PHASE 1b OPEN-LABEL STUDY OF THE SAFETY, REACTOGENICITY, AND IMMUNOGENICITY OF A PROPHYLACTIC COVID-19 VACCINATION USING A 2ND GENERATION E1/E2B/E3-DELETED ADENOVIRAL PLATFORM IN HEALTHY SOUTH AFRICAN ADULTS (ProVIVA-SA-1)

Study Number:	AW_001_ProVIVA-SA-1
Study Sponsor:	ImmunityBio, Inc. 9920 Jefferson Blvd Culver City, CA 90232
Sponsor Contact: (For medical questions/emergencies)	Sandeep Bobby Reddy, MD Medical Monitor ImmunityBio, Inc. 9920 Jefferson Blvd Culver City, CA 90232 Cell Phone: +1-562-631-4945 Email: Bobby.Reddy@ImmunityBio.com

Protocol Version	Date
Version 4.0	6 April 2021

PROTOCOL SYNOPSIS

Name of Sponsor/Company: ImmunityBio Inc,
Name of Investigational Products: 1. hAd5-S-Fusion+N-ETSD
Name of Active Ingredients: 1. hAd5-S-Fusion+N-ETSD
Title of Study: Phase 1b Open-Label Study of the Safety, Reactogenicity, and Immunogenicity of a Prophylactic COVID-19 Vaccination using a 2nd Generation E1/E2B/E3-Deleted Adenoviral Platform in Healthy South African Adults(ProVIVA-SA-1)
Study Number: AW_001_ProVIVA-SA-1
Study Phase: Phase 1b
Rationale and Purpose: In December 2019, a group of pneumonia cases was reported at a wholesale seafood market in Wuhan in the Hubei province of China. The disease, which has subsequently become known as COVID-19, was found to be caused by a previously unknown coronavirus since named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first detected case of COVID-19 in South Africa was on 5th March 2020. The global and local pandemic that followed the initial outbreak has already resulted in a significant number of cases and deaths, as well as major and long-term economic, social and health sector damage. In countries that have already been severely affected, cross-sectional screening of the general population indicates that we are far from reaching “herd immunity” in those populations. There is therefore an urgent and unmet need for identification of therapies for treating COVID-19 disease and vaccines for preventing the disease. These interventions are essential to reducing morbidity and mortality and returning to a form of social and economic normalcy. Human adenovirus type 5 (hAd5) is an attractive vector for vaccine development against COVID-19 because it can be readily produced at scale and has a history of safe clinical use in a vaccine setting. However, the utility of first-generation hAd5 vectors is increasingly constrained due to widespread prevalence of adenoviral (i.e. vector) immunity in the general population. A phase 1 trial of an Ad5 candidate vaccine against SARS-CoV-2 in Wuhan has already demonstrated that there is a negative impact on immunogenicity in those with high Ad5 neutralising antibodies at baseline. The prior demonstration of an increased risk for HIV-1 acquisition in men who received a hAd5 vectored HIV vaccine, thought to be related to hAd5 vector induced immune responses, also needs to be considered when developing and testing a vaccine that needs inclusion of high HIV prevalence settings, such as a COVID-19 vaccine. To address the urgent need for a scalable, safe vaccine that can overcome the limitations of first-generation hAd5 vaccines a 2nd generation oncology hAd5 platform has been leveraged to

create a vaccine containing SARS-CoV-2 spike (S) and nucleocapsid(N) antigens. The 2nd generation hAd5 platform has already demonstrated safety and efficacy in 125 patients in 13 clinical trials including at the National Cancer Institute.
To avoid the adenovirus (Ad) immunization barrier for first generation Ad5 [E1-, E3-] vectors, the 2nd-generation hAd5 vector has two additional deletions in the E2b region, removing the DNA polymerase and the preterminal protein genes (E1-, E2b-, E3-). Deletion of the E2b region confers advantageous immune properties on the novel hAd5 vectors, eliciting potent immune responses to inserted antigens while minimizing the immune responses to Ad5 proteins. Thus, the hAd5 [E1-, E2b-, E3-] vector overcomes limitations of early generation vectors, as it permits the immunization of people who have been previously exposed to Ad5. Further, overcoming this vector induced immune responses thought to contribute to increased HIV acquisition risk makes the candidate feasible for testing in high HIV prevalence settings. We believe that hAd5 [E1-, E2b-, E3-] vectors are likely superior to Ad5 [E1-, E3-] vectors in immunogenicity and safety and are the best platform to develop a COVID-19 vaccine in a rapid and efficient manner.

