae, not recovered (death due to other cause), death (due to the SAE), lost to follow-up, or otherwise explained. Any follow-up data will be detailed in a subsequent SAE Report Form and sent to Sponsor Drug Safety. If a participant died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Sponsor Drug Safety as soon as these become available.

7.5.3. Expedited Reporting of Adverse Events

Sponsor Drug Safety, in compliance with 21 CFR 312.32, will be responsible for determining the expectedness of events suspected of being related to study treatments based on the Investigators Brochure, and will notify the SAHPRA and Investigators of any AEs that are suspected, unexpected, and serious as soon as possible but no later than the required 7 or 15 calendar days after Sponsor Drug Safety initial receipt of the information. As per SAHPRA guidance, Sponsor Drug Safety will notify SAHPRA and any other applicable party of any new information impacting the risk-benefit profile of the study treatment or conduct of the trial within 3 calendar days.

The Sponsor or its authorized representativ shall notify the regulatory authorities and Investigators of the following information:

- Any serious and unexpected AE suspected of being related to the use of study treatment in this study or in other studies.
- Any finding from tests in laboratory animals that suggests a significant risk for human participants, including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator is responsible for informing the IRB/IEC of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with the Sponsor and the IRB/IEC.

7.6. Reporting of Pregnancy

7.6.1. Females of Childbearing Potential

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female participant occurring during study participation are considered immediately reportable events. The study regimen is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Sponsor Drug Safety immediately by facsimile, or other appropriate method, using the Initial Pregnancy Questionnaire Report Form. The female participant may be referred to an obstetrician-

gynecologist (not necessarily one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

Safety assessments including collection of AEs and concomitant medications should continue as scheduled in Table 9 until completion of the study.

The Investigator will follow the female participant until completion of the pregnancy and must notify Sponsor Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Follow-up Pregnancy Report Form. The participant will be contacted up to six months following a live birth for information on the health of the child.

If the outcome of the pregnancy was abnormal (eg, spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Sponsor Drug Safety immediately by facsimile, email, or other appropriate method within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

All neonatal deaths that occur within 28 days of birth should be reported as SAEs, without regard to causality. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to study drug should also be reported to Sponsor Drug Safety immediately by facsimile, email, or other appropriate method within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

7.6.2. Male Participants

If a female partner of a male participant receiving study treatment becomes pregnant within 1 month after the last dose of vaccine, the male participant receiving study treatment should notify the Investigator as soon as possible. The Investigator will provide a copy of the Pregnant Partner Informed consent form and a copy of the pr gnancy questionnaire to the male study patient for delivery to the pregnant partner.

If the pregnant partner agrees, she will need to meet with study staff to further discuss the study and ask any questions she may have on the consent form or questionnaire, and sign the Pregnant Partner Informed Consent form in the presence of study staff. The pregnant partner will be contacted for information regarding the outcome of the pregnancy (eg, live birth, etc.) and will be contacted up to 6 months following a live birth for information on the health of the child.

If the pregnant partner refuses to consent, the Investigator will record that a pregnancy occurred and that the pregnant partner refused consent.

7.7. Safety Queries

Queries pertaining to SAEs will be communicated from Sponsor Drug Safety to the site via email or fax. The response time is expected to be no more than 5 business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

7.8. Safety Oversight

Sponsor Drug Safety reviews SAEs as they are reported, and routinely reviews safety data monthly, including AEs, medical history, and concomitant medications, for trends which might suggest a safety signal. Detection of possible safety signals results in a review by the SRC, a cross-functional team. The SRC is responsible for determining if new safety information should result in modification or termination of the study.

7.8.1. Safety Review Committee

7.8.1.1. Safety Review Committee Members

The SRC will include the medical monitor, the Principal Investigator (or designee), Investigators of active sites as deemed appropriate, Pharmacovigilance staff, and at least one qualified infectious disease physician independent of the Sponsor and trial, and representatives of any other function as deemed necessary. Sponsor clinical operations personnel are responsible for organizing and documenting the meetings.

7.8.2. Phase 1 Study Toxicity Study Stopping Rules

Safety will be monitored throughout the study.

In the phase 1 study, the first 7 days after vaccine administration are defined as the toxicity assessment period. The SRC will also review each treatment-related SAE and toxicity, during the toxicity assessment period and each treatment-rel ted SAE and grade ≥ 3 AE after the toxicity assessment period, to determine if the event warrants stopping the trial, modifying the trial, or continuing without modification. In the event of a death that is suspected to be related to the treatment regimen, further enrollment will be delayed until the SRC approves continuation of enrollment in order to allow for proper review and notification to the IRB and the SAHPRA. In the event of a pause in clinical trial enrollment due to toxicity, both the SRC and the SAHPRA will be notified.

