PHASE 1b OPEN-LABEL STUDY OF THE SAFETY, REACTOGENICITY, AND IMMUNOGENICITY OF SUBCUTANEOUSLY AND ORALLY ADMINISTERED PROPHYLACTIC VACCINATION WITH 2ND GENERATION E1/E2B/E3-DELETED ADENOVIRAL-COVID-19 IN NORMAL HEALTHY VOLUNTEERS

Study Number:	COVID-4.005
IND Sponsor:	ImmunityBio, Inc. 9920 Jefferson Blvd Culver City, CA 90232
Sponsor Contact: **(For medical questions/emergencies)**	Lennie Sender, MD Medical Monitor ImmunityBio, Inc 9920 Jefferson Blvd Culver City, CA 90232 Email: lennie.sender@nantkwest.com Cell Phone: 714-615-2350

Protocol Version	**Date**
Version 1	22 December 2020

STATEMENT OF COMPLIANCE

This trial will be conducted in accordance with Good Clinical Practice (GCP) as described in the International Conference on Harmonization (ICH) Guideline for GCP (E6 [R2]) and in accordance with United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312) and the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an Institutional Review Board (IRB) prior to commencement. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Signed: _____ Date: _____

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
ImmunityBio, Inc.

Name of Investigational Products:
1. hAd5-S-Fusion+N-ETSD (Suspension for injection)
2. hAd5-S-Fusion+N-ETSD (Oral capsule)

Name of Active Ingredients:
1. hAd5-S-Fusion+N-ETSD
2. hAd5-S-Fusion+N-ETSD

Title of Study:
Phase 1b Open-Label Study of the Safety, Reactogenicity, and Immunogenicity of Subcutaneously and Orally Administered Prophylactic Vaccination with 2nd Generation E1/E2B/E3-Deleted Adenoviral-COVID-19 in Normal Healthy Volunteers

Study Number:
COVID-4.005

Study Phase:
Phase 1b

Rationale and Purpose: In December 2019, numerous pneumonia cases originating at a wholesale seafood market in Wuhan in the Hubei province of China were reported. The disease, which has subsequently become known as coronavirus disease 2019 (COVID-19), was found to be caused by a previously unknown coronavirus since named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The global pandemic that followed the initial outbreak has already resulted in approximately 75 million infections and over 1 million deaths as of December 2020, as well as significant economic damage due to shutdown of whole sectors in an effort to contain the virus. The United States (US) alone has reported more than 16 million infections and over 300,000 deaths. The virus continues to circulate in the human global population requiring continued preventive measures like social distancing and closing of nonessential businesses in the US and throughout the world. Identification of therapies for treating COVID-19 disease and vaccines for preventing the disease will be essential to reducing morbidity and mortality and returning to social and economic normalcy.

To address the urgent need for a vaccine, we have rapidly repurposed our 2nd generation oncology adenovirus type 5 (hAd5) platform into vaccines containing SARS-CoV-2 spike (S) and nucleocapsid (N) antigens. Our 2nd generation hAd5 platform has demonstrated safety and efficacy in 150 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, our 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 our 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. We believe that hAd5 [E1-, E2b-, E3-] vectors are 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, vaccine strategies in development all involve developing immunogenicity against S protein. However, recent evidence from Grifoni et al in patients who recovered from COVID-19 demonstrates Th1 immunity generated against N protein. 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. Our hAd5 vector with E1/E2b/E3 deletions has been engineered to express optimized forms of SARS-CoV-2 S and N proteins, known collectively as the hAd5-COVID-19-Product Series (PS). The first candidate in the hAd5-COVID-19-PS to be investigated in a clinical trial is hAd5-S-Fusion+N-ETSD (Suspension for injection), which is currently being assessed in an ongoing phase 1b clinical trial (QUILT-4.001; NCT04591717). The current trial is designed to investigate the safety and immunogenicity of hAd5-S-Fusion+N-ETSD (Oral capsule) in combination with hAd5-S-Fusion+N-ETSD (Suspension for injection) in healthy volunteers.

hAd5-S-Fusion+N-ETSD encodes for an optimized S protein (S-Fusion) to enhance stability and cell surface expression of 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 receptor binding domain (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 induced Th1 response. Sera from mice vaccinated with hAd5-S-Fusion+N-ETSD demonstrated robust neutralizing activity when tested in vitro 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 our hypothesis that this combination of S-Fusion+N-ETSD could provide long-lasting immunity beyond short term neutralizing antibodies.

Moreover, analyses of nonclinical studies in Sprague Dawley (SD) rats have shown that oral administration of hAd5-S-Fusion+N-ETSD results in no remarkable changes in clinical signs, hematology, clinical pathology, or urinalysis. Similarly, studies in non-human primates (NHPs) have shown that SC injection of hAd5-S-Fusion+N-ETSD followed by oral administration of enteric-coated capsules in rhesus macaques did not result in any treatment-related toxicities post a single SC injection or 7 days after an oral boost. Preliminary analysis of results from these studies have shown that all vaccinated NHP generated anti-S IgG and following SARS-CoV-2 challenge, viral replication was inhibited in all vaccinated NHP from day 1 post-challenge with complete protection in both nasal passages and lung. Furthermore, replicating SARS-CoV-2 dropped immediately and was undetectable as soon 3 days post-challenge in some NHP. In contrast, placebo-controlled animals demonstrated ongoing viral replication.

Together, these data suggest that the hAd5-S-Fusion+N-ETSD (Suspension for injection) is well tolerated when administered to human subjects SC; that there is little evidence of toxicity associated with the oral formulation of hAd5-S-Fusion+N-ETSD in either rodents or NHP; and further, that the combination holds promise in stimulating SARS-CoV-2-specific antibody production and rapid viral clearance. Advantages of the oral vaccine formulation are 1) that it offers ease of administration and the potential to increase patient compliance with scheduled vaccinations and 2) that it incorporates the gastrointestinal tract into the antigen sampling mechanism and therefore, the resultant immunity, which may result in the production of mucosal immunity and protection from invasion of epithelial tissues by SARS-CoV-2 virus.

Thus, the current study will investigate the safety, reactogenicity, and immunogenicity of the combination of SC and oral formulations of hAd5-S-Fusion+N-ETSD and identify an optimal dose for future clinical studies.

Study Objectives	Study Endpoints
Primary	
Safety: To determine the safety and reactogenicity of the combination of hAd5-S-Fusion+N-ETSD (Suspension for injection) and hAd5-S-Fusion+N-ETSD (Oral capsule).	• Incidence of medically-attended adverse events (MAAEs) and serious adverse events (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 post final vaccine administration • Incidence of abnormal changes of laboratory safety examinations • Changes in vital signs
Secondary	
Immunogenicity: To determine immunogenicity of the combination of hAd5-S-Fusion+N-ETSD (Suspension for injection) and hAd5-S-Fusion+N-ETSD (Oral capsule) as determined by changes in humoral and cellular response.	*Humoral Immunogenicity (Timing per Schedule of Events):* • GMFR in IgG titer • GMT of S-specific, RBD-specific, and N-specific antibodies against 2019 novel coronavirus tested by ELISA in serum • Percentage of subjects who seroconverted (as defined as 4-fold change in antibody titer relative to baseline) • GMFR in neutralizing antibody • GMT of neutralizing antibody

	• Seroconversion rate of neutralizing antibody (as defined as 4-fold change in antibody titer relative to baseline) *Cellular Immunogenicity (Timing per Schedule of Events):* • $CD8^+$ T-Cell activity against SARS-CoV-2 S protein, RBD, and N protein measured by ELISPOT assay • $CD4^+$ T-Cell activity against SARS-CoV-2 S protein, RBD, and N protein measured by standard immune assay

Study Design:

This is a phase 1b, open-label study in adult healthy subjects. This clinical trial is designed to assess the safety, reactogenicity, and immunogenicity the combination of hAd5-S-Fusion+N-ETSD (Suspension for injection) and hAd5-S-Fusion+N-ETSD (Oral capsule) and to select an optimal combination dose for future studies.

The study will be divided into 2 stages. Up to 40 healthy subjects will be enrolled to evaluate the safety, reactogenicity, and immunogenicity of four different treatment regimes. In this evaluation stage, subjects will be divided into 4 dosing cohorts with dosing schedule, mode of administration, and dosage as follows:

Cohort	Number of Subjects	Dosing Schedule	Mode of Administration	Dosage
1	10	Day 1	SC	1×10^{11} VP/dose
			Oral (PO)	1×10^{10} infectious units (IU)/dose
		Day 22	SC	1×10^{11} VP/dose
2	10	Day 1	SC	1×10^{11} VP/dose
			PO	1×10^{10} IU/dose
		Day 22	PO	1×10^{10} IU/dose
3	10	Day 1	PO	1×10^{10} IU/dose
		Day 22	PO	1×10^{10} IU/dose
4	10	Day 1	SC	1×10^{11} VP/dose
			PO	1×10^{10} IU/dose
		Day 15	PO	1×10^{10} IU/dose
		Day 22	PO	1×10^{10} IU/dose

PO (oral) doses are ± 0.5 log.

For subjects in cohorts 1 and 2, hAd5-S-Fusion+N-ETSD (Suspension for injection) and hAd5-S-Fusion+N-ETSD (Oral capsule) will be administered on day 1 (prime). Subjects in cohort 1 will be administered hAd5-S-Fusion+N-ETSD (Suspension for injection) again on day 22 (boost) and subjects in cohort 2 will be administered hAd5-S-Fusion+N-ETSD (Oral capsule) on day 22 (boost). For subjects in cohort 3, hAd5-S-Fusion+N-ETSD (Oral capsule) will be administered on days 1 (prime) and on day 22 (boost). For subjects in cohort 4, hAd5-S-Fusion+N-ETSD (Suspension for injection) and hAd5-S-Fusion+N-ETSD (Oral capsule) will be administered on day 1 (prime) and hAd5-S-Fusion+N-ETSD (Oral capsule) will be administered on days 15 (boost) and 22 (boost).

Up to 25 additional subjects will be enrolled in the expansion stage of the study. Based on safety and immunogenicity data gathered from cohorts 1-4, one treatment regimen will be selected for administration to subjects in cohort 5.

In addition to dosing visits described above, all subjects will have follow up study visits for the collection of safety, reactogenicity, and/or immunogenicity data. Additional follow up for safety information will occur via telephone contact as noted in the Schedule of Events.

Safety will be assessed for all subjects 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). Solicited local and systemic AEs will be collected using diaries for 7 days following any dose of vaccine. Solicited local AEs to be assessed include pain, itching, induration, swelling, and erythema at the injection site. Solicited systemic AEs to be assessed include chills, fever, nausea, vomiting, diarrhea, headache, fatigue, and myalgia. Unsolicited AEs will be recorded in a diary from time of first vaccine dose until 30 days after last vaccine dose. Safety visits and telephone calls will occur at scheduled times for one year after the last vaccine dose, and will be used to collect unsolicited AEs for 30 days post last vaccine dose, all MAAEs and SAEs for 6 months post last vaccine dose (related MAAEs and SAEs at any time), as well as any solicited AEs continuing beyond the 7-day period after vaccination.

Immunogenicity analyses will be conducted by collecting serum and peripheral blood mononuclear cell (PBMC) samples from individual patients before and after vaccinations to test for humoral- and cell-mediated immune responses. Neutralizing antibodies will be assessed. Immunogenicity assessments will be conducted for 1 year after the last vaccine dose.

Enrollment (planned):

Up to 65 subjects will be enrolled in this study.

Eligibility Criteria:

Inclusion Criteria:

1. Healthy adults, age 18 – 55 years, inclusive, at time of enrollment.
2. Able to understand and provide a signed informed consent that fulfills the relevant Institutional Review Board (IRB) or Independent Ethics Committee (IEC) guidelines.
3. Agrees to the collection of biospecimens (eg, nasopharyngeal [NP] swabs) and venous blood per protocol.
4. Ability to attend required study visits and return for adequate follow-up, as required by this protocol.
5. Ability to swallow a capsule.
6. Temperature < 38°C.
7. Negative for SARS-CoV-2 (qPCR or LAMP test) and no known previous COVID-19 exposure or disease.
8. Agreement to practice effective contraception for female subjects of childbearing potential and non-sterile males. Female subjects of childbearing potential must agree to use effective contraception while on study until at least 1 month after the last dose of vaccine. Non-sterile male subjects 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) used with spermicide, intrauterine devices (IUDs), oral contraceptives, and abstinence.