To date, the majority of vaccine strategies in development involve developing immunogenicity against S protein. However, recent evidence in patients who recovered from COVID-19 demonstrates Th1 immunity generated against N protein (Grifoni 2020). A second report by Grifoni et al. further confirmed that in the predictive bioinformatics model, T and B cell epitopes were highest for both S and N (Grifoni 2020b).

The hAd5 vector with E1/E2b/E3 deletions has been engineered to express optimized forms of SARS-CoV-2 S and N proteins. The vaccine product, known as hAd5-S-Fusion+N-ETSD, encodes for an optimized S protein (S-Fusion) to enhance stability and cell surface expression of the critical Receptor Binding Domain(RBD); and N protein with an enhanced T-cell stimulation domain (N-ETSD) to enhance cell-mediated immunity. In vitro experiments showed that hAd5-S-Fusion+N-ETSD demonstrates enhanced expression and exposure of the S protein RBD relative to S alone. In an *in vivo* mouse model, hAd5-S-Fusion+N-ETSD was shown to stimulate antibody production and cell-mediated immunity following vaccination. IgG isotyping analysis demonstrated that hAd5-S-Fusion+N-ETSD also induced Th1 response. Sera from mice vaccinated with hAd5-S-Fusion+N-ETSD demonstrated robust neutralizing activity when tested in a live virus neutralization assay and in a surrogate neutralization assay probing RBD binding to receptor. Furthermore, on the basis of the recent clinical data from patients recovered from COVID-19 reported by Grifoni et al, as well as the corroborating preclinical data that the N protein induces long lasting CD4+ and Th1 cell-mediated immunity, it is hypothesized that this combination of S-Fusion+N-ETSD could provide long-lasting immunity beyond short term neutralizing antibodies.

Thus, it is the purpose of this trial to confirm the potential that by combining S with N, long-term cell- mediated immunity with a Th1 phenotype can be induced. The potential exists for this combination vaccine to serve as a long-term “universal” COVID-19 vaccine in light of mutations undergoing in S and the finding that the structural N protein is highly conserved in the coronavirus family. The trial is designed to assess the safety, reactogenicity and immunogenicity of hAd5-S-Fusion+N-ETSD and identify an optimal dose for future clinical studies.

In cohorts 3, 4, 5, and 6 of the study only participants who are SARS-CoV-2 antibody serology positive will be enrolled to evaluate boosting of pre-existing SARS-CoV-2 immune responses and compare the effect of route of administration on the efficacy (and magnitude thereof), reactogenicity and safety of the boosting effect. Our objective is to evaluate this novel vaccine candidate for its potential to boost pre-existing immune responses, where it might well have an important application in future to increase the magnitude and breadth of pre-existing immune responses to SARS-CoV-2 (due to either prior infection or prior vaccination) and provide enhanced, more durable immunity and protection against variants. We will test different routes of administration of the booster – that being subcutaneous, sublingual, subcutaneous plus sublingual, and intranasal. The sublingual administration involves use of the same study product but administered by syringe sublingually. The intranasal also involves the same study product with a delivery device designed for intranasal delivery through atomisation.

Study Objectives	**Study Endpoints**
Primary	
Safety: To determine the safety and reactogenicity of the hAd5-S-Fusion+N-ETSD vaccine at two dose levels for subcutaneous administration, and for sublingual and intranasal dosing.	Safety: • Incidence of MAAEs and SAEs through 1 week post final vaccine administration • Incidence and severity of solicited local reactogenicity AEs through 1 week post final vaccine administration • Incidence and severity of solicited systemic reactogenicity AEs through 1 week post final vaccine administration • Incidence and severity of unsolicited AEs through 1 week post final vaccine administration • Incidence of MAAEs and SAEs through 30 days and 6 months post final vaccine administration • Incidence and severity of unsolicited AEs through 30 days and 6 months post final vaccine administration • Incidence of abnormal changes of laboratory safety examinations • Changes in vital signs
Immunogenicity: To determine immunogenicity of hAd5-S-Fusion+N-ETSD as determined by changes in humoral response.	Immunogenicity: *Timing per Schedule of Events* • GMFR in IgG titer to SARS-CoV-2 S, RBD and N. • GMT of S-specific, RBD-specific, and N- specific antibodies against 2019 novel coronavirus tested by ELISA in serum . • Percentage of participants who seroconverted (defined as 4-fold change in antibody titer relative to baseline) . • GMFR in neutralizing antibody .