Stopping/pausing guidelines are predefined criteria that halt the conduct of a study. Toxicities that may warrant stopping of the trial, based on SAHPRA guidance and with grading scales from the Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007) (see Section 7.1), include the following:

1. If 1 or more participants experience a Grade 4 AE (Section 7.1), vital sign or laboratory abnormality that is judged related to study vaccine, all vaccinations will be suspended until a full safety review is performed.
2. If 3 or more participants report the same or similar Grade 3 solicited AE, unsolicited AE, or clinically relevant laboratory abnormality judged related to the study vaccine, all vaccinations will be suspended until a full safety review is performed.
3. The study will be halted (no new enrollments and no further investigational product administered until a full safety review and consultation with the health authorities completed) if one of the following occurs:
    a. One participant experiences an SAE judged related to the study vaccine, or
    b. There is a participant death judged related to the study vaccine.

If any of the halting rules are met, vaccination of participants will be suspended until after full review of safety data by the SRC. The Investigator must inform the Sponsor and IRB if any of the halting rules are met. The Sponsor then must inform the SRC and SAHPRA.

7.8.2.1. Planned Safety Review Committee Meetings

For each cohort in phase 1, after all 10 participants have completed the toxicity assessment period, the SRC will review safety results to determine if the event warrants stopping the trial, modifying the trial, or continuing without modification.

Enrollment into subsequent cohorts will be suspended for safety review if:

a. ≥ 3 participants report a Grade 3 or above AE, vital sign or laboratory abnormality judged related to study vaccine (see Section 7.1 for toxicity grading), or
b. ≥ 1 participant reports a Grade 4 AE that is judged related to study vaccine

If safety concerns are identified for any cohort in phase 1, the phase 1 study may be closed to further enrollment, and phase 2 study may enroll using a lower dose of an saRNA-based vaccine, provided the SRC recommends it is safe to proceed.

In addition to planned SRC meetings, ad hoc SRC meetings will be called at any time to evaluate safety concerns throughout the trial.

7.8.3. Phase 2 Safety Review Committee Review

The SRC will provide ongoing safety review in the phase 2 study. If the SRC detects a possible safety signal, the statistical team will provide support to the SRC for a full review. The SRC will determine if the event warrants stopping the trial, modifying the trial, or continuing without modification.

8. STATISTICAL CONSIDERATIONS

8.1. Statistical and Analytical Plans

Methodology for statistical analyses and summary of the data collected in this study is described here and further detailed in a statistical analysis plan (SAP) which will be maintained by the Sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

8.2. Analysis Population(s)

The following analysis populations are defined:

Population	Definition
Modified Intent-to-Treat (mITT)	All randomiz d participants who receive at least one dose of vaccine. Participants will be analyzed according to their randomized arm.
Safety	All randomized participants who receive at least one dose of vaccine. Participants will be analyzed according to the actual study intervention received. The Safety Population will be used for all safety analyses.
Immunogenicity	All randomized participants who received at least one dose of vaccine with at least 1 valid follow-up assessment immunogenicity result. Participants will be analyzed according to the actual study intervention received. The Immunogenicity Population will be used for the phase 1 and 2 immunogenicity analyses.

8.3. Statistical Methods

8.3.1. General Approach

The purpose of this phase 1/2 study is to determine the safety, reactogenicity, and immunogenicity of saRNA COVID-19 boost vaccines in participants that have been previously vaccinated against or previously infected with COVID-19. Participants enrolled will include individuals previously vaccinated against COVID-19 or previously infected with COVID-19 > 3 months prior to enrollment. The phase 1 study is a single arm, open-label study. The phase 2 is a randomized open-label study. For the phase 2 study, laboratory analyses of immunogenicity assessments will be performed blind to participants' vaccine treatment on study. Results for phase 1 will be summarized by cohort and results for phase 2 will be summarized for each randomized arm.

Descriptive statistics will be presented for all study endpoints. Continuous variables will be summarized as mean, median, standard deviation, and minimum and maximum values. Categorical variables will be summarized as the number and percentage of participants in each category. Data from all investigational sites will be pooled in the analyses and summary tables.