Exclusion Criteria:

1. Allergy to any component of the investigational vaccine, or a more severe allergic reaction and history of allergies in the past.
2. Pregnant and nursing women. 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 subject of childbearing potential.
3. Live in a nursing home or long-term care facility.
4. Chronic lung disease including chronic obstructive pulmonary disease (COPD) or moderate to severe asthma.
5. Pulmonary fibrosis.
6. Current or former smoker.
7. Bone marrow or organ transplantation.
8. Obesity (defined as body mass index [BMI] of 30 kg/m^2 or higher).
9. Diabetes.
10. Chronic kidney disease.
11. Liver disease.
12. Sickle cell disease.
13. Thalassemia.
14. Doctors, nurses, first responders, and other healthcare workers working in direct contact with COVID-19 patients.
15. Any disease associated with acute fever, or any infection.
16. Self-reported history of severe acute respiratory syndrome (SARS).
17. History of hepatitis B or hepatitis C.
18. HIV or other acquired or hereditary immunodeficiency.
19. Serious cardiovascular diseases, such as heart failure, coronary artery disease, cardiomyopathies, arrhythmia, conduction block, myocardial infarction, pulmonary hypertension, severe hypertension without controllable drugs, etc.
20. Cerebrovascular disease.
21. Cystic fibrosis.
22. Neurologic conditions, such as dementia.
23. Hereditary or acquired angioneurotic edema.
24. Urticaria in the last 12 months.
25. No spleen or functional asplenia.
26. Platelet disorder or other bleeding disorder that may cause injection contraindication.

27. Chronic use (more than 14 continuous days) of any medications that may be associated with impaired immune responsiveness within 3 months before administration of study vaccine. (Including, but not limited to, systemic corticosteroids exceeding 10 mg/day of prednisone equivalent, allergy injections, immunoglobulin, interferon, immunomodulators. The use of low dose topical, ophthalmic, inhaled and intranasal steroid preparations will be permitted.)
28. Prior administration of blood products in last 4 months.
29. Prior administration of other research medicines in last 1 month.
30. Received or plans to receive an attenuated vaccine within 1 month before or after each study vaccination.
31. Received or plans to receive an inactivated vaccine within 14 days before or after each study vaccination.
32. Current treatment with investigational, authorized, or approved agents for prophylaxis of COVID-19.
33. Have a household contact that has been diagnosed with COVID-19.
34. Current anti-tuberculosis prophylaxis or therapy.
35. 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).
36. According to the judgement of investigator, various medical, psychological, social or other conditions that could affect the subjects' ability to sign informed consent.
37. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.

Duration of Treatment:

In the evaluation stage of the study, subjects in cohorts 1-3 will receive vaccine on days 1 and 22. Subjects in cohort 4 will receive vaccine on days 1, 15, and 22.

In the expansion stage of the study, subjects' duration of treatment will be determined by the corresponding cohort treatment regimen selected from the evaluation stage.

Duration of Follow-up:

Subjects who receive vaccine will be followed by a health care professional until either death (by any cause) or for 1 year past last administration of hAd5-S-Fusion+N-ETSD (Suspension for injection) or hAd5-S-Fusion+N-ETSD (Oral capsule).

Reference Therapy, Dosage, and Mode of Administration:

Not applicable

Evaluation of Endpoints:

Safety: Safety endpoints include assessments of treatment-emergent MAAEs, SAEs, reactogenicity AEs, unsolicited AEs, safety laboratory tests, 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: Immunogenicity endpoints will include GMFR in IgG and additional antibody titers from baseline, and percentage of subjects who seroconverted defined as a 4-fold change in antibody titer from baseline. Neutralizing antibodies will be determined. ImmunityBio will calculate a relative IgG/Neutralization titer based on those data. $CD8^+$ T-Cell activity against SARS-CoV-2 S protein, RBD, and N protein will be measured by ELISPOT assay and $CD4^+$ T-Cell activity against SARS-CoV-2 S protein, RBD, and N protein will be measured by standard immune assays.

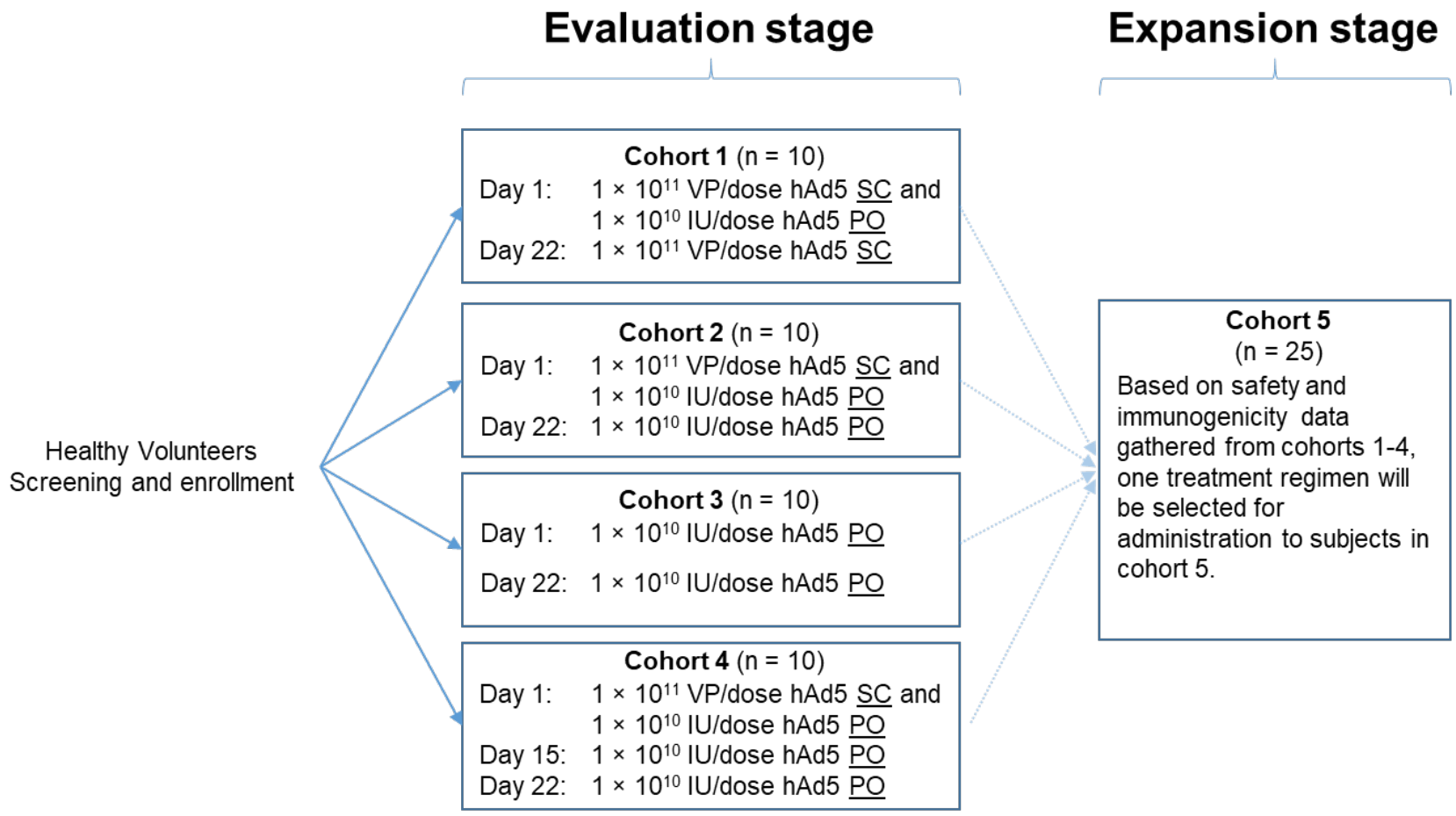
Statistical Methods:

The purpose of this study is to determine the safety, reactogenicity, and immunogenicity of the combination of hAd5-S-Fusion+N-ETSD (Suspension for injection) and hAd5-S-Fusion+N-ETSD (Oral capsule) and to select an optimal combination dose for future studies. Descriptive statistics will be presented for all study endpoints by individual cohort 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.

Immunology analyses will be used to provide an assessment of immune responses. Geometric mean fold rises (GMFRs) and geometric mean titers (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 subjects 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 will also be summarized. $CD8^+$ and $CD4^+$ T-Cell activity also will be summarized.

Figure 1: Phase 1b Study Schema



Abbreviations: hAd5 SC, hAd5-S-Fusion+N-ETSD (Suspension for injection); hAD5 PO, hAd5-S-Fusion+N-ETSD (Oral capsule); SC, subcutaneous; PO, by mouth (oral); IU, infectious units; VP, viral particles.

Table 10: Evaluation Stage (Cohorts 1-4): Schedule of Events

Study Period	**Baseline/ Screening[a]**	**Vaccine Administration and Initial Follow Up**							**Extended Follow Up**							**EOS**
Study Day	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**52**	**82**	**112**	**142**	**172**	**202**	**292**	**387**
Clinical visit number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**		**7**		**8**			**9**	**10**	**11**
Days post 1st dose			**7**	**14**	**21**											
Days post final dose						**7**	**14**	**21**	**30**	**60**	**90**	**120**	**150**	**180**	**270**	**365**
Windows (Days)		**± 1**							**± 5**		**± 14**				**± 28**	
General Assessments																
Informed consent	X															
Inclusion/ exclusion	X															
Demographics	X															
Medical history	X															
COVID-19 history of disease or exposure[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Confirm contraceptive measures	X	X		C4 only	X				X							
Physical exam: height, weight[c]	X	X	X	C4 only	X	X			X		X			X	X	X
Vital signs[d]	X	X	X	C4 only	X	X			X		X			X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Period	**Baseline/ Screening[a]**	**Vaccine Administration and Initial Follow Up**							**Extended Follow Up**							**EOS**
Study Day	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**52**	**82**	**112**	**142**	**172**	**202**	**292**	**387**
Clinical visit number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**		**7**		**8**			**9**	**10**	**11**
Days post 1st dose			**7**	**14**	**21**											
Days post final dose						**7**	**14**	**21**	**30**	**60**	**90**	**120**	**150**	**180**	**270**	**365**
Subject training on AE diaries		X														
Issue diaries for solicited and unsolicited AEs		X		C4 only	X											
Review and collect solicited AE diary			X		C4 only	X										
Review and collect unsolicited AE diary			X	X	X	X	X	X	X							
In office AE collection[e]		X	X	X	X	X	X		X		X			X	X	X
Telephone safety follow up								X		X		X	X			
Vaccine Administration																
Cohort 1		X[f]			X[g]											
Cohort 2		X[f]			X[h]											
Cohort 3		X[h]			X[h]											
Cohort 4		X[f]		X[h]	X[h]											

Study Period	**Baseline/ Screening[a]**	**Vaccine Administration and Initial Follow Up**							**Extended Follow Up**							**EOS**
Study Day	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**52**	**82**	**112**	**142**	**172**	**202**	**292**	**387**
Clinical visit number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**		**7**		**8**			**9**	**10**	**11**
Days post 1st dose			**7**	**14**	**21**											
Days post final dose						**7**	**14**	**21**	**30**	**60**	**90**	**120**	**150**	**180**	**270**	**365**
Laboratory Assessments																
Chemistry panel[a,i]	X	X	X	C4 only	X	X			X		X			X		
Hematology[a,j]	X	X	X	C4 only	X	X			X		X			X		
Urinalysis[a,k]	X	X	X	C4 only	X	X			X		X			X		
Collect biospecimens for SARS-CoV-2 testing[a]	X	X		C4 only	X				X		X			X	X	X
Collect whole blood for immunogenicity[l]		X	X	X	X	X	X		X		X			X	X	X
Pregnancy test[a,m]	X	X		C4 only	X											

Abbreviations: C4, cohort 4

[a] Day 1 chemistry, hematology, and urinalysis assessments do not need to be repeated if screening assessments were performed within 1 week prior to the start of treatment. Day 1 biospecimen collection for SARS-CoV-2 testing does not need to be repeated if screening assessments were performed within 48 hours prior to the start of treatment. Day 1 pregnancy testing does not need to be repeated if screening assessments were performed within 48 hours prior to the start of treatment.