	• GMT of neutralizing antibody . • Seroconversion rate of neutralizing antibody (defined as 4-fold change in antibody titer relative to baseline) .
Secondary	
Safety: • Ascertainment of HIV infections in vaccine recipients through 12 months post final vaccine administration	Safety: • New HIV infections in vaccine recipients by either two locally approved rapid antibody tests or by ELISA, conducted per Schedule of Events through 12 months post final vaccine administration
Exploratory	
Immunogenicity: To determine cellular and mucosal immunogenicity of hAd5-S-Fusion+N-ETSD. To assess for any induction or enhancement of Ad5 immune response by the Ad5 vector in hAd5-S-Fusion+N-ETSD.	Immunogenicity: *Timing per Schedule of Events* • T cell activity against SARS-CoV-2 S, RBD and N protein • Mucosal Immunogenicity as assessed by GMT of IgA antibody levels to SARS CoV-2 S protein, RBD and N protein • T cell activity and IgG titres against Ad5, comparing baseline to day 29 and day 181 and 202(in cohorts 3, 4, 5, 6 and cohorts 1 and 2 respectively)

Study Design:

This is a phase 1b, open-label study in adult healthy participants. This clinical trial is designed to assess the safety, reactogenicity, and immunogenicity of the hAd5-S-Fusion+N-ETSD vaccine and select a dose for future studies. The hAd5-S-Fusion+N-ETSD vaccine is a hAd5 [E1-, E2b-, E3-] vector-based targeting vaccine encoding the SARS-CoV-2 S and N proteins. The hAd5-S-Fusion+N-ETSD vaccine is designed to induce both humoral and cellular responses even in individuals with pre-existing adenoviral immunity. Thus, the potential exists for the hAd5-S-Fusion+N-ETSD to induce SARS-CoV-2 immunity and prevent or lessen the health impact of COVID-19 infection in healthy participants.
Up to 60 healthy participants will be divided into 6 cohorts:

Study Cohorts, Dosing Schedules, Mode of Administration and Dose of hAd5-S-Fusion+N-ETSD

Cohort	Number of participants	Dosing Schedule	Mode of Administration	Dose
1	10	Day 1	SC	5×10^{10} VP
		Day 22	SC	5×10^{10} VP
2	10	Day 1	SC	1×10^{11} VP*
		Day 22	SC	1×10^{11} VP*
3	10	Day 1	SC	1×10^{11} VP*
4	10	Day 1	SL	1×10^{11} VP
5	10	Day 1	SC and SL	1×10^{11} VP* and 1×10^{11} VP
6	10	Day 1	IN	2 x10^{10} VP into each nostril**

SC= subcutaneous; SL= sublingual; IN= intranasal; VP= viral particles; * In the event of safety concerns participants will be dosed at 5×10^{10} VP/dose; ** Total IN dose is given is 4 x 10^{10} VP as vaccine will be administered into both nostrils

Cohort 1-2 enrolled participants who were SARS-CoV-2 antibody serology negative. For cohorts 3-6, only participants who are SARS-CoV-2 antibody serology positive will be enrolled to evaluate boosting of pre-existing SARS-CoV-2 immune responses and compare the effect of route of administration on the efficacy (and magnitude thereof), reactogenicity and safety of the boosting effect.

The Safety Review Committee (SRC), including at least one qualified infectious disease physician independent of the Sponsor and trial reviews safety data.

The SRC will first assess safety when all Cohort 1 participants have completed the toxicity assessment period (defined as 7 days after first vaccine dose, i.e. study day 8). In the absence of safety concerns, enrolment in Cohort 2 will be initiated. The SRC will similarly also assess safety when each of Cohort 2, 3, 4 and 5 participants have completed the toxicity assessment period (defined as 7 days after first vaccine dose, i.e. study day 8). In the absence of safety concerns, enrolment in Cohort 3, 4, 5 and 6 respectively will proceed. Cohorts 3 and 5 will be dosed at 1×10^{11} VP/dose for SC administrations. If safety concerns are identified at the higher dose of 1×10^{11} VP/dose, Cohort 3 and 5 participants will be dosed at 5×10^{10} VP/dose for SC administrations.