No statistical comparisons of the phase 2 arms is planned. Subgroup analyses providing descriptive statistics for the various randomization strata levels may be performed depending on the number of participant's in each strata. Details of the subgroup analyses will be provided in the Statistical Analysis Plan.

Data for participants who are screen failures will not be included in the study database or in any analyses or summary tables.

8.3.2. Analyses of Safety

Safety analyses will be summarized with descriptive statistics and performed on the Safety population.

For all phases, safety will be assessed by the incidence of treatment-emergent MAAEs, SAEs, solicited local and systemic reactogenicity AEs, and unsolicited AEs for the time period of interest, overall and by grade according to the Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007). Clinically significant changes in safety laboratory tests and vital signs will be summarized.

8.3.3. Analyses of Immunogenicity

In phase 1 and phase 2, immunogenicity endpoints will be summarized using descriptive statistics for the immunogenicity population. Data will be log-transformed for analyses, as appropriate. GMTs and their associated 95% confidence intervals (CIs) will be computed based by exponentiation of the corresponding log-transformed means and 95% CIs at each time point.

8.4. Sample Size

The sample sizes for phases 1 and 2 are not based on statistical justification. A total of 60 participants will be treated in phase 1 (10 participants for each cohort). A total of 120 participants will be randomized in phase 2 to receive either the control arm or one of the experimental arms (30 participants/arm).

8.5. Randomization

In the phase 2, 30 participants will be randomly assigned to each arm based a 1:1:1:1 randomization ratio. The phase 2 randomization will be stratified by age (18 to 55 years or > 55 years), by previous infection (previously infected or not), and by HIV status (positive or negative). The randomization for the phase 2 portion of the study will be performed by site personnel through the study EDC system.

9. INVESTIGATOR RESPONSIBILITIES

Investigator responsibilities are set out in the ICH Guideline for GCP and in the local regulations. Sponsor staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, and study treatments as well as study-related duties and functions. The Investigator should maintain a list of sub-Investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all participants who sign an informed consent document and are screened for entry into the study. Participants who fail screening must have the reason(s) recorded in the participant's source documents.

The Investigator or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to participant records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of CRFs and queries.

10. REGULATORY CONSIDERATIONS

10.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Sponsor, its authorized representative(s), and Investigator(s) abide by GCP, as described in the ICH E6 R2 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/IEC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

10.2. Participant Information and Informed Consent

The Investigator must obtain written informed consent from the participant or a legal representative prior to performing any study-related procedures. Each Investigator has both ethical and legal responsibility to ensure that the participan s being considered for inclusion in this study are provided a full explanation of the protocol and the roles and responsibilities of the participant for participation in the study.

Documentation that written informed consent was obtained prior to the study participant's entry into the study and of the informed consent process should be recorded in the study participant's source documents, including the date. The original informed consent document signed and dated by the study participant and by the person consenting the study participant prior to the study participant's entry into the study must b maintained in the Investigator's study files and a copy given to the study participant. In addition, if a protocol is amended and the amendment(s) impact the content of the informed consent, the informed consent document must be revised. Study participants participating in the study when the amended protocol is implemented must be re-consented with the revised version of the informed consent document. The revised informed consent document signed and dated by the study participant and by the person consenting the study participant must be maintained in the Investigator's study files and a copy given to the study participant.

10.3. Confidentiality

The Sponsor affirms the participant's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). The Sponsor requires the Investigator to permit Sponsor and/or their designated representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the participant's signed informed consent document, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

Participants will be identified only by unique participant numbers in CRFs.

10.4. Protocol Amendment

Any amendment to this protocol must be approved by the Sponsor or its designated clinical research physician/medical monitor. Amendments will be submitted to the IRB/IEC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/IEC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

10.5. Institutional Review Board/Independent Ethics Committee Review and Approval

The Investigator must obtain IRB/IEC approval for the investigation. Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this study, including the participant consent form and recruitment materials, must be maintained by the Investigator and made available for inspection.

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to the Sponsor before he or she can enroll any participant into the study.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In additi n, the IRB or IEC must approve all advertising used to recruit participants for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and at least annually, as local regulations require.

The Investigator is also responsible for pr viding the IRB/IEC with reports of any reportable serious adverse drug reactions from any other study conducted with study regimen. The Sponsor will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC in accordance with local regulations and guidelines.

10.6. Closure of Study

The Sponsor reserves the right to terminate this study at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented in accordance with local requirements (eg, IRB/IEC, regulatory authorities).