[b] Potential exposure to SARS-CoV-2, symptoms of COVID-19, or outside testing results for SARS-CoV-2 infection will be collected at every study follow up visit and phone call.

[c] Full 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.
[d] 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.
[e] In office AE collection will continue to occur for 1 year, but only applicable AEs will be collected (see Section 7.2).
[f] Both hAd5-S-Fusion+N-ETSD (Suspension for injection) and hAd5-S-Fusion+N-ETSD (Oral capsule) will be administered.
[g] hAd5-S-Fusion+N-ETSD (Suspension for injection) will be administered only.
[h] hAd5-S-Fusion+N-ETSD (Oral capsule) will be administered only.
[i] See Table 9 for additional details on laboratory assessments. Blood draws for lab assessments should occur prior to vaccine administration.
[j] Hematology to include CBC with differential (5 part) as outlined in Table 9. Blood draws for lab assessments should occur prior to vaccine administration.
[k] Urinalysis testing will include at a minimum protein, glucose, and presence of red blood cells. Sample collection should occur prior to vaccine administration.
[l] Immunogenicity testing includes measures of antibody response and cell-mediated immunity against target antigens, as well as hAd5 serostatus for determining baseline hAd5 immunity and monitoring for anti-vector immune responses. 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.
[m] Serum or urine pregnancy tests for females of childbearing potential at baseline/screening and each visit where study drug is administered. Day 1 pregnancy testing does not need to be repeated if screening assessment was performed within 48 hours prior to the start of treatment.

Table 11: Escalation Stage (Cohort 5): Schedule of Events

The schedule below shows assessments for each of the evaluation stage cohorts 1-4. Based on safety and immunogenicity data gathered from cohorts 1-4, one treatment regimen will be selected for administration to subjects in cohort 5; only the corresponding assessments will apply in this escalation stage.

Study Period	**Baseline/ Screening[a]**	**Vaccine Administration and Initial Follow Up**							**Extended Follow Up**							**EOS**
Study Day	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**52**	**82**	**112**	**142**	**172**	**202**	**292**	**387**
Clinical visit number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**		**7**		**8**			**9**	**10**	**11**
Days post 1st dose			**7**	**14**	**21**											
Days post final dose						**7**	**14**	**21**	**30**	**60**	**90**	**120**	**150**	**180**	**270**	**365**
Windows (Days)		**± 1**							**± 5**		**± 14**				**± 28**	
General Assessments																
Informed consent	X															
Inclusion/ exclusion	X															
Demographics	X															
Medical history	X															
COVID-19 history of disease or exposure[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Confirm contraceptive measures	X	X		C4 only	X				X							
Physical exam: height, weight[c]	X	X	X	C4 only	X	X			X		X			X	X	X

Study Period	**Baseline/ Screening[a]**	**Vaccine Administration and Initial Follow Up**							**Extended Follow Up**							**EOS**
Study Day	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**52**	**82**	**112**	**142**	**172**	**202**	**292**	**387**
Clinical visit number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**		**7**		**8**			**9**	**10**	**11**
Days post 1st dose			**7**	**14**	**21**											
Days post final dose						**7**	**14**	**21**	**30**	**60**	**90**	**120**	**150**	**180**	**270**	**365**
Vital signs[d]	X	X	X	C4 only	X	X			X		X			X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject training on AE diaries		X														
Issue diaries for solicited and unsolicited AEs		X		C4 only	X											
Review and collect solicited AE diary			X		C4 only	X										
Review and collect unsolicited AE diary			X	X	X	X	X	X	X							
In office AE collection[e]		X	X	X	X	X	X		X		X			X	X	X
Telephone safety follow up								X		X		X	X			
Vaccine Administration																
Cohort 1		X[f]			X[g]											
Cohort 2		X[f]			X[h]											

Study Period	**Baseline/ Screening[a]**	**Vaccine Administration and Initial Follow Up**							**Extended Follow Up**							**EOS**
Study Day	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**52**	**82**	**112**	**142**	**172**	**202**	**292**	**387**
Clinical visit number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**		**7**		**8**			**9**	**10**	**11**
Days post 1st dose			**7**	**14**	**21**											
Days post final dose						**7**	**14**	**21**	**30**	**60**	**90**	**120**	**150**	**180**	**270**	**365**
Cohort 3		X[h]			X[h]											
Cohort 4		X[f]		X[h]	X[h]											
Laboratory Assessments																
Collect biospecimens for SARS-CoV-2 testing[a]	X	X		C4 only	X				X		X			X	X	X
Collect whole blood for immunogenicity[i]		X	X	X	X	X	X		X		X			X	X	X
Pregnancy test[a,j]	X	X		C4 only	X											

Abbreviations: C4, cohort 4

[a] Day 1 chemistry, hematology, and urinalysis assessments do not need to be repeated if screening assessments were performed within 1 week prior to the start of treatment. Day 1 biospecimen collection for SARS-CoV-2 testing does not need to be repeated if screening assessments were performed within 48 hours prior to the start of treatment. Day 1 pregnancy testing does not need to be repeated if screening assessments were performed within 48 hours prior to the start of treatment.

[b] Potential exposure to SARS-CoV-2, symptoms of COVID-19, or outside testing results for SARS-CoV-2 infection will be collected at every study follow up visit and phone call.

[c] Full 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.

[d] 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.

[e] In office AE collection will continue to occur for 1 year, but only applicable AEs will be collected (see Section 7.2).

[f] Both hAd5-S-Fusion+N-ETSD (Suspension for injection) and hAd5-S-Fusion+N-ETSD (Oral capsule) will be administered.

[g] hAd5-S-Fusion+N-ETSD (Suspension for injection) will be administered only.
[h] hAd5-S-Fusion+N-ETSD (Oral capsule) will be administered only.
[i] Immunogenicity testing includes measures of antibody response and cell-mediated immunity against target antigens, as well as hAd5 serostatus for determining baseline hAd5 immunity and monitoring for anti-vector immune responses. 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.
[j] Serum or urine pregnancy tests for females of childbearing potential at baseline/screening and each visit where study drug is administered. Day 1 pregnancy testing does not need to be repeated if screening assessment was performed within 48 hours prior to the start of treatment.

APPENDIX 4. SPONSOR SIGNATURE

Study Title:	Phase 1b Open-Label Study of the Safety, Reactogenicity, and Immunogenicity of Subcutaneously and Orally Administered Prophylactic Vaccination with 2nd Generation E1/E2B/E3-Deleted Adenoviral-COVID-19 in Normal Healthy Volunteers
Study Number:	COVID-4.005
Version Number:	1
Final Date:	22 December 2020

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

Signed: _____ Date: 12/22/2020

Lennie Sender, MD
Medical Monitor
ImmunityBio, Inc
9920 Jefferson Blvd
Culver City, CA 90232
Email: lennie.sender@nantkwest.com
Cell Phone: 714-615-2350

PHASE 1b OPEN-LABEL STUDY OF THE SAFETY, REACTOGENICITY, AND IMMUNOGENICITY OF SUBCUTANEOUSLY AND ORALLY ADMINISTERED PROPHYLACTIC VACCINATION WITH 2ND GENERATION E1/E2B/E3-DELETED ADENOVIRAL-COVID-19 IN NORMAL HEALTHY VOLUNTEERS

Study Number:	COVID-4.005
IND Sponsor:	ImmunityBio, Inc. 9920 Jefferson Blvd Culver City, CA 90232
Sponsor Contact: **(For medical questions/emergencies)**	Lennie Sender, MD Medical Monitor ImmunityBio, Inc 9920 Jefferson Blvd Culver City, CA 90232 Email: lennie.sender@nantkwest.com Cell Phone: 714-615-2350

Protocol Version	**Date**
Version 1	22 December 2020
Version 2	21 January 2021

STATEMENT OF COMPLIANCE

This trial will be conducted in accordance with Good Clinical Practice (GCP) as described in the International Conference on Harmonization (ICH) Guideline for GCP (E6 [R2]) and in accordance with United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312) and the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an Institutional Review Board (IRB) prior to commencement. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Signed: _____ Date: _____

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
ImmunityBio, Inc.

Name of Investigational Products:
1. hAd5-S-Fusion+N-ETSD (Suspension for injection)
2. hAd5-S-Fusion+N-ETSD (Oral capsule)

Name of Active Ingredients:
1. hAd5-S-Fusion+N-ETSD
2. hAd5-S-Fusion+N-ETSD

Title of Study:
Phase 1b Open-Label Study of the Safety, Reactogenicity, and Immunogenicity of Subcutaneously and Orally Administered Prophylactic Vaccination with 2nd Generation E1/E2B/E3-Deleted Adenoviral-COVID-19 in Normal Healthy Volunteers

Study Number:
COVID-4.005

Study Phase:
Phase 1b

Rationale and Purpose: In December 2019, numerous pneumonia cases originating at a wholesale seafood market in Wuhan in the Hubei province of China were reported. The disease, which has subsequently become known as coronavirus disease 2019 (COVID-19), was found to be caused by a previously unknown coronavirus since named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The global pandemic that followed the initial outbreak has already resulted in approximately 75 million infections and over 1 million deaths as of December 2020, as well as significant economic damage due to shutdown of whole sectors in an effort to contain the virus. The United States (US) alone has reported more than 16 million infections and over 300,000 deaths. The virus continues to circulate in the human global population requiring continued preventive measures like social distancing and closing of nonessential businesses in the US and throughout the world. Identification of therapies for treating COVID-19 disease and vaccines for preventing the disease will be essential to reducing morbidity and mortality and returning to social and economic normalcy.

To address the urgent need for a vaccine, we have rapidly repurposed our 2nd generation oncology adenovirus type 5 (hAd5) platform into vaccines containing SARS-CoV-2 spike (S) and nucleocapsid (N) antigens. Our 2nd generation hAd5 platform has demonstrated safety and efficacy in 150 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, our 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 our 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. We believe that hAd5 [E1-, E2b-, E3-] vectors are 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, vaccine strategies in development all involve developing immunogenicity against S protein. However, recent evidence from Grifoni et al in patients who recovered from COVID-19 demonstrates Th1 immunity generated against N protein. 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. Our hAd5 vector with E1/E2b/E3 deletions has been engineered to express optimized forms of SARS-CoV-2 S and N proteins, known collectively as the hAd5-COVID-19-Product Series (PS). The first candidate in the hAd5-COVID-19-PS to be investigated in a clinical trial is hAd5-S-Fusion+N-ETSD (Suspension for injection), which is currently being assessed in an ongoing phase 1b clinical trial (QUILT-4.001; NCT04591717). The current trial is designed to investigate the safety and immunogenicity of hAd5-S-Fusion+N-ETSD (Oral capsule) in combination with hAd5-S-Fusion+N-ETSD (Suspension for injection) in healthy volunteers.

hAd5-S-Fusion+N-ETSD encodes for an optimized S protein (S-Fusion) to enhance stability and cell surface expression of 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 receptor binding domain (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 induced Th1 response. Sera from mice vaccinated with hAd5-S-Fusion+N-ETSD demonstrated robust neutralizing activity when tested in vitro 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 our hypothesis that this combination of S-Fusion+N-ETSD could provide long-lasting immunity beyond short term neutralizing antibodies.

Moreover, analyses of nonclinical studies in Sprague Dawley (SD) rats have shown that oral administration of hAd5-S-Fusion+N-ETSD results in no remarkable changes in clinical signs, hematology, clinical pathology, or urinalysis. Similarly, studies in non-human primates (NHPs) have shown that SC injection of hAd5-S-Fusion+N-ETSD followed by oral administration of enteric-coated capsules in rhesus macaques did not result in any treatment-related toxicities post a single SC injection or 7 days after an oral boost. Preliminary analysis of results from these studies have shown that all vaccinated NHP generated anti-S IgG and following SARS-CoV-2 challenge, viral replication was inhibited in all vaccinated NHP from day 1 post-challenge with complete protection in both nasal passages and lung. Furthermore, replicating SARS-CoV-2 dropped immediately and was undetectable as soon 3 days post-challenge in some NHP. In contrast, placebo-controlled animals demonstrated ongoing viral replication.