All participants will have follow up study visits for the collection of safety, reactogenicity, and/or immunogenicity data at 7 and 14 days after each vaccine dose, 30 days after the last dose, and at 90, 180 and 365 days following the last dose. Additional follow up for safety information will occur via telephone contact as noted in the Schedule of Events.
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 haematology 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). Solicited local and systemic AEs and unsolicited AEs will be collected using diary cards for 7 days following any dose of vaccine.
Solicited local AEs to be assessed include
Subcutaneous dosing includes injection site:

- Pain,
- Itching,
- Induration,
- Swelling,
- Erythema.

Sublingual dosing include:

- Oral burning,
- Oral swelling,
- Difficulty swallowing,
- Difficulty breathing.

Intranasal dosing include:

- Nasal congestion and coryza
- Epistaxis,
- Pain in the nose,

Solicited systemic AEs to be assessed include chills, fever, nausea, vomiting, diarrhoea, headache, fatigue, and myalgia. Safety visits and telephone calls will occur at scheduled times until 6 months after the last vaccine dose, and will be used to collect unsolicited AEs occurring since the last study contact, as well as any solicited AEs continuing beyond the 7-day period after vaccination.
Immunogenicity analyses will be conducted by collecting serum, peripheral blood mononuclear cell (PBMC) and saliva samples from individual patients before and after vaccinations to test for humoral- and cell- mediated immune responses. Immunogenicity assessments will be conducted for up to 1 year after the last vaccine dose.

Enrolment (planned): Up to 60 participants will be enrolled in this study.

Eligibility Criteria:
Inclusion Criteria:

1. Adults, age 18 – 50 years, inclusive, at time of first study vaccination.
2. SARS-CoV-2 antibody positive for cohorts 3, 4, 5, and 6 (by a locally approved serology assay)
3. Able to understand and provide a signed informed consent that fulfils the relevant Institutional Review Board (IRB) or Independent Ethics Committee (IEC) guidelines.
4. Agrees to the collection of biospecimens (e.g., nasopharyngeal [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. Body mass index(BMI) <30.00kg/m^2
7. Temperature < 38°C on day of first study vaccination.
8. Good general health as shown by medical history, physical exam, and screening laboratory tests
9. Screen negative for Tuberculosis per local screening guidelines
10. Male participants should all be at low risk of HIV acquisition based on pre-specified, validated criteria i.e. answering YES to any of the following questions:
    a. Are you sexually abstinent?
    b. Are you in a mutually monogamous relationship with a known HIV-uninfected partner?
    c. Have you had only one partner in the preceding 12 months who is believed to be HIV-uninfected and with whom condoms were used regularly?

Laboratory Inclusion Values/ Results:

11. Alanine aminotransferase (ALT) <1.1 times the upper limit of normal
12. Serum Creatinine <80 umol/L in females and <106 umol/L in males
13. Haemoglobin >12.0g/dL in females and >13.5g/dL in males
14. Platelets >150 x 10^9/L in all participants
15. No serological evidence of chronic infection with Hepatitis B (hepatitis B surface antigen (HepBSAg) negative by a locally approved assay) done during the screening period
16. No serological evidence of chronic infection with Hepatitis C (hepatitis C antibody(anti-HCV) negative by a locally approved assay) done during the screening period
17. Negative for SARS-CoV-2 (PCR test) on NP swab(or other appropriate respiratory specimen) within 3 days (calendar days) prior to the first study vaccination

18. A negative serum or urine pregnancy test during screening and on the day of and prior to each dose must be documented before the vaccine is administered to a female participant of childbearing potential.
19. Negative for HIV-1 and -2 on blood test(by either 2 rapid tests or an ELISA, both must be locally approved assays) done during the screening period.