In addition, the Investigator or the Sponsor has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment.
- GCP noncompliance.
- Inaccurate or incomplete data collection.
- Falsification of records.
- Failure to adhere to the study protocol.

11. DATA HANDLING AND RECORDKEEPING

11.1. Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study regimen are complete, accurate, filed, and retained. Examples of source documents include hospital records, clinic and office charts, laboratory notes, memoranda, participant's diaries or evaluation checklists, dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiche, x-ray film and reports, and records kept at the pharmacy and the laboratories, as well as copies of CRFs and any study data/source documents that have been stored to a flash drive, portable hard drive, or CD-ROM.

11.2. Data Management

Study data will be collected via an Electronic Data Capture (EDC) system and will be managed through the use of programmed electronic edit checks. Data discrepancies will be brought to the attention of the clinical team and investigational site personnel, if necessary. An audit trail of the resolution of data discrepancies will be maintained in th EDC system.

11.3. Inspection of Records

The Sponsor will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, investigational agent tocks, drug accountability records, participant charts and study source documents, and other records relative to study conduct.

11.4. Retention of Records

Essential documents must be retained by the Investigator for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal notification to regulatory authorities of discontinuation of clinical development of the IP; and for a period of at least 3 years after the Sponsor notifies the Investigator that the final report has been filed with regulatory authorities. The Investigator must retain these documents for the time period described above or in accordance with local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed informed consent documents for all participants.
- Participant identification code list, screening log (if applicable), and enrollment log.
- Record of all communications between the Investigator and the IRB/IEC.
- Composition of the IRB/IEC.
- Record of all communications between the Investigator, Sponsor, and their authorized representative(s).

- List of sub-Investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures.
- Copies of CRFs (if paper) and of documentation of corrections for all participants.
- Investigational agent accountability records.

If it becomes necessary for the Sponsor or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

12. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by the Sponsor or its authorized representative(s) to ensure compliance with applicable government regulations with respect to current ICH GCP, the study protocol, and all relevant standard operating procedures (SOPs).

12.1. Audits and Inspections

The Investigator and/or institution will allow monitors and auditors direct access to source documentation to perform verification duties. Authorized representatives of the Sponsor, a regulatory authority, or an IRB/IEC may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. The Investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs, and applicable supporting records of study participant participation for audits and inspections by company authorized representatives, regulatory authorities, and IRB/IECs. The Investigator should make every effort to be available for the audits and/or inspections. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

13. PUBLICATION POLICY

The results of this study may be published in a medical journal, presented at a medical congress, or used for teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

Authorship will be based on the International Committee of Medical Journal Editors criteria for authorship:

4. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and
5. Drafting the work or revising it critically for important intellectual content; and
6. Final approval of the version to be published/presented; and
7. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All four conditions must be met to qualify for authorship

The Sponsor must be informed of any plans to publish the results of this study and has the right to review any publication (eg, manuscript, abstract, oral/slide presentation, book chapter) resulting from this study before it is submitted/presented.

14. REFERENCES

1. Ball RL, Bajaj P, Whitehead KA. Achieving long-term stability of lipid nanoparticles: examining the effect of pH, temperature, and lyophilization. Int J Nanomedicine. 2017;12:305-315.
2. Erasmus JH, Khandhar AP, Guderian J, et al. A Nanostructured Lipid Carrier for Delivery of a Replicating Viral RNA Provides Single, Low-Dose Protection against Zika. Mol Ther. 2018;26:2507-2522.
3. Tegally H, Wilkinson E, Lessells RJ, et al. Sixteen novel lineages of SARS-CoV-2 in South Africa. Nat Med. 2021;27:440-446.
4. US Food and Drug Administration. Moderna COVID-19 Vaccine: Emergency Use Authorization Fact Sheet. 2021.
5. Wibmer CK, Ayres F, Hermanus T, et al. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma. Nat Med. 2021;27:622-625.
6. Zhang C, Maruggi G, Shan H, et al. Advances in mRNA Vaccines for Infectious Diseases. Front Immunol. 2019;10:594.

APPENDIX 1. SAMPLE DIARY FOR SOLICITED EVENTS

STUDY NUMBER*:_____

Patient Number*		Date of Vaccine Administration	/ /	*To be completed by the site

Please answer all questions below daily for 7 days, beginning with day of treatment. Be sure to bring back this completed diary to your next clinic visit.