Together, these data suggest that the hAd5-S-Fusion+N-ETSD (Suspension for injection) is well tolerated when administered to human subjects SC; that there is little evidence of toxicity associated with the oral formulation of hAd5-S-Fusion+N-ETSD in either rodents or NHP; and further, that the combination holds promise in stimulating SARS-CoV-2-specific antibody production and rapid viral clearance. Advantages of the oral vaccine formulation are 1) that it offers ease of administration and the potential to increase patient compliance with scheduled vaccinations and 2) that it incorporates the gastrointestinal tract into the antigen sampling mechanism and therefore, the resultant immunity, which may result in the production of mucosal immunity and protection from invasion of epithelial tissues by SARS-CoV-2 virus.

Thus, the current study will investigate the safety, reactogenicity, and immunogenicity of the combination of SC and oral formulations of hAd5-S-Fusion+N-ETSD and identify an optimal dose for future clinical studies.

Study Objectives	Study Endpoints
Primary	
Safety: To determine the safety and reactogenicity of the combination of hAd5-S-Fusion+N-ETSD (Suspension for injection) and hAd5-S-Fusion+N-ETSD (Oral capsule).	• Incidence of medically-attended adverse events (MAAEs) and serious adverse events (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 post final vaccine administration • Incidence of abnormal changes of laboratory safety examinations • Changes in vital signs
Secondary	
Immunogenicity: To determine immunogenicity of the combination of hAd5-S-Fusion+N-ETSD (Suspension for injection) and hAd5-S-Fusion+N-ETSD (Oral capsule) as determined by changes in humoral and cellular response.	*Humoral Immunogenicity (Timing per Schedule of Events):* • GMFR in IgG titer • GMT of S-specific, RBD-specific, and N-specific antibodies against 2019 novel coronavirus tested by ELISA in serum • Percentage of subjects who seroconverted (as defined as 4-fold change in antibody titer relative to baseline) • GMFR in neutralizing antibody • GMT of neutralizing antibody

	• Seroconversion rate of neutralizing antibody (as defined as 4-fold change in antibody titer relative to baseline) *Cellular Immunogenicity (Timing per Schedule of Events):* • $CD8^+$ T-Cell activity against SARS-CoV-2 S protein, RBD, and N protein measured by ELISPOT assay • $CD4^+$ T-Cell activity against SARS-CoV-2 S protein, RBD, and N protein measured by standard immune assay

Study Design:

This is a phase 1b, open-label study in adult healthy subjects. This clinical trial is designed to assess the safety, reactogenicity, and immunogenicity the combination of hAd5-S-Fusion+N-ETSD (Suspension for injection) and hAd5-S-Fusion+N-ETSD (Oral capsule) and to select an optimal combination dose for future studies.

The study will be divided into 2 stages. Up to 40 healthy subjects will be enrolled to evaluate the safety, reactogenicity, and immunogenicity of four different treatment regimens. In this evaluation stage, subjects will be divided into 4 dosing cohorts with dosing schedule, mode of administration, and dosage as follows:

Cohort	Number of Subjects	Dosing Schedule	Mode of Administration	Dosage
1	10	Day 1	SC	1×10^{11} VP/dose
			Oral (PO)	1×10^{10} infectious units (IU)/dose
		Day 22	SC	1×10^{11} VP/dose
2	10	Day 1	SC	1×10^{11} VP/dose
			PO	1×10^{10} IU/dose
		Day 22	PO	1×10^{10} IU/dose
3	10	Day 1	PO	1×10^{10} IU/dose
		Day 22	PO	1×10^{10} IU/dose
4	10	Day 1	SC	1×10^{11} VP/dose
			PO	1×10^{10} IU/dose
		Day 15	PO	1×10^{10} IU/dose
		Day 22	PO	1×10^{10} IU/dose

PO (oral) doses are ± 0.5 log.

For subjects in cohorts 1 and 2, hAd5-S-Fusion+N-ETSD (Suspension for injection) and hAd5-S-Fusion+N-ETSD (Oral capsule) will be administered on day 1 (prime). Subjects in cohort 1 will be administered hAd5-S-Fusion+N-ETSD (Suspension for injection) again on day 22 (boost) and subjects in cohort 2 will be administered hAd5-S-Fusion+N-ETSD (Oral capsule) on day 22 (boost). For subjects in cohort 3, hAd5-S-Fusion+N-ETSD (Oral capsule) will be administered on days 1 (prime) and on day 22 (boost). For subjects in cohort 4, hAd5-S-Fusion+N-ETSD (Suspension for injection) and hAd5-S-Fusion+N-ETSD (Oral capsule) will be administered on day 1 (prime) and hAd5-S-Fusion+N-ETSD (Oral capsule) will be administered on days 15 (boost) and 22 (boost).

Enrollment of the first 6 subjects will be staggered, with no more than 3 subjects enrolled per day for the first 2 days. On each of these days, vaccinations will occur at ≥ 3 hour intervals. Safety for these 6 subjects will be assessed by telephone follow up 24 and 48 hours after receiving the priming vaccination. The ImmunityBio Safety Review Committee (SRC) will conduct a review of 48 hour safety data on the first 6 subjects; vaccination of additional subjects will proceed if no safety concerns are identified.

Up to 25 additional subjects will be enrolled in the expansion stage of the study. Based on safety and immunogenicity data gathered from cohorts 1-4, one treatment regimen will be selected for administration to subjects in cohort 5.

In addition to dosing visits described above, all subjects will have follow up study visits for the collection of safety, reactogenicity, and/or immunogenicity data. Additional follow up for safety information will occur via telephone contact as noted in the Schedule of Events.

Safety will be assessed for all subjects 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). Solicited local and systemic AEs will be collected using diaries for 7 days following any dose of vaccine. Solicited local AEs to be assessed include pain, itching, induration, swelling, and erythema at the injection site. Solicited systemic AEs to be assessed include chills, fever, nausea, vomiting, diarrhea, headache, fatigue, and myalgia. Unsolicited AEs will be recorded in a diary from time of first vaccine dose until 30 days after last vaccine dose. Safety visits and telephone calls will occur at scheduled times for one year after the last vaccine dose, and will be used to collect unsolicited AEs for 30 days post last vaccine dose, all MAAEs and SAEs for 6 months post last vaccine dose (related MAAEs and SAEs at any time), as well as any solicited AEs continuing beyond the 7-day period after vaccination.

Immunogenicity analyses will be conducted by collecting serum and peripheral blood mononuclear cell (PBMC) samples from individual patients before and after vaccinations to test for humoral- and cell-mediated immune responses. Neutralizing antibodies will be assessed. Immunogenicity assessments will be conducted for 1 year after the last vaccine dose.

Enrollment (planned):

Up to 65 subjects will be enrolled in this study.

Eligibility Criteria:

Inclusion Criteria:

1. Healthy adults, age 18 – 55 years, inclusive, at time of enrollment.
2. Able to understand and provide a signed informed consent that fulfills the relevant Institutional Review Board (IRB) or Independent Ethics Committee (IEC) guidelines.
3. Agrees to the collection of biospecimens (eg, nasopharyngeal [NP] swabs) and venous blood per protocol.
4. Ability to attend required study visits and return for adequate follow-up, as required by this protocol.
5. Ability to swallow a capsule.
6. Temperature < 38°C.
7. Negative for SARS-CoV-2 (qPCR or LAMP test) and no known previous COVID-19 exposure or disease.
8. Agreement to practice effective contraception for female subjects of childbearing potential and non-sterile males. Female subjects of childbearing potential must agree to use effective contraception while on study until at least 1 month after the last dose of vaccine. Non-sterile

male subjects 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) used with spermicide, intrauterine devices (IUDs), oral contraceptives, and abstinence.

Exclusion Criteria:

1. Allergy to any component of the investigational vaccine, or a more severe allergic reaction and history of allergies in the past.
2. Pregnant and nursing women. 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 subject of childbearing potential.
3. Live in a nursing home or long-term care facility.
4. Chronic lung disease including chronic obstructive pulmonary disease (COPD) or moderate to severe asthma.
5. Pulmonary fibrosis.
6. Current or former smoker.
7. Bone marrow or organ transplantation.
8. Obesity (defined as body mass index [BMI] of 30 kg/m^2 or higher).
9. Diabetes.
10. Chronic kidney disease.
11. Liver disease.
12. Sickle cell disease.
13. Thalassemia.
14. Doctors, nurses, first responders, and other healthcare workers working in direct contact with COVID-19 patients.
15. Any disease associated with acute fever, or any infection.
16. Self-reported history of severe acute respiratory syndrome (SARS).
17. History of hepatitis B or hepatitis C.
18. HIV or other acquired or hereditary immunodeficiency.
19. Serious cardiovascular diseases, such as heart failure, coronary artery disease, cardiomyopathies, arrhythmia, conduction block, myocardial infarction, pulmonary hypertension, severe hypertension without controllable drugs, etc.
20. Cerebrovascular disease.
21. Cystic fibrosis.
22. Neurologic conditions, such as dementia.
23. Hereditary or acquired angioneurotic edema.

24. Urticaria in the last 12 months.
25. No spleen or functional asplenia.
26. Platelet disorder or other bleeding disorder that may cause injection contraindication.
27. Chronic use (more than 14 continuous days) of any medications that may be associated with impaired immune responsiveness within 3 months before administration of study vaccine. (Including, but not limited to, systemic corticosteroids exceeding 10 mg/day of prednisone equivalent, allergy injections, immunoglobulin, interferon, immunomodulators. The use of low dose topical, ophthalmic, inhaled and intranasal steroid preparations will be permitted.)
28. Prior administration of blood products in last 4 months.
29. Prior administration of other research medicines in last 1 month.
30. Received or plans to receive an attenuated vaccine within 1 month before or after each study vaccination.
31. Received or plans to receive an inactivated vaccine within 14 days before or after each study vaccination.
32. Current treatment with investigational, authorized, or approved agents for prophylaxis of COVID-19.
33. Have a household contact that has been diagnosed with COVID-19.
34. Current anti-tuberculosis prophylaxis or therapy.
35. 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).
36. According to the judgement of investigator, various medical, psychological, social or other conditions that could affect the subjects' ability to sign informed consent.
37. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.

Duration of Treatment:

In the evaluation stage of the study, subjects in cohorts 1-3 will receive vaccine on days 1 and 22. Subjects in cohort 4 will receive vaccine on days 1, 15, and 22.

In the expansion stage of the study, subjects' duration of treatment will be determined by the corresponding cohort treatment regimen selected from the evaluation stage.

Duration of Follow-up:

Subjects who receive vaccine will be followed by a health care professional until either death (by any cause) or for 1 year past last administration of hAd5-S-Fusion+N-ETSD (Suspension for injection) or hAd5-S-Fusion+N-ETSD (Oral capsule).

Reference Therapy, Dosage, and Mode of Administration:

Not applicable

Evaluation of Endpoints:

Safety: Safety endpoints include assessments of treatment-emergent MAAEs, SAEs, reactogenicity AEs, unsolicited AEs, safety laboratory tests, 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: Immunogenicity endpoints will include GMFR in IgG and additional antibody titers from baseline, and percentage of subjects who seroconverted defined as a 4-fold change in antibody titer from baseline. Neutralizing antibodies will be determined. ImmunityBio will calculate a relative IgG/Neutralization titer based on those data. $CD8^+$ T-Cell activity against SARS-CoV-2 S protein, RBD, and N protein will be measured by ELISPOT assay and $CD4^+$ T-Cell activity against SARS-CoV-2 S protein, RBD, and N protein will be measured by standard immune assays.