Reproductive Status:

20. Female participants of childbearing potential must agree to consistently practice effective contraception for sexual activity that may lead to pregnancy while on study and until at least 30 days after the last dose of the study vaccine. Effective contraception for female participants includes:
21. Intrauterine device (IUD), or
22. Hormonal contraception (oral/ injectable/ implant/ transdermal etc.)

Or;

23. Non-sterile male participants must agree to use a condom or spermicide while on study until at least 30 days after the last dose of the study vaccine.

Or;

24. Participant must not be of reproductive potential or sterile(as verified by medical records), such as:
    - Having been diagnosed with menopause(with no menses for 1 year)
    - Having undergone hysterectomy, bilateral oophorectomy or orchidectomy
    - Having undergone surgical sterilization (e.g., vasectomy, tubal ligation)

Exclusion Criteria:

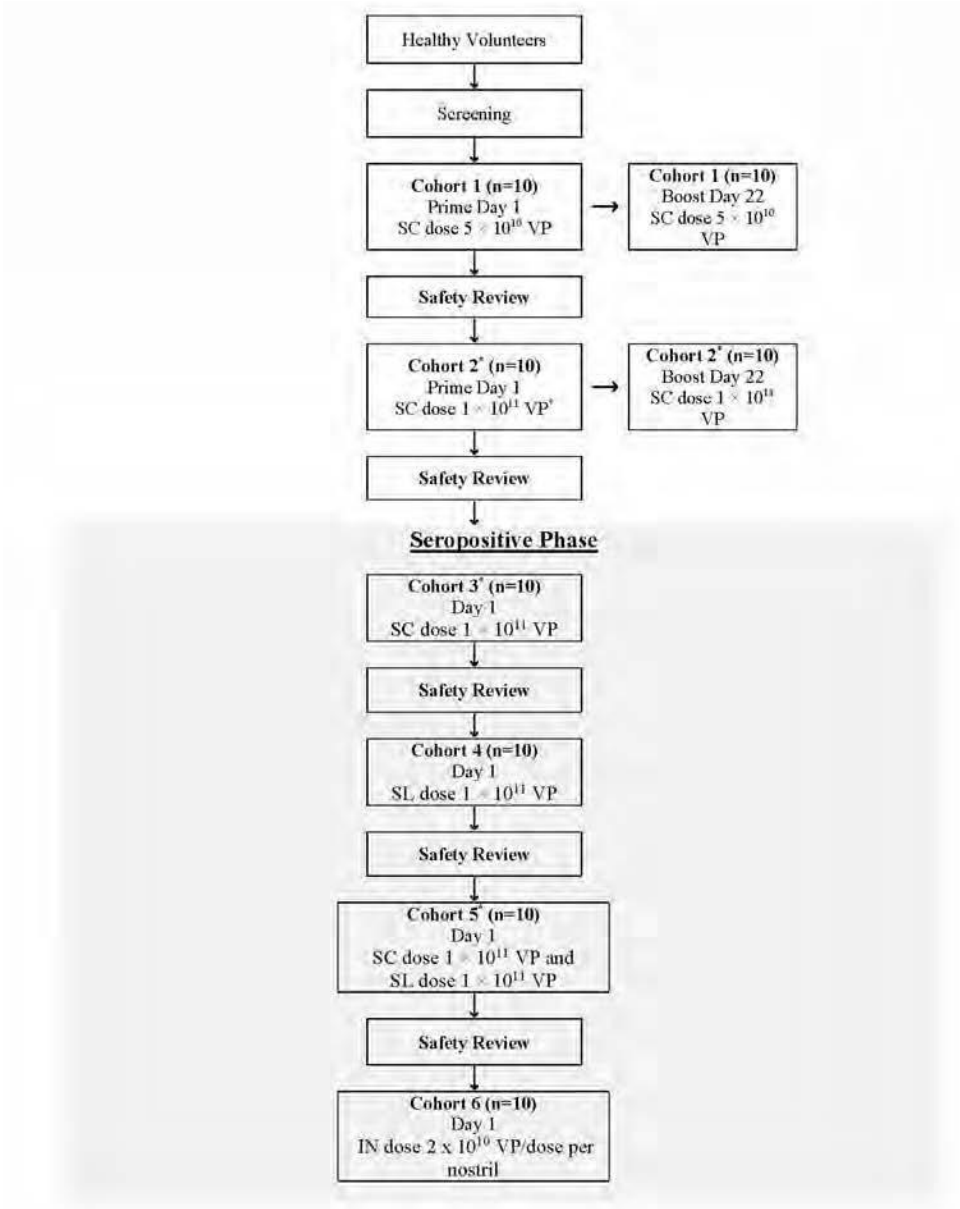
1. Serious adverse reaction to any vaccine, any unrelated medication or any component of the investigational vaccine, including a history of anaphylaxis and symptoms of a severe allergic reaction and history of allergies in the past.
2. Pregnant or breastfeeding women.
3. Live in a nursing home or long-term care facility.
4. Chronic lung disease or moderate to severe asthma
5. Bone marrow or organ transplant recipient
6. Diabetes.
7. Chronic kidney disease requiring dialysis.
8. Liver disease.
9. Any disease associated with acute fever, or any infection.
10. Chronic hepatitis B or hepatitis C infection.