Intramuscular: Solicited local AEs	Instructions	Date / /	Date / /	Date / /	Date / /	Date / /	Date / /	Date / /
1. Is there redness at the injection site?	Check: ☐Yes or ☐No If yes, measure longest diameter in cm	☐Yes or ☐No _____cm	☐Yes or ☐No _____cm	☐Yes or ☐No _____cm	☐Yes or ☐No _____cm	☐Yes or ☐No _____cm	☐Yes or ☐No _____cm	☐Yes or ☐No _____cm
2. Is there firmness at the injection site?	Check: ☐Yes or ☐No	☐Yes or ☐No	☐Yes or ☐No	☐Yes or ☐No	☐Yes or ☐No	☐Yes or ☐No	☐Yes or ☐No	☐Yes or ☐No
3. Is there swelling at the injection site?	Check: ☐Yes or ☐No If yes, measure longest diameter in cm	☐Yes or ☐No _____cm	☐Yes or ☐No _____cm	☐Yes or ☐No _____cm	☐Yes or ☐No _____cm	☐Yes or ☐No _____cm	☐Yes or ☐No _____cm	☐Yes or ☐No _____cm
4. Have you experienced any pain or itching at the injection site?	Check: ☐Pain or ☐Itch or ☐No Pain/Itch Circle mild, moderate or severe	☐Pain ☐Itch Mild Mild Mod Mod Severe Severe ☐No Pain/Itch	☐Pain ☐Itch Mild Mild Mod Mod Severe Severe ☐No Pain/Itch	☐Pain ☐Itch Mild Mild Mod Mod Severe Severe ☐No Pain/Itch	☐Pain ☐Itch Mild Mild Mod Mod Severe Severe ☐No Pain/Itch	☐Pain ☐Itch Mild Mild Mod Mod Severe Severe ☐No Pain/Itch	☐Pain ☐Itch Mild Mild Mod Mod Severe Severe ☐No Pain/Itch	☐Pain ☐Itch Mild Mild Mod Mod Severe Severe ☐No Pain/Itch
5. Have you taken or applied any medication for injection site pain or itching?	Check: ☐Yes or ☐No Provide name of medication(s)	☐Yes or ☐No Name(s):	☐Yes or ☐No Name(s):	☐Yes or ☐No Name(s):	☐Yes or ☐No Name(s):	☐Yes or ☐No Name(s):	☐Yes or ☐No Name(s):	☐Yes or ☐No Name(s):
6. Is there tingling or numbness at the injection site?	Check: ☐Yes or ☐No	☐Yes or ☐No	☐Yes or ☐No	☐Yes or ☐No	☐Yes or ☐No	☐Yes or ☐No	☐Yes or ☐No	☐Yes or ☐No
7. Is there bleeding at the injection site?	Check: ☐Yes or ☐No	☐Yes or ☐No	☐Yes or ☐No	☐Yes or ☐No	☐Yes or ☐No	☐Yes or ☐No	☐Yes or ☐No	☐Yes or ☐No
8. Is there bruising at the injection site?	Check: ☐Yes or ☐No	☐Yes or ☐No	☐Yes or ☐No	☐Yes or ☐No	☐Yes or ☐No	☐Yes or ☐No	☐Yes or ☐No	☐Yes or ☐No

Grading Injection Site Pain or Itching:
Mild – Noticeable, does not interfere with activity
Moderate – Interferes with activity, limiting activities of daily life
Severe – Severely limiting self-care activities of daily living, incapacitating

STUDY NUMBER*:_____

Patient Number*		Date of Vaccine Administration	/ /	*To be completed by the site

Please answer all questions below daily for 7 days, beginning with day of treatment. Be sure to bring back this completed diary to your next clinic visit.

Solicited systemic AEs	Instructions	Date / /	Date / /	Date / /	Date / /	Date / /	Date / /	Date / /
1. Have you experienced any chills?	Check: ☐Yes or ☐No If yes, tell us if the chills are mild, moderate or severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe
2. Have you experienced nausea?	Check: ☐Yes or ☐No If yes, tell us if the nausea is mild, moderate or severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe
3. Have you experienced vomiting?	Check: ☐Yes or ☐No If yes, tell us if the vomiting is mild, moderate or severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe
4. Have you experienced diarrhea?	Check: ☐Yes or ☐No If yes, tell us if the diarrhea is mild, moderate or severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe
5. Have you experienced any headache?	Check: ☐Yes or ☐No If yes, tell us if the headache is mild, moderate or severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe
6. Have you experienced any fatigue?	Check: ☐Yes or ☐No If yes, tell us if the fatigue is mild, moderate or severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe
7. Have you experienced any muscle pain?	Check: ☐Yes or ☐No If yes, tell us if the muscle pain is mild, moderate or severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe
8. Have you experienced any abdominal discomfort/pain?	Check: ☐Yes or ☐No If yes, tell us if the abdominal discomfort/pain is mild, moderate or severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe
9. Have you experienced any joint pain?	Check: ☐Yes or ☐No If yes, tell us if the joint pain is mild, moderate or severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe	☐Yes or ☐No Mild Moderate Severe