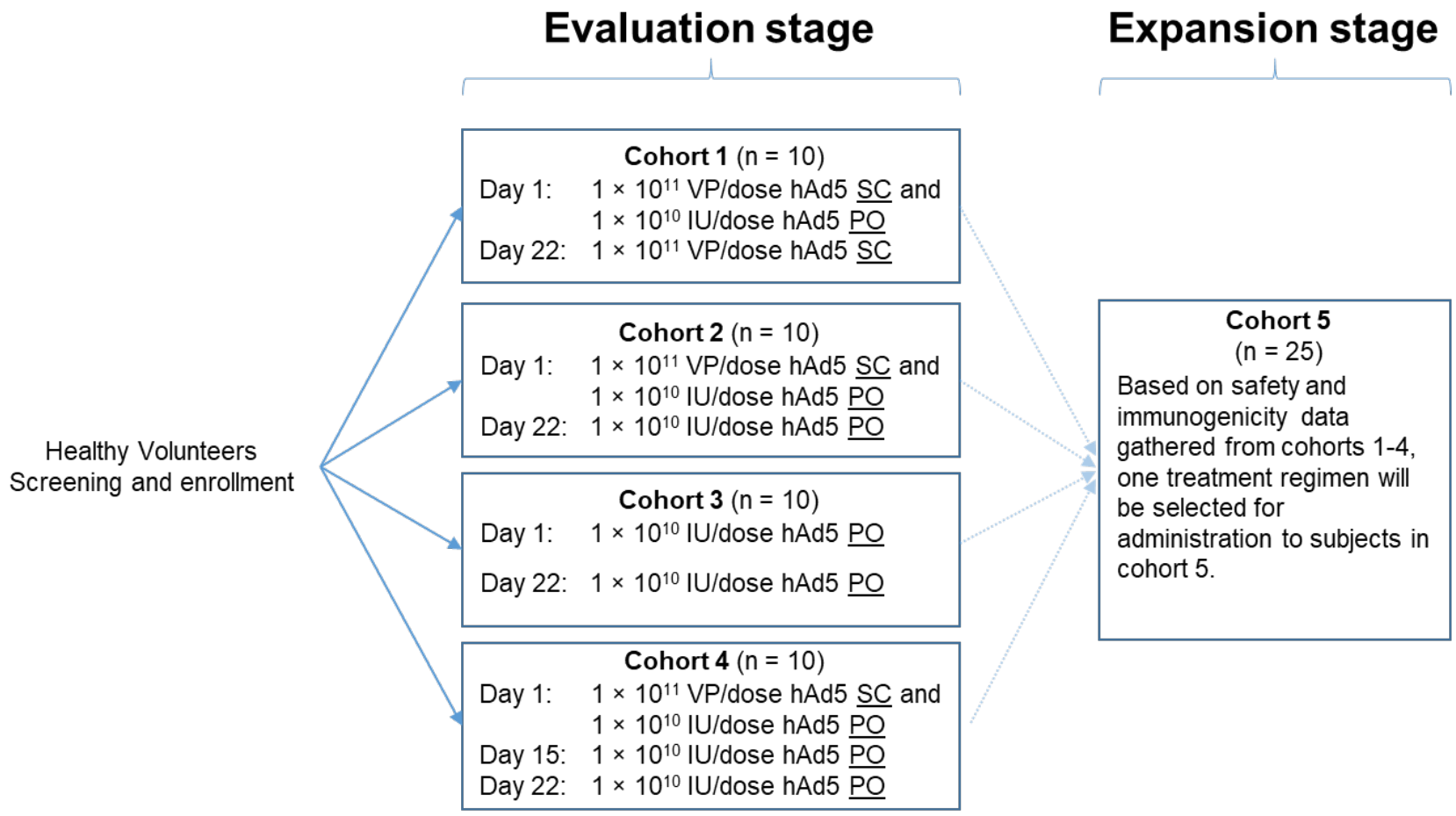
Statistical Methods:

The purpose of this study is to determine the safety, reactogenicity, and immunogenicity of the combination of hAd5-S-Fusion+N-ETSD (Suspension for injection) and hAd5-S-Fusion+N-ETSD (Oral capsule) and to select an optimal combination dose for future studies. Descriptive statistics will be presented for all study endpoints by individual cohort 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.

Immunology analyses will be used to provide an assessment of immune responses. Geometric mean fold rises (GMFRs) and geometric mean titers (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 subjects 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 will also be summarized. $CD8^+$ and $CD4^+$ T-Cell activity also will be summarized.

Figure 1: Phase 1b Study Schema



Abbreviations: hAd5 SC, hAd5-S-Fusion+N-ETSD (Suspension for injection); hAD5 PO, hAd5-S-Fusion+N-ETSD (Oral capsule); SC, subcutaneous; PO, by mouth (oral); IU, infectious units; VP, viral particles.

Table 10: Evaluation Stage (Cohorts 1-4): Schedule of Events

Study Period	**Baseline/ Screening[a]**	**Vaccine Administration and Initial Follow Up**							**Extended Follow Up**							**EOS**
Study Day	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**52**	**82**	**112**	**142**	**172**	**202**	**292**	**387**
Clinical visit number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**		**7**		**8**			**9**	**10**	**11**
Days post 1st dose			**7**	**14**	**21**											
Days post final dose						**7**	**14**	**21**	**30**	**60**	**90**	**120**	**150**	**180**	**270**	**365**
Windows (Days)		**± 1**							**± 5**		**± 14**				**± 28**	
General Assessments																
Informed consent	X															
Inclusion/ exclusion	X															
Demographics	X															
Medical history	X															
COVID-19 history of disease or exposure[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Confirm contraceptive measures	X	X		C4 only	X				X							
Physical exam: height, weight[c]	X	X	X	C4 only	X	X			X		X			X	X	X
Vital signs[d]	X	X	X	C4 only	X	X			X		X			X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Period	**Baseline/ Screening[a]**	**Vaccine Administration and Initial Follow Up**							**Extended Follow Up**							**EOS**
Study Day	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**52**	**82**	**112**	**142**	**172**	**202**	**292**	**387**
Clinical visit number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**		**7**		**8**			**9**	**10**	**11**
Days post 1st dose			**7**	**14**	**21**											
Days post final dose						**7**	**14**	**21**	**30**	**60**	**90**	**120**	**150**	**180**	**270**	**365**
Subject training on AE diaries		X														
Issue diaries for solicited and unsolicited AEs		X		C4 only	X											
Review and collect solicited AE diary			X		C4 only	X										
Review and collect unsolicited AE diary			X	X	X	X	X	X	X							
In office AE collection[e]		X	X	X	X	X	X		X		X			X	X	X
Telephone safety follow up								X		X		X	X			
Vaccine Administration																
Cohort 1		X[f]			X[g]											
Cohort 2		X[f]			X[h]											
Cohort 3		X[h]			X[h]											
Cohort 4		X[f]		X[h]	X[h]											

Study Period	**Baseline/ Screening[a]**	**Vaccine Administration and Initial Follow Up**							**Extended Follow Up**							**EOS**
Study Day	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**52**	**82**	**112**	**142**	**172**	**202**	**292**	**387**
Clinical visit number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**		**7**		**8**			**9**	**10**	**11**
Days post 1st dose			**7**	**14**	**21**											
Days post final dose						**7**	**14**	**21**	**30**	**60**	**90**	**120**	**150**	**180**	**270**	**365**
Laboratory Assessments																
Chemistry panel[a,i]	X	X	X	C4 only	X	X			X		X			X		
Hematology[a,j]	X	X	X	C4 only	X	X			X		X			X		
Urinalysis[a,k]	X	X	X	C4 only	X	X			X		X			X		
Collect biospecimens for SARS-CoV-2 testing[a]	X	X		C4 only	X				X		X			X	X	X
Collect whole blood for immunogenicity[l]		X	X	X	X	X	X		X		X			X	X	X
Pregnancy test[m]	X	X		C4 only	X											

Abbreviations: C4, cohort 4

[a] Day 1 chemistry, hematology, and urinalysis assessments do not need to be repeated if screening assessments were performed within 1 week prior to the start of treatment. Day 1 biospecimen collection for SARS-CoV-2 testing does not need to be repeated if screening assessments were performed within 48 hours prior to the start of treatment.

[b] Potential exposure to SARS-CoV-2, symptoms of COVID-19, or outside testing results for SARS-CoV-2 infection will be collected at every study follow up visit and phone call.

[c] Full 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.

[d] 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.
[e] Safety for the first 6 subjects enrolled will be assessed by telephone follow up 24 and 48 hours after receiving the priming vaccination. The ImmunityBio SRC will conduct a review of 48 hour safety data on the first 6 subjects; vaccination of additional subjects will proceed if no safety concerns are identified. In office AE collection will continue to occur for 1 year, but only applicable AEs will be collected (see Section 7.2).
f Both hAd5-S-Fusion+N-ETSD (Suspension for injection) and hAd5-S-Fusion+N-ETSD (Oral capsule) will be administered.
[g] hAd5-S-Fusion+N-ETSD (Suspension for injection) will be administered only.
[h] hAd5-S-Fusion+N-ETSD (Oral capsule) will be administered only.
[i] See Table 9 for additional details on laboratory assessments. Blood draws for lab assessments should occur prior to vaccine administration.
[j] Hematology to include CBC with differential (5 part) as outlined in Table 9. Blood draws for lab assessments should occur prior to vaccine administration.
[k] Urinalysis testing will include at a minimum protein, glucose, and presence of red blood cells. Sample collection should occur prior to vaccine administration.
[l] Immunogenicity testing includes measures of antibody response and cell-mediated immunity against target antigens, as well as hAd5 serostatus for determining baseline hAd5 immunity and monitoring for anti-vector immune responses. 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.
[m] Serum or urine pregnancy tests for females of childbearing potential at baseline/screening and each visit where study drug is administered.

Table 11: Escalation Stage (Cohort 5): Schedule of Events

The schedule below shows assessments for each of the evaluation stage cohorts 1-4. Based on safety and immunogenicity data gathered from cohorts 1-4, one treatment regimen will be selected for administration to subjects in cohort 5; only the corresponding assessments will apply in this escalation stage.

Study Period	**Baseline/ Screening[a]**	**Vaccine Administration and Initial Follow Up**							**Extended Follow Up**							**EOS**
Study Day	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**52**	**82**	**112**	**142**	**172**	**202**	**292**	**387**
Clinical visit number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**		**7**		**8**			**9**	**10**	**11**
Days post 1st dose			**7**	**14**	**21**											
Days post final dose						**7**	**14**	**21**	**30**	**60**	**90**	**120**	**150**	**180**	**270**	**365**
Windows (Days)		**± 1**							**± 5**		**± 14**				**± 28**	
General Assessments																
Informed consent	X															
Inclusion/ exclusion	X															
Demographics	X															
Medical history	X															
COVID-19 history of disease or exposure[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Confirm contraceptive measures	X	X		C4 only	X				X							
Physical exam: height, weight[c]	X	X	X	C4 only	X	X			X		X			X	X	X

Study Period	**Baseline/ Screening[a]**	**Vaccine Administration and Initial Follow Up**							**Extended Follow Up**							**EOS**
Study Day	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**52**	**82**	**112**	**142**	**172**	**202**	**292**	**387**
Clinical visit number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**		**7**		**8**			**9**	**10**	**11**
Days post 1st dose			**7**	**14**	**21**											
Days post final dose						**7**	**14**	**21**	**30**	**60**	**90**	**120**	**150**	**180**	**270**	**365**
Vital signs[d]	X	X	X	C4 only	X	X			X		X			X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject training on AE diaries		X														
Issue diaries for solicited and unsolicited AEs		X		C4 only	X											
Review and collect solicited AE diary			X		C4 only	X										
Review and collect unsolicited AE diary			X	X	X	X	X	X	X							
In office AE collection[e]		X	X	X	X	X	X		X		X			X	X	X
Telephone safety follow up								X		X		X	X			
Vaccine Administration																
Cohort 1		X[f]			X[g]											
Cohort 2		X[f]			X[h]											

Study Period	**Baseline/ Screening[a]**	**Vaccine Administration and Initial Follow Up**							**Extended Follow Up**							**EOS**
Study Day	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**52**	**82**	**112**	**142**	**172**	**202**	**292**	**387**
Clinical visit number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**		**7**		**8**			**9**	**10**	**11**
Days post 1st dose			**7**	**14**	**21**											
Days post final dose						**7**	**14**	**21**	**30**	**60**	**90**	**120**	**150**	**180**	**270**	**365**
Cohort 3		X[h]			X[h]											
Cohort 4		X[f]		X[h]	X[h]											
Laboratory Assessments																
Collect biospecimens for SARS-CoV-2 testing[a]	X	X		C4 only	X				X		X			X	X	X
Collect whole blood for immunogenicity[i]		X	X	X	X	X	X		X		X			X	X	X
Pregnancy test[j]	X	X		C4 only	X											

Abbreviations: C4, cohort 4

[a] Day 1 chemistry, hematology, and urinalysis assessments do not need to be repeated if screening assessments were performed within 1 week prior to the start of treatment. Day 1 biospecimen collection for SARS-CoV-2 testing does not need to be repeated if screening assessments were performed within 48 hours prior to the start of treatment.