11. HIV positive or other acquired or hereditary immunodeficiency.
12. Serious cardiovascular diseases, such as arrhythmia, conduction block, previous myocardial infarction, uncontrolled severe hypertension
13. History of hereditary, idiopathic or acquired angioedema.
14. Urticaria 12 months prior to screening.
15. No spleen or functional asplenia.
16. Platelet disorder or other bleeding disorder that may cause injection contraindication.
17. 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.
18. Prior administration of blood products within 120 days before first study vaccination.
19. Prior administration of other research medicines or investigational product within 30 days before first study vaccination.
20. Prior administration of attenuated vaccine within 30 days before first study vaccination.
21. Prior administration of inactivated vaccine within 14 days before first study vaccination.
22. Prior administration of SARS-CoV-2 vaccine or likely to receive SARS-CoV-2 vaccination within the upcoming 28 days
23. Current treatment with investigational agents for prophylaxis of COVID-19.
24. Have a household contact that has been diagnosed with COVID-19 within 14 days before first study vaccination.
25. Current anti-tuberculosis prophylaxis or therapy.
26. Currently receiving treatment for cancer or history of cancer in the last five years (except basal cell carcinoma of the skin and cervical carcinoma in situ).
27. 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.
28. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.

Duration of Treatment:
Each participant will receive hAd5-S-Fusion+N-ETSD on Day 1. Cohorts 1 & 2 receive a second dose of hAd5-S-Fusion+N-ETSD at Day 22.

Duration of Follow-up: Participants who receive study treatment will be followed by a health care professional until either death (by any cause) or for a minimum of 12 months past administration of last administration of hAd5-S-Fusion+N-ETSD.
Reference Therapy, Dosage, and Mode of Administration: Not applicable
Evaluation of Endpoints: **Safety**: Safety endpoints include assessments of treatment-emergent MAAEs, SAEs, solicited local and systemic reactogenicity AEs, unsolicited AEs, safety laboratory tests, HIV testing and vital signs. 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). **Immunogenicity:** GMT of S-specific and N specific antibodies against 2019 novel coronavirus, GMT of neutralizing antibody, and GMT of IgA antibody levels will be evaluated. T cell activity against SARS-CoV-2 S, RBD and N protein will be measured by standard immune assays. Humoral and cellular immunity against the Ad5 vector will be measured at baseline, day 29 and day 181 and 202 (in cohorts 3, 4, 5, 6 and cohorts 1 and 2 respectively) to assess for any induction or enhancement of Ad5 immune responses.
Statistical Methods: The purpose of this study is to determine the safety, reactogenicity, and immunogenicity of hAd5-S-Fusion+N-ETSD and select an optimal dose and formulation for future studies. Descriptive statistics will be presented for all study endpoints by individual cohort, pooled by dose level, and for all cohorts combined. Safety will be assessed by the incidence of treatment-emergent MAAEs, SAEs, and solicited local and systemic reactogenicity AEs, and unsolicited AEs for the time period of interest, overall and by grade using 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 also will be summarized. As suggested by the Ad5 literature and expert opinion, participants will be monitored for incident HIV infection during the follow up period . Immunology analyses will be used to provide an assessment of immune responses. GMFRs and GMTs and their associated 95% confidence intervals (CIs) will be computed by exponentiation of the corresponding log-transformed means and 95% CIs. The percentage of participants who seroconverted (as defined as 4-fold change in antibody titer relative to baseline) and 95% Clopper-Pearson CI will be summarized. Neutralizing antibody levels and CD8+ and CD4+ T-Cell activity also will be summarized.