STUDY NUMBER*:

Solicited systemic AEs	Instructions	Date / /	Date / /	Date / /	Date / /	Date / /	Date / /	Date / /
10. Record your daily temperature upon waking (do not drink anything 5 minutes before taking your temperature)	Fill in the temperature and time: If you temperature is 38°C for more than 24 hours, call your doctor	_____°C Time: ____:____ AM / PM ☐Not done	_____° C Time: ____:____ AM / PM ☐Not done	_____° C Time: ____:____ AM / PM ☐Not done	_____° C Time: ____:____ AM / PM ☐Not done	_____° C Time: ____:____ AM / PM ☐Not done	_____° C Time: ____:____ AM / PM ☐Not done	_____° C Time: ____:____ AM / PM ☐Not done

Grading Chills:
Mild: Mild sensation of cold, shivering, chattering of teeth
Moderate: Moderate tremor of entire body, medication taken
Severe: Prolonged or severe, does not respond to medication

Grading Nausea and Vomiting:
Mild: No interference with activity or 1 – 2 episodes/24 hours
Moderate: Some interference with activity or > 2 episodes/24 hours
Severe: Prevents daily activity, requires outpatient IV hydration

Grading Diarrhea:
Mild: 2 – 3 loose stools or < 400 gms/24 hours
Moderate: 4 – 5 stools or 400 – 800 gms/24 hours
Severe: 6 or more watery stools or > 800 gms/24 hours or requires outpatient IV hydration

Grading Headache:
Mild: No interference with activity
Moderate: Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity
Severe: Significant; any use of narcotic pain reliever or prevents daily activity

Grading Fatigue:
Mild: No interference with activity
Moderate: Some interference with activity
Severe: Significant; prevents daily activity

Grading Muscle Pain:
Mild: No interference with activity
Moderate: Some interference with activity
Severe: Significant; prevents daily activity

Grading Abdominal Discomfort/Pain:
Mild: No interference with activity
Moderate: Some interference with activity
Severe: Significant; prevents daily activity

Grading Joint Pain:
Mild: No interference with activity
Moderate: Some interference with activity
Severe: Significant; prevents daily activity

APPENDIX 2. SAMPLE DIARY FOR UNSOLICITED EVENTS

STUDY NUMBER*:_____

Patient Number*		**Date of Vaccine Administration**	/ /	***To be completed by the site**

Please complete this diary every day beginning on the day you receive the first dose of study vaccine until 30 days after you receive the last dose of study vaccine. Each page has space for recording 7 days of information. You will be provided with enough pages to last until 30 days after you receive the last dose of study vaccine. Be sure to bring this diary each time you visit the clinic and refer to this diary when study personnel contact you by telephone for schedule safety follow up assessments.

Unsolicited AEs	**Date** / /	**Date** / /	**Date** / /	**Date** / /	**Date** / /	**Date** / /	**Date** / /
Please describe any unusual feelings of discomfort, signs or symptoms that are not specified on the other daily diaries. If you do not experience these feelings, signs, or symptoms, please mark "no additional symptoms to report". For each separate sign and symptom you report in the diary, please note the following: • How intense it is, either **Mild** (no interference with activity), **Moderate** (some interference with activity), or **Severe** (significant; prevents daily activity) • How long it lasts • Any actions you took to manage the symptoms (for instance, taking medication)							

APPENDIX 3. SPONSOR SIGNATURE

Study Title:	Themba II T-Cell Vaccine: Phase 1/2 Study of the Safety, Reactogenicity, and Immunogenicity, of Vaccination with saRNA COVID-19 Vaccines
Study Number:	COVID-4.015
Version Number:	4
Final Date:	27 October 2022

This clinical trial protocol was subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed: _____ Date: _____

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