[b] Potential exposure to SARS-CoV-2, symptoms of COVID-19, or outside testing results for SARS-CoV-2 infection will be collected at every study follow up visit and phone call.

[c] Full 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.

[d] 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.

[e] In office AE collection will continue to occur for 1 year, but only applicable AEs will be collected (see Section 7.2).

[f] Both hAd5-S-Fusion+N-ETSD (Suspension for injection) and hAd5-S-Fusion+N-ETSD (Oral capsule) will be administered.

[g] hAd5-S-Fusion+N-ETSD (Suspension for injection) will be administered only.

[h] hAd5-S-Fusion+N-ETSD (Oral capsule) will be administered only.
[i] Immunogenicity testing includes measures of antibody response and cell-mediated immunity against target antigens, as well as hAd5 serostatus for determining baseline hAd5 immunity and monitoring for anti-vector immune responses. 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.
[j] Serum or urine pregnancy tests for females of childbearing potential at baseline/screening and each visit where study drug is administered.

APPENDIX 4. SPONSOR SIGNATURE

Study Title:	Phase 1b Open-Label Study of the Safety, Reactogenicity, and Immunogenicity of Subcutaneously and Orally Administered Prophylactic Vaccination with 2nd Generation E1/E2B/E3-Deleted Adenoviral-COVID-19 in Normal Healthy Volunteers
Study Number:	COVID-4.005
Version Number:	2
Final Date:	21 January 2021

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

Signed: _____ Date: 1-21-2021

Lennie Sender, MD
Medical Monitor
ImmunityBio, Inc
9920 Jefferson Blvd
Culver City, CA 90232
Email: lennie.sender@nantkwest.com
Cell Phone: 714-615-2350

PHASE 1b OPEN-LABEL STUDY OF THE SAFETY, REACTOGENICITY, AND IMMUNOGENICITY OF SUBCUTANEOUSLY-, INTRAMUSCULARLY-, AND ORALLY-ADMINISTERED PROPHYLACTIC VACCINATION WITH 2ND GENERATION E1/E2B/E3-DELETED ADENOVIRAL-COVID-19 IN NORMAL HEALTHY VOLUNTEERS

Study Number:	COVID-4.005
IND Sponsor:	ImmunityBio, Inc. 9920 Jefferson Blvd Culver City, CA 90232
Sponsor Contact: **(For medical questions/emergencies)**	Lennie Sender, MD Medical Monitor ImmunityBio, Inc. 9920 Jefferson Blvd Culver City, CA 90232 Email: lennie.sender@immunitybio.com Cell Phone: 714-615-2350

Protocol Version	**Date**
Version 1	22 December 2020
Version 2	21 January 2021
Version 3	31 March 2021

STATEMENT OF COMPLIANCE

This trial will be conducted in accordance with Good Clinical Practice (GCP) as described in the International Conference on Harmonization (ICH) Guideline for GCP (E6 [R2]) and in accordance with United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312) and the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an Institutional Review Board (IRB) prior to commencement. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Signed: _____ Date: _____

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
ImmunityBio, Inc.

Name of Investigational Products:
1. hAd5-S-Fusion+N-ETSD (Suspension for injection and sublingual administration); hereafter referred to as hAd5-S-Fusion+N-ETSD (Suspension for injection)
2. hAd5-S-Fusion+N-ETSD (Oral capsule)

Name of Active Ingredients:
1. hAd5-S-Fusion+N-ETSD
2. hAd5-S-Fusion+N-ETSD

Title of Study:
Phase 1b Open-Label Study of the Safety, Reactogenicity, and Immunogenicity of Subcutaneously-, Intramuscularly-, and Orally-Administered Prophylactic Vaccination with 2nd Generation E1/E2B/E3-Deleted Adenoviral-COVID-19 in Normal Healthy Volunteers

Study Number:
COVID-4.005

Study Phase:
Phase 1b

Rationale and Purpose: In December 2019, numerous pneumonia cases originating at a wholesale seafood market in Wuhan in the Hubei province of China were reported. The disease, which has subsequently become known as coronavirus disease 2019 (COVID-19), was found to be caused by a previously unknown coronavirus since named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The global pandemic that followed the initial outbreak has resulted in significant morbidity and mortality in the US and throughout the world. The virus continues to circulate in the human global population requiring continued preventive measures like social distancing and closing of nonessential businesses in the US and throughout the world. Identification of therapies for treating COVID-19 disease and vaccines for preventing the disease will be essential to reducing morbidity and mortality and returning to social and economic normalcy.

To address the urgent need for a vaccine, we have rapidly repurposed our 2nd generation oncology adenovirus type 5 (hAd5) platform into vaccines containing SARS-CoV-2 spike (S) and nucleocapsid (N) antigens. Our 2nd generation hAd5 platform has demonstrated safety and efficacy in 150 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, our 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 our 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. We believe that hAd5 [E1-, E2b-, E3-] vectors are 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, vaccine strategies in development all involve developing immunogenicity against S protein. However, recent evidence from Grifoni et al in patients who recovered from COVID-19 demonstrates Th1 immunity generated against N protein. 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. Our hAd5 vector with E1/E2b/E3 deletions has been engineered to express optimized forms of SARS-CoV-2 S and N proteins, known collectively as the hAd5-COVID-19-Product Series (PS). The first candidate in the hAd5-COVID-19-PS to be investigated in a clinical trial is hAd5-S-Fusion+N-ETSD (Suspension for injection), which is currently being assessed in an ongoing phase 1b clinical trial (QUILT-4.001; NCT04591717). The current trial is designed to investigate the safety and immunogenicity of hAd5-S-Fusion+N-ETSD (Oral capsule) in combination with hAd5-S-Fusion+N-ETSD (Suspension for injection) in healthy volunteers.

hAd5-S-Fusion+N-ETSD encodes for an optimized S protein (S-Fusion) to enhance stability and cell surface expression of 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 receptor binding domain (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 induced Th1 response. Sera from mice vaccinated with hAd5-S-Fusion+N-ETSD demonstrated robust neutralizing activity when tested in vitro 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 our hypothesis that this combination of S-Fusion+N-ETSD could provide long-lasting immunity beyond short term neutralizing antibodies.

Moreover, analyses of nonclinical studies in Sprague Dawley (SD) rats have shown that oral administration of hAd5-S-Fusion+N-ETSD results in no remarkable changes in clinical signs, hematology, clinical pathology, or urinalysis. Similarly, studies in non-human primates (NHPs) have shown that SC injection of hAd5-S-Fusion+N-ETSD followed by oral administration of enteric-coated capsules in rhesus macaques did not result in any treatment-related toxicities post a single SC injection or 7 days after an oral boost. Preliminary analysis of results from these studies have shown that all vaccinated NHP generated anti-S IgG and following SARS-CoV-2 challenge, viral replication was inhibited in all vaccinated NHP from day 1 post-challenge with complete protection in both nasal passages and lung. Furthermore, replicating SARS-CoV-2 dropped immediately and was undetectable as soon 3 days post-challenge in some NHP. In contrast, placebo-controlled animals demonstrated ongoing viral replication.

Together, these data suggest that the hAd5-S-Fusion+N-ETSD (Suspension for injection) is well tolerated when administered to human subjects SC; that there is little evidence of toxicity associated with the oral formulation of hAd5-S-Fusion+N-ETSD in either rodents or NHP; and further, that the combination holds promise in stimulating SARS-CoV-2-specific antibody production and rapid viral clearance. Advantages of the oral vaccine formulation are 1) that it offers ease of administration and the potential to increase patient compliance with scheduled vaccinations and 2) that it incorporates the gastrointestinal tract into the antigen sampling mechanism and therefore, the resultant immunity, which may result in the production of mucosal immunity and protection from invasion of epithelial tissues by SARS-CoV-2 virus. Intramuscular (IM) administration of hAd5-based COVID-19 vaccines has not been explored in clinical trials, but hAd5 [E1-] vectors have been administered IM in human clinical trials and currently authorized vaccines have utilized this route of administration with proven effectiveness. Moreover, one vaccine authorized by FDA, Janssen Ad26.COV2.S, employs an adenovirus vector and is administered IM. Therefore, we have included IM administration of hAd5-S-

Fusion+N-ETSD in the current study to allow the comparison of safety and immunogenicity to SC administration. Thus, the current study will investigate the safety, reactogenicity, and immunogenicity of the combination of SC/IM and oral formulations of hAd5-S-Fusion+N-ETSD and identify an optimal dose for future clinical studies.	
Study Objectives	**Study Endpoints**
Primary	
Safety: To determine the safety and reactogenicity of the combination of hAd5-S-Fusion+N-ETSD (Suspension for injection) and hAd5-S-Fusion+N-ETSD (Oral capsule).	• Incidence of medically-attended adverse events (MAAEs) and serious adverse events (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 post final vaccine administration • Incidence of abnormal changes of laboratory safety examinations • Changes in vital signs
Secondary	
Immunogenicity: To determine immunogenicity of the combination of hAd5-S-Fusion+N-ETSD (Suspension for injection) and hAd5-S-Fusion+N-ETSD (Oral capsule) as determined by changes in humoral and cellular response.	*Humoral Immunogenicity (Timing per Schedule of Events):* • GMFR in IgG titer • GMT of S-specific, RBD-specific, and N-specific antibodies against 2019 novel coronavirus tested by ELISA in serum

	• Percentage of subjects who seroconverted (as defined as 4-fold change in antibody titer relative to baseline) • GMFR in neutralizing antibody • GMT of neutralizing antibody • Seroconversion rate of neutralizing antibody (as defined as 4-fold change in antibody titer relative to baseline) *Cellular Immunogenicity (Timing per Schedule of Events):* • $CD8^+$ T-Cell activity against SARS-CoV-2 S protein and N protein measured by ELISPOT assay • $CD4^+$ T-Cell activity against SARS-CoV-2 S protein and N protein measured by standard immune assay

Study Design:

This is a phase 1b, open-label study in adult healthy subjects. This clinical trial is designed to assess the safety, reactogenicity, and immunogenicity the combination of hAd5-S-Fusion+N-ETSD (Suspension for injection) and hAd5-S-Fusion+N-ETSD (Oral capsule) and to select an optimal combination dose for future studies.

The study will be divided into 2 stages. Up to 50 healthy subjects will be enrolled to evaluate the safety, reactogenicity, and immunogenicity of 5 different treatment regimens. In this evaluation stage, subjects will be divided into 5 dosing cohorts with dosing schedule, mode of administration, and dosage as follows:

Cohort	Number of Subjects	Dosing Schedule	Mode of Administration	Dosage
1	10	Day 1	SC	1×10^{11} VP/dose (4×10^{9} infectious units [IU]/dose)
			Oral (PO)	1×10^{10} IU/dose
		Day 22	SC	1×10^{11} VP/dose (4×10^{9} IU/dose)
2	10	Day 1	SC	1×10^{11} VP/dose (4×10^{9} IU/dose)
			PO	1×10^{10} IU/dose
		Day 22	PO	1×10^{10} IU/dose
3	10	Day 1	PO	1×10^{10} IU/dose
		Day 22	PO	1×10^{10} IU/dose
4	10	Day 1	SC	1×10^{11} VP/dose (4×10^{9} IU/dose)
			PO	1×10^{10} IU/dose
		Day 15	PO	1×10^{10} IU/dose
		Day 22	PO	1×10^{10} IU/dose
5	10	Day 1	Intramuscular (IM)	1×10^{11} VP/dose (4×10^{9} IU/dose)
			PO	1×10^{10} IU/dose
		Day 22	PO	1×10^{10} IU/dose

PO (oral) doses are ± 0.5 log.
Number of IU in this table and throughout protocol was calculated in accordance with Certificate of Analysis (COA) for lot number CO5028002.