Figure 1: Study Schema



* In the event of safety concerns participants will be dosed at 5×10^{10} VP/dose
SC= subcutaneous, SL= sublingual, IN= intranasal.

Table 9: Schedule of Events(A)

Cohorts 1 & 2

Study Period	**Baseline/ Screening**	**Dose 1 and initial follow up**			**Dose 2 and initial follow up**			**Extended Follow-up**								
Visit code	**Screening**	**01.0**	**02.0**	**03.0**	**04.0**	**05.0**	**06.0**	**07.0**	**08.0**	**09.0**	**10.0**	**11.0**	**12.0**	**13.0**	**14.0**	**EOS**
Study Day	**-14 to 0**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**52**	**82**	**112**	**142**	**172**	**202**	**292**	**387**
Days post 1st dose	**-**	**-**	**7**	**14**	**21**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Days post 2nd dose	**-**	**-**	**-**	**-**	**-**	**7**	**14**	**21**	**30**	**60**	**90**	**120**	**150**	**180**	**270**	**365**
Visit Type	☺	☺	☺	📞	☺	☺	📞	📞	☺	📞	☺	📞	📞	☺	☺	☺
Visit Windows (days)	-	**-**	± 1	± 1	± 1	± 1	± 1	± 1	± 5	± 5	± 14	± 14	± 14	± 14	± 14	± 28
Study Procedures																
Informed consent	X															
Assessment of Understanding	X															
Eligibility confirmation	X	X														
Demographics	X															
Medical history	X															
Tuberculosis Screening [l]	X															
HIV Risk Reduction Counselling [m]	X					X			X		X			X	X	X
COVID-19 history	X	**X**	X	X	**X**	X	X	X	X	X	X	X	X	X		X
Confirmation of contraceptive measures	X	**X**			**X**				X							
Symptom enquiry		**X**	X		**X**	X			X		X			X		X
Physical exam[i]: height, weight[b] and vital signs[c]	X	**X**	X		**X**	X			X		X			X		X
Concomitant medications	X	**X**	X		**X**	X			X		X			X		X
Study product administration																

hAd5-S-Fusion+N- ETSD		**X**			**X**											
Baseline reactogenicity assessment		**X**			**X**											
Assessment of immediate reactogenicity AEs[j]		**X**			**X**											
Subject training on diary card		**X**														
Diary cards issued		**X**			**X**											
Diary cards received and collected, solicited reactogenicity AEs reconciled			X			X										
In office unsolicited adverse event collection		**X**	X		**X**	X			X		X			X		
Telephone check-in 3 days (± 2) after vaccine administration		**X**			**X**											
Telephone safety follow up for unsolicited AEs and solicited reactogenicity AEs extending beyond 7 days				X			X	X		X		X	X			
Specimen Collection & Laboratory Assessments																
Urine or serum for Pregnancy test [h]	X	**X**			**X**				X							
Serum for chemistry panel [a,d]	X	**X**	X		**X**	X			X		X			X		
Whole blood for Haematology [a,e]	X	**X**	X		**X**	X			X		X			X		
Urine for Urinalysis [a,f]	X	**X**	X		**X**	X			X		X			X		
Whole blood/ Serum for HIV test[k]	X										X			X	X	X
Serum for Hepatitis B and C serology	X															
Serum for SARS-CoV-2 serology	X															

Biospecimens (e.g., NP swabs) for SARS-CoV-2 PCR	X	**X**	X		**X**	X			X		X			X	X	X
Whole blood, serum and saliva for immunogenicity [g]		**X**	X		**X**	X			X		X			X		X