For subjects in cohorts 1 and 2, hAd5-S-Fusion+N-ETSD (Suspension for injection) and hAd5-S-Fusion+N-ETSD (Oral capsule) will be administered on day 1 (prime). Subjects in cohort 1 will be administered hAd5-S-Fusion+N-ETSD (Suspension for injection) again on day 22 (boost) and subjects in cohort 2 will be administered hAd5-S-Fusion+N-ETSD (Oral capsule) on day 22 (boost). For subjects in cohort 3, hAd5-S-Fusion+N-ETSD (Oral capsule) will be administered on days 1 (prime) and on day 22 (boost). For subjects in cohort 4, hAd5-S-Fusion+N-ETSD (Suspension for injection) and hAd5-S-Fusion+N-ETSD (Oral capsule) will be administered on day 1 (prime) and hAd5-S-Fusion+N-ETSD (Oral capsule) will be administered on days 15 (boost) and 22 (boost). For subjects in cohort 5, hAd5-S-Fusion+N-ETSD (Suspension for injection) and hAd5-S-Fusion+N-ETSD (Oral

capsule) will be administered on day 1 (prime) and hAd5-S-Fusion+N-ETSD (Oral capsule) will be administered on day 22 (boost). Subjects in cohorts 1, 2, and 4 will be administered hAd5-S-Fusion+N-ETSD (Suspension for injection) via SC injection and subjects in cohort 5 will be administered hAd5-S-Fusion+N-ETSD (Suspension for injection) via IM injection.

Enrollment of the first 6 subjects will be staggered, with no more than 3 subjects enrolled per day for the first 2 days. On each of these days, vaccinations will occur at ≥ 3 hour intervals. Safety for these 6 subjects will be assessed by telephone follow up 24 and 48 hours after receiving the priming vaccination. The ImmunityBio Safety Review Committee (SRC) will conduct a review of 48 hour safety data on the first 6 subjects; vaccination of additional subjects will proceed if no safety concerns are identified.

Up to 25 additional subjects will be enrolled in the expansion stage of the study. Based on safety and immunogenicity data gathered from cohorts 1–5, one treatment regimen will be selected for administration to subjects in cohort 6.

In addition to dosing visits described above, all subjects will have follow up study visits for the collection of safety, reactogenicity, and/or immunogenicity data. Additional follow up for safety information will occur via telephone contact as noted in the Schedule of Events.

Safety will be assessed for all subjects 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). Solicited local and systemic AEs will be collected using diaries for 7 days following any dose of vaccine. Solicited local AEs to be assessed following both SC and IM administration include pain, itching, induration, swelling, and erythema at the injection site. Bleeding, bruising, and tingling/numbness will also be assessed following IM administration. Solicited systemic AEs to be assessed include chills, fever, nausea, vomiting, diarrhea, headache, fatigue, myalgia, and abdominal pain/discomfort. Unsolicited AEs will be recorded in a diary from time of first vaccine dose until 30 days after last vaccine dose. Safety visits and telephone calls will occur at scheduled times for one year after the last vaccine dose, and will be used to collect unsolicited AEs for 30 days post last vaccine dose, all MAAEs and SAEs for 6 months post last vaccine dose (related MAAEs and SAEs at any time), as well as any solicited AEs continuing beyond the 7-day period after vaccination.

Immunogenicity analyses will be conducted by collecting serum and peripheral blood mononuclear cell (PBMC) samples from individual patients before and after vaccinations to test for humoral- and cell-mediated immune responses. Neutralizing antibodies will be assessed. Immunogenicity assessments will be conducted for 1 year after the last vaccine dose.

Enrollment (planned):

Up to 75 subjects will be enrolled in this study.

Eligibility Criteria:

Inclusion Criteria:

1. Healthy adults, age 18 – 55 years, inclusive, at time of enrollment.
2. Able to understand and provide a signed informed consent that fulfills the relevant Institutional Review Board (IRB) or Independent Ethics Committee (IEC) guidelines.
3. Agrees to the collection of biospecimens (eg, nasopharyngeal [NP] swabs and saliva) and venous blood per protocol.

4. Ability to attend required study visits and return for adequate follow-up, as required by this protocol.
5. Ability to swallow a capsule.
6. Temperature < 38°C.
7. Negative for SARS-CoV-2 (qPCR or LAMP test).
8. Agreement to practice effective contraception for female subjects of childbearing potential and non-sterile males. Female subjects of childbearing potential must agree to use effective contraception while on study until at least 1 month after the last dose of vaccine. Non-sterile male subjects 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) used with spermicide, intrauterine devices (IUDs), oral contraceptives, and abstinence.

Exclusion Criteria:

1. Allergy to any component of the investigational vaccine, or a more severe allergic reaction and history of allergies in the past.
2. Pregnant and nursing women. 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 subject of childbearing potential.
3. Live in a nursing home or long-term care facility.
4. Chronic lung disease including chronic obstructive pulmonary disease (COPD) or moderate to severe asthma.
5. Pulmonary fibrosis.
6. Bone marrow or organ transplantation.
7. Obesity (defined as body mass index [BMI] of 30 kg/m^2 or higher).
8. Diabetes.
9. Chronic kidney disease.
10. Liver disease.
11. Sickle cell disease.
12. Thalassemia.
13. Doctors, nurses, first responders, and other healthcare workers working in direct contact with COVID-19 patients.
14. Any disease associated with acute fever, or any infection.
15. Self-reported history of severe acute respiratory syndrome (SARS).
16. History of hepatitis B or hepatitis C.
17. HIV or other acquired or hereditary immunodeficiency.

18. Serious cardiovascular diseases, such as heart failure, coronary artery disease, cardiomyopathies, arrhythmia, conduction block, myocardial infarction, pulmonary hypertension, severe hypertension without controllable drugs, etc.
19. Cerebrovascular disease.
20. Cystic fibrosis.
21. Neurologic conditions, such as dementia.
22. Hereditary or acquired angioneurotic edema.
23. Urticaria in the last 12 months.
24. No spleen or functional asplenia.
25. Platelet disorder or other bleeding disorder that may cause injection contraindication.
26. Chronic use (more than 14 continuous days) of any medications that may be associated with impaired immune responsiveness within 3 months before administration of study vaccine. (Including, but not limited to, systemic corticosteroids exceeding 10 mg/day of prednisone equivalent, allergy injections, immunoglobulin, interferon, immunomodulators. The use of low dose topical, ophthalmic, inhaled and intranasal steroid preparations will be permitted.)
27. Prior administration of blood products in last 4 months.
28. Prior administration of other research medicines in last 1 month.
29. Received or plans to receive an attenuated vaccine within 1 month before or after each study vaccination.
30. Received or plans to receive an inactivated vaccine within 14 days before or after each study vaccination.
31. Current treatment with investigational, authorized, or approved agents for prophylaxis of COVID-19.
32. Have a household contact that has been diagnosed with COVID-19.
33. Current anti-tuberculosis prophylaxis or therapy.
34. 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).
35. According to the judgement of investigator, various medical, psychological, social or other conditions that could affect the subjects' ability to sign informed consent.
36. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.

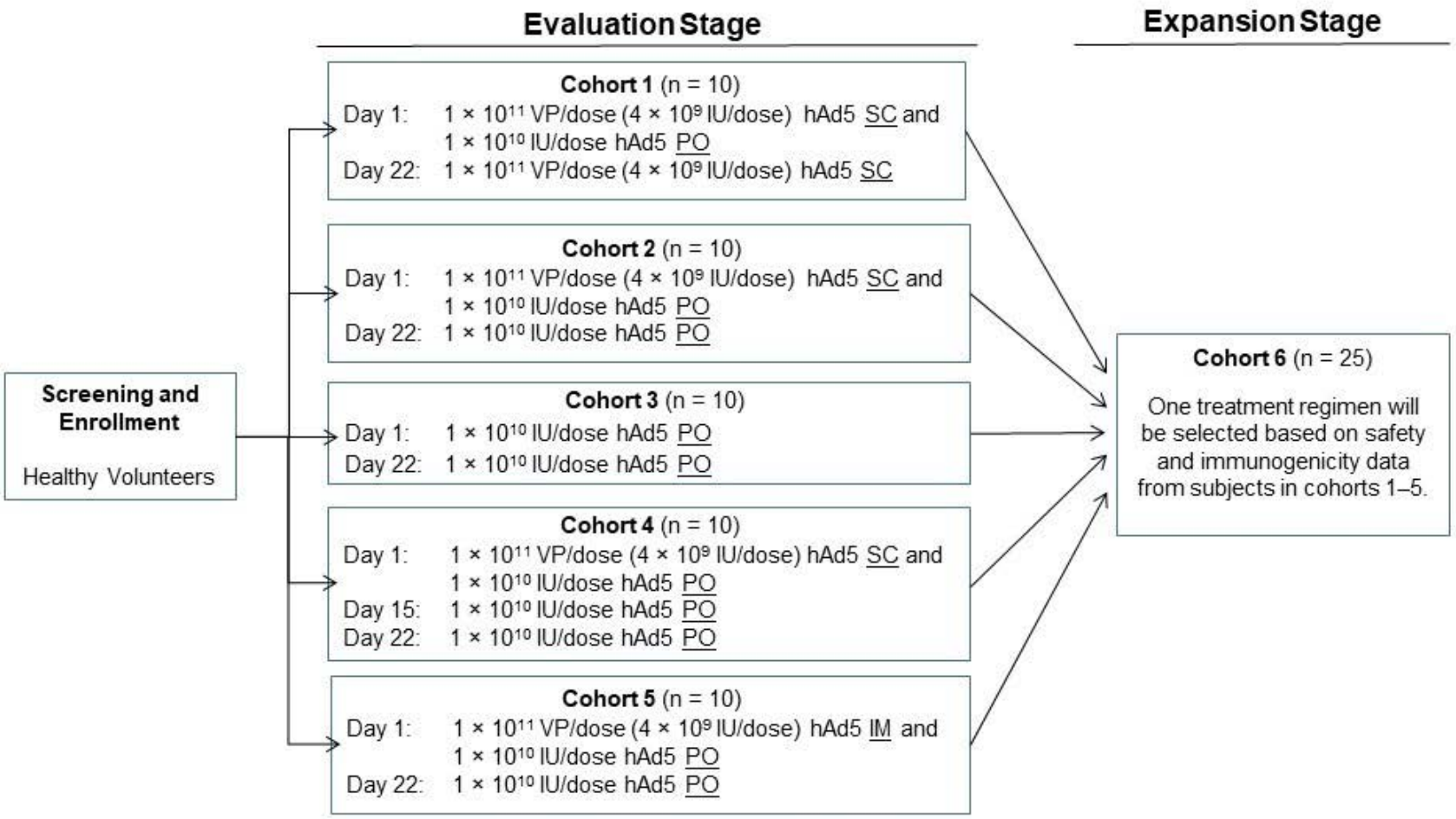
Duration of Treatment:

In the evaluation stage of the study, subjects in cohorts 1, 2, 3, and 5 will receive vaccine on days 1 and 22. Subjects in cohort 4 will receive vaccine on days 1, 15, and 22.

In the expansion stage of the study, subjects' duration of treatment will be determined by the corresponding cohort treatment regimen selected from the evaluation stage.

Duration of Follow-up: Subjects who receive vaccine will be followed by a health care professional until either death (by any cause) or for 1 year past last administration of hAd5-S-Fusion+N-ETSD (Suspension for injection) or hAd5-S-Fusion+N-ETSD (Oral capsule).
Reference Therapy, Dosage, and Mode of Administration: Not applicable
Evaluation of Endpoints: **Safety:** Safety endpoints include assessments of treatment-emergent MAAEs, SAEs, reactogenicity AEs, unsolicited AEs, safety laboratory tests, 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**: Immunogenicity endpoints will include GMFR in IgG and additional antibody titers from baseline, and percentage of subjects who seroconverted defined as a 4-fold change in antibody titer from baseline. Neutralizing antibodies will be determined. ImmunityBio will calculate a relative IgG/Neutralization titer based on those data. $CD8^+$ T-Cell activity against SARS-CoV-2 S protein and N protein will be measured by ELISPOT assay and $CD4^+$ T-Cell activity against SARS-CoV-2 S protein and N protein will be measured by standard immune assays.
Statistical Methods: The purpose of this study is to determine the safety, reactogenicity, and immunogenicity of the combination of hAd5-S-Fusion+N-ETSD (Suspension for injection) and hAd5-S-Fusion+N-ETSD (Oral capsule) and to select an optimal combination dose for future studies. Descriptive statistics will be presented for all study endpoints by individual cohort 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. Immunology analyses will be used to provide an assessment of immune responses. Geometric mean fold rises (GMFRs) and geometric mean titers (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 subjects 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 will also be summarized. $CD8^+$ and $CD4^+$ T-Cell activity also will be summarized.

Figure 1: Phase 1b Study Schema



Number of IU in this figure and throughout the protocol is calculated in accordance with Certificate of Analysis (COA) lot number CO5028002.
Abbreviations: hAd5 IM, hAd5-S-Fusion+N-ETSD (Suspension for injection) administered intramuscularly; hAd5 SC, hAd5-S-Fusion+N-ETSD (Suspension for injection) administered subcutaneously; hAD5 PO, hAd5-S-Fusion+N-ETSD (Oral capsule) administered by mouth (oral); IU, infectious units; VP, viral particles.

Table 10: Evaluation Stage (Cohorts 1–5): Schedule of Events

Study Period	**Baseline/ Screening[a]**	**Vaccine Administration and Initial Follow Up**							**Extended Follow Up**							**EOS**
Study Day	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**52**	**73**	**112**	**142**	**172**	**202**	**292**	**387**
Clinical visit number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**		**7**	**8**	**9**			**10**	**11**	**12**
Days post 1st dose			**7**	**14**	**21**											
Days post final dose						**7**	**14**	**21**	**30**	**51**	**90**	**120**	**150**	**180**	**270**	**365**
Windows (Days)		**± 1**							**± 5**		**± 14**				**± 28**	
General Assessments																
Informed consent	X															
Inclusion/ exclusion	X															
Demographics	X															
Medical history	X															
COVID-19 history of disease or exposure[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Confirm contraceptive measures	X	X		C4 only	X				X							
Physical exam: height, weight[c]	X	X	X	C4 only	X	X			X		X			X	X	X
Vital signs[d]	X	X	X	C4 only	X	X			X		X			X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Period	**Baseline/ Screening[a]**	**Vaccine Administration and Initial Follow Up**							**Extended Follow Up**							**EOS**
Study Day	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**52**	**73**	**112**	**142**	**172**	**202**	**292**	**387**
Clinical visit number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**		**7**	**8**	**9**			**10**	**11**	**12**
Days post 1st dose			**7**	**14**	**21**											
Days post final dose						**7**	**14**	**21**	**30**	**51**	**90**	**120**	**150**	**180**	**270**	**365**
Subject training on AE diaries		X														
Issue diaries for solicited and unsolicited AEs		X		C4 only	X											
Review and collect solicited AE diary			X		C4 only	X										
Review and collect unsolicited AE diary			X	X	X	X	X	X	X							
In office AE collection[e]		X	X	X	X	X	X		X	X	X			X	X	X
Telephone safety follow up[e]								X				X	X			
Vaccine Administration																
Cohort 1		X[f]			X[g]											
Cohort 2		X[f]			X[h]											
Cohort 3		X[h]			X[h]											
Cohort 4		X[f]		X[h]	X[h]											
Cohort 5		X[f]			X[h]											

Study Period	**Baseline/ Screening[a]**	**Vaccine Administration and Initial Follow Up**							**Extended Follow Up**							**EOS**
Study Day	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**52**	**73**	**112**	**142**	**172**	**202**	**292**	**387**
Clinical visit number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**		**7**	**8**	**9**			**10**	**11**	**12**
Days post 1st dose			**7**	**14**	**21**											
Days post final dose						**7**	**14**	**21**	**30**	**51**	**90**	**120**	**150**	**180**	**270**	**365**
Laboratory Assessments																
Chemistry panel[a,i]	X	X	X	C4 only	X				X		X			X		
Hematology[a,j]	X	X	X	C4 only	X				X		X			X		
Urinalysis[a,k]	X	X	X	C4 only	X				X		X			X		
Collect biospecimens for SARS-CoV-2 testing[a]	X	X		C4 only	X				X		X			X	X	X
Collect whole blood/saliva for immunogenicity[l]		X		C4 only	X		X		X	X	X			X	X	X
Pregnancy test[m]	X	X		C4 only	X											

Abbreviations: C4, cohort 4

[a] Day 1 chemistry, hematology, and urinalysis assessments do not need to be repeated if screening assessments were performed within 1 week prior to the start of treatment. Day 1 biospecimen collection for SARS-CoV-2 testing does not need to be repeated if screening assessments were performed within 72 hours prior to the start of treatment.

[b] Potential exposure to SARS-CoV-2, symptoms of COVID-19, or outside testing results for SARS-CoV-2 infection will be collected at every study follow up visit and phone call.

[c] Full 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.
[d] Vital signs of temperature, heart rate, blood pressure, and respiratory rate will be assessed. Temperature will be documented upon collection of vital signs and subsequently if clinically indicated. Day 1 collection of vital signs does not need to be repeated if screening assessments were performed within 72 hours prior to the start of treatment.
[e] Safety for the first 6 subjects enrolled will be assessed by telephone follow up 24 and 48 hours after receiving the priming vaccination. The ImmunityBio SRC will conduct a review of 48-hour safety data on the first 6 subjects; vaccination of additional subjects will proceed if no safety concerns are identified. In office AE collection will continue to occur for 1 year, but only applicable AEs will be collected (see Section 7.2).
[f] Both hAd5-S-Fusion+N-ETSD (Suspension for injection) and hAd5-S-Fusion+N-ETSD (Oral capsule) will be administered. hAd5-S-Fusion+N-ETSD (Suspension for injection) will be administered either SC (subjects in cohorts 1, 2, and 4) or IM (subjects in cohort 5).
[g] hAd5-S-Fusion+N-ETSD (Suspension for injection) will be administered SC only.
[h] hAd5-S-Fusion+N-ETSD (Oral capsule) will be administered only.
[i] See Table 9 for additional details on laboratory assessments. Blood draws for lab assessments should occur prior to vaccine administration.
[j] Hematology to include CBC with differential (5 part) as outlined in Table 9. Blood draws for lab assessments should occur prior to vaccine administration.
[k] Urinalysis testing will include at a minimum protein, glucose, and presence of red blood cells. Sample collection should occur prior to vaccine administration.
[l] Immunogenicity testing includes measures of antibody response and cell-mediated immunity against target antigens, as well as hAd5 serostatus for determining baseline hAd5 immunity and monitoring for antivector immune responses. Sample collection should occur prior to vaccine administration. A lab manual will be provided to the sites with detailed guidance for saliva collection, serum and PBMC preparation, storage, and shipping. Saliva and blood will be collected on all days indicated except days 10 (cohort 4 only) and 22, on which only blood will be collected.
[m] Serum or urine pregnancy tests for females of childbearing potential at baseline/screening and at each visit where study drug is administered.

Table 11: Escalation Stage (Cohort 6): Schedule of Events

The schedule below shows assessments for each of the evaluation stage cohorts 1–5. Based on safety and immunogenicity data gathered from cohorts 1–5, one treatment regimen will be selected for administration to subjects in cohort 6; only the corresponding assessments will apply in this escalation stage.

Study Period	**Baseline/ Screening[a]**	**Vaccine Administration and Initial Follow Up**							**Extended Follow Up**							**EOS**
Study Day	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**52**	**73**	**112**	**142**	**172**	**202**	**292**	**387**
Clinical visit number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**		**7**	**8**	**9**			**10**	**11**	**12**
Days post 1st dose			**7**	**14**	**21**											
Days post final dose						**7**	**14**	**21**	**30**	**51**	**90**	**120**	**150**	**180**	**270**	**365**
Windows (Days)		**± 1**							**± 5**		**± 14**				**± 28**	
General Assessments																
Informed consent	X															
Inclusion/ exclusion	X															
Demographics	X															
Medical history	X															
COVID-19 history of disease or exposure[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Confirm contraceptive measures	X	X		C4 only	X				X							
Physical exam: height, weight[c]	X	X	X	C4 only	X	X			X		X			X	X	X

Study Period	**Baseline/ Screening[a]**	**Vaccine Administration and Initial Follow Up**							**Extended Follow Up**							**EOS**
Study Day	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**52**	**73**	**112**	**142**	**172**	**202**	**292**	**387**
Clinical visit number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**		**7**	**8**	**9**			**10**	**11**	**12**
Days post 1st dose			**7**	**14**	**21**											
Days post final dose						**7**	**14**	**21**	**30**	**51**	**90**	**120**	**150**	**180**	**270**	**365**
Vital signs[d]	X	X	X	C4 only	X	X			X		X			X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject training on AE diaries		X														
Issue diaries for solicited and unsolicited AEs		X		C4 only	X											
Review and collect solicited AE diary			X		C4 only	X										
Review and collect unsolicited AE diary			X	X	X	X	X	X	X							
In office AE collection[e]		X	X	X	X	X	X		X	X	X			X	X	X
Telephone safety follow up								X				X	X			
Vaccine Administration																
Cohort 1		X[f]			X[g]											
Cohort 2		X[f]			X[h]											

Study Period	**Baseline/ Screening[a]**	**Vaccine Administration and Initial Follow Up**							**Extended Follow Up**							**EOS**
Study Day	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**52**	**73**	**112**	**142**	**172**	**202**	**292**	**387**
Clinical visit number	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**		**7**	**8**	**9**			**10**	**11**	**12**
Days post 1st dose			**7**	**14**	**21**											
Days post final dose						**7**	**14**	**21**	**30**	**51**	**90**	**120**	**150**	**180**	**270**	**365**
Cohort 3		X[h]			X[h]											
Cohort 4		X[f]		X[h]	X[h]											
Cohort 5		X[f]			X[h]											
Laboratory Assessments																
Collect biospecimens for SARS-CoV-2 testing[a]	X	X		C4 only	X				X		X			X	X	X
Collect whole blood/saliva for immunogenicity[i]		X		C4 only	X		X		X	X	X			X	X	X
Pregnancy test[j]	X	X		C4 only	X											

Abbreviations: C4, cohort 4

[a] Day 1 biospecimen collection for SARS-CoV-2 testing does not need to be repeated if screening assessments were performed within 72 hours prior to the start of treatment.

[b] Potential exposure to SARS-CoV-2, symptoms of COVID-19, or outside testing results for SARS-CoV-2 infection will be collected at every study follow up visit and phone call.

[c] Full 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.

[d] Vital signs of temperature, heart rate, blood pressure, and respiratory rate will be assessed. Temperature will be documented upon collection of vital signs and subsequently if clinically indicated. Day 1 collection of vital signs does not need to be repeated if screening assessments were performed within 72 hours prior to the start of treatment.

[e] In office AE collection will continue to occur for 1 year, but only applicable AEs will be collected (see Section 7.2).
[f] Both hAd5-S-Fusion+N-ETSD (Suspension for injection) and hAd5-S-Fusion+N-ETSD (Oral capsule) will be administered. hAd5-S-Fusion+N-ETSD (Suspension for injection) will be administered either SC (subjects in cohorts 1, 2, and 4) or IM (subjects in cohort 5).
[g] hAd5-S-Fusion+N-ETSD (Suspension for injection) will be administered SC only.
[h] hAd5-S-Fusion+N-ETSD (Oral capsule) will be administered only.
[i] Immunogenicity testing includes measures of antibody response and cell-mediated immunity against target antigens, as well as hAd5 serostatus for determining baseline hAd5 immunity and monitoring for anti-vector immune responses. Sample collection should occur prior to vaccine administration. A lab manual will be provided to the sites with detailed guidance for saliva collection, serum and PBMC preparation, storage, and shipping. Saliva and blood will be collected on all days indicated except days 10 (cohort 4 only) and 22, on which only blood will be collected.
[j] Serum or urine pregnancy tests for females of childbearing potential at baseline/screening and each visit where study drug is administered.

APPENDIX 3. SPONSOR SIGNATURE

Study Title:	Phase 1b Open-Label Study of the Safety, Reactogenicity, and Immunogenicity of Subcutaneously-, Intramuscularly-, and Orally-Administered Prophylactic Vaccination with 2nd Generation E1/E2B/E3-Deleted Adenoviral-COVID-19 in Normal Healthy Volunteers
Study Number:	COVID-4.005
Version Number:	3
Final Date:	31 March 2021

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

Signed: _____ Date: 04-01-2021

Lennie Sender, MD
Medical Monitor
ImmunityBio, Inc
9920 Jefferson Blvd
Culver City, CA 90232
Email: lennie.sender@immunitybio.com
Cell Phone: 714-615-2350