Cohorts 3, 4, 5 and 6

Study Period	**Baseline/ Screening**	**Dose 1 and initial follow up**			**Extended Follow-up**								
Visit code	**Screening**	**01.0**	**02.0**	**03.0**	**04.0**	**05.0**	**06.0**	**07.0**	**08.0**	**09.0**	**10.0**	**11.0**	**EOS**
Study Day	**-14 to 0**	**1**	**8**	**15**	**22**	**31**	**61**	**91**	**121**	**151**	**181**	**271**	**366**
Days post dose	**-**	**-**	**7**	**14**	**21**	**30**	**60**	**90**	**120**	**150**	**180**	**270**	**365**
Visit Type	☺	☺	☺	📞	📞	☺	📞	☺	📞	📞	☺	☺	☺
Visit Windows (days)	-	**-**	± 1	± 1	± 1	± 5	± 5	± 14	± 14	± 14	± 14	± 14	± 28
Study Procedures													
Informed consent	X												
Assessment of Understanding	X												
Eligibility confirmation	X	X											
Demographics	X												
Medical history	X												
Tuberculosis Screening [l]	X												
HIV Risk Reduction Counselling [m]	X					X		X			X	X	X
COVID-19 history	X	**X**	X	X	X	X	X	X	X	X	X		X
Confirmation of contraceptive measures	X	**X**				X							
Symptom enquiry		**X**	X			X		X			X		X
Physical exam[i]: height, weight[b] and vital signs[c]	X	**X**	X			X		X			X		X

Concomitant medications	X	**X**	X			X		X			X		X
Study product administration													
hAd5-S-Fusion+N- ETSD		**X**											
Baseline reactogenicity assessment		**X**											
Assessment of immediate reactogenicity AEs[j]		**X**											
Subject training on diary card		**X**											
Diary cards issued		**X**											
Diary cards received and collected, solicited reactogenicity AEs reconciled			X										
In office unsolicited adverse event collection		**X**	X			X		X			X		
Telephone check-in 3 days (± 2) after vaccine administration		**X**											
Telephone safety follow up for unsolicited AEs and solicited reactogenicity AEs extending beyond 7 days				X	X		X		X	X			
Specimen Collection & Laboratory Assessments													
Urine or serum for Pregnancy test [h]	X	**X**				X							
Serum for chemistry panel [a,d]	X	**X**	X			X		X			X		
Whole blood for Haematology [a,e]	X	**X**	X			X		X			X		
Urine for Urinalysis [a,f]	X	**X**	X			X		X			X		
Whole blood/ Serum for HIV test[k]	X							X			X	X	X
Serum for Hepatitis B and C serology	X												

Serum for SARS-CoV-2 serology	X												
Biospecimens (e.g., NP swabs) for SARS-CoV-2 PCR	X	**X**	X			X		X			X	X	X
Whole blood, serum and saliva for immunogenicity [g]		**X**	X			X		X			X		X

[a] Day 1 chemistry, haematology, and urinalysis assessments do not need to be repeated if screening assessments were performed within 7 days prior to the first study vaccination; [b] Height required at screening visit only; [c] Vital signs of temperature, heart rate, blood pressure, and respiratory rate will be assessed at every visit. Temperature will be documented at each visit and subsequently if clinically indicated; [d] See Table 12 or additional details on laboratory assessments. Blood draws for lab assessments at vaccination visits should occur prior to vaccine administration; [e] Haematology to include FBC with differential (5 part) as outlined in Table 12. Blood draws for lab assessments at vaccination visits should occur prior to vaccine administration; [f] Urinalysis testing will include at a minimum protein, glucose, and presence of red blood cells. Sample collection at vaccination visits should occur prior to vaccine administration; [g] Immunogenicity testing includes measures of antibody response and cell-mediated immunity against target antigens, as well as hAd5 serostatus for determining baseline, day 29 and day 181 and 202(in cohorts 3, 4, 5, 6 and cohorts 1 and 2 respectively) hAd5 immunity and monitoring for anti-vector immune responses. Sample collection at vaccination visits should occur prior to vaccine administration.

[h] Serum or urine pregnancy tests for females of child-bearing potential at baseline/screening and each visit where study drug is administered, and at 30 days post last dose of vaccine; [I] Complete physical exam at screening visit. A routine symptom directed physical exam at subsequent visits; [J] Assessment of reactogenicity AEs includes a baseline assessment of the injection site and any signs or symptoms that may overlap with reactogenicity, as well as an assessment of immediate reactogenicity AEs 30 minutes after vaccine administration; [k] HIV pre- and post-test counselling are done at each visits where blood is taken for HIV testing; [l]Tuberculosis Screening per local guidelines

☺= In-person visit; 📞= Telephonic follow-up