A PHASE 2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF A 2ND GENERATION E1/E2B/E3-DELETED ADENOVIRAL COVID-19 VACCINE: THE TCELLVACCINE TRIAL

Study Number:	COVID-3.001
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Protocol Version	**Date**
Version 1	16 November 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 subjects.

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

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

Title of Study:
A Phase 2/3, Placebo-Controlled, Randomized, Observer-Blind Study To Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of a 2nd Generation E1/E2B/E3-Deleted Adenoviral COVID-19 Vaccine: The TCELLVACCINE TRIAL

Study Number:
COVID-3.001

Study Phase:
Phase 2/3

Rationale and Purpose:

Introduction

The emergence of the novel coronavirus Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in late 2019 has led to the current Coronavirus Infectious Disease 2019 (COVID-19) pandemic that has had a catastrophic impact on global healthcare systems and economies. The WHO declared the spread of SARS-CoV-2 infection a pandemic on March 11, 2020. As of November 2020, 50 million people have been infected with the virus, resulting in 1.2 million deaths globally. In the United States, the pandemic has reached a rate of over 100,000 newly diagnosed infections per day. The ongoing COVID-19 pandemic requires expedited timelines to develop COVID-19 vaccine candidates as well as to identify vaccine platforms that can be implemented rapidly to respond to the inevitable next pandemic. Currently, numerous vaccine candidates intended to prevent COVID-19 are in development globally.

A failure to accomplish early control of SARS-CoV-2 infection in the respiratory tract results in high viral burden and continued shedding of virus, making individuals with such uncontrolled infection potential super-spreaders, particularly if they are asymptomatic and not in quarantine. A COVID-19 vaccine that can induce both humoral and cell-mediated immunity (CMI) has the potential to provide early viral control by facilitating adaptive CMI activation.

The Need to Induce T cell Response for Viral Clearance

Vaccine candidates currently in clinical testing have focused on the SARS-CoV-2 wild type spike (S) protein (S-WT) as the major antigen of choice and while pre-clinical and early clinical testing have shown that S elicits an antibody response, we believe the optimal vaccine candidate should be capable of inducing robust, durable T-cell responses as well as humoral responses. Antibody responses to SARS-CoV-2 can be detected in most COVID-19 patients 10-15 days following symptom onset, but these antibody responses decline to baseline in many patients within 3 months.

These findings suggest that vaccines focused solely on eliciting neutralizing antibodies to the S protein may be insufficient to elicit durable long-term immunity or reduce morbidity associated with SARS-CoV-2. We believe developing effective vaccines requires robust response from the adaptive immune system in order to ultimately clear the virus from infected cells. Evidence to support the notion that both T cells and antibodies are needed has been mounting since the outbreak of the pandemic.

The Importance of Both S and N Proteins for Broad CD4+ and CD8+ Memory T Cell Response

The importance of selecting SARS-CoV-2 vaccine antigens beyond the spike protein is supported by findings both from the outbreak of SARS-CoV in 2003 and the most recent reports on the importance of the nucleocapsid (N) protein found within the viral particle for T-cell activation in patients recovered from SARS-CoV-2.

Ferretti *et al.* determined the precise peptide sequences in SARS-CoV-2 that are recognized by memory $CD8^+$ T cells of COVID-19 patients. They reported that only 3 of 29 epitopes were located in the spike protein, with most epitopes located in ORF1 or the nucleocapsid protein. The importance of N for T-cell responses was also highlighted by Peng *et al.* in their 2006 report on immune responses to SARS-CoV wherein they stated in subjects who recovered from SARS-CoV, virus-N protein-specific memory $CD8^+$ T cells persist for at least 11 years, while memory B cells and antiviral antibodies were largely undetectable at these later time points. This was confirmed by Ng *et al.*, who also showed that memory T cell responses targeting the SARS coronavirus N-protein persist up to 11 years post-infection.

Specifically relevant for the current pandemic, Le Bert *et al.* showed that patients (n = 36) recovering from COVID-19 all had $CD4^+$ and $CD8^+$ T cells that recognized multiple regions of the N protein. Le Bert also looked at patients who recovered from SARS (the disease associated with SARS-CoV infection) and found they possess long-lasting memory T cells that are reactive to the N protein of SARS-CoV 17 years after the outbreak of SARS in 2003. These memory T cells from SARS-CoV patients displayed robust cross-reactivity to the N protein of SARS-CoV-2, reflecting the highly conserved nature of the N protein.

Consistent with the findings of T-cell protection following SARS-CoV-1 infection, recent studies have demonstrated that in SARS-CoV-2, T cells play an important role independent of seroconversion, that is, antibody production. Recently, Sekine *et al.* reported that in convalescent individuals with asymptomatic or mild COVID-19, SARS-CoV-2 specific CD4+ and CD8+ T cells were identified and these T cells displayed an activated cytotoxic phenotype. Of significance was the finding of polyfunctional SARS-CoV-2 specific T cells in seronegative, asymptomatic individuals. Confirmation of the protective effect of T cells was provided by an English study of hospital workers and first responders, in which it was found that SARS-CoV-2 responsive T cell numbers were associated with protection from COVID-19.

In further support of the merits of the addition of N as an antigen in our vaccine candidate to stimulate T-cell activation and provide protection even if antibody responses wane, is a concern that mutation of the spike protein may render neutralizing antibodies less effective. Recently, reports from Denmark and Scotland indicated that SARS-CoV-2 strains expressing mutated versions of spike have been identified and that anti-spike antibodies from convalescent sera are less effective in neutralizing these mutated SARS-CoV-2 viruses.

Rational Design of a COVID-19 Vaccine to Induce Humoral and Cell Mediated Immunity

Based on the above knowledge and concerns, ImmunityBio has developed a second-generation COVID-19 vaccine, targeting not just spike (S), but also the highly antigenic and T-cell activating viral nucleocapsid protein. This COVID-19 vaccine, hAd5-S-Fusion+N-ETSD, is distinctive in multiple aspects of design including: (1) use of a second-generation adenovirus vector platform capable of delivering the transgene even in the presence of pre-existing adenovirus immunity; (2) targeting of both spike and nucleocapsid immunogenic SARS-CoV-2 proteins; (3) generation of enhanced antibody and CD4+/CD8+ T cell Th1 dominant immune activation responses by molecular trafficking of N to the endo/lysosomal compartment through the design of ETSD (Enhanced T cell Stimulating Domain); (4) suitability for delivery by multiple routes including subcutaneous, oral and intranasal to achieve mucosal, antibody and long-term cell mediated immunity; and (5) practicality of storage such as refrigerated and room temperature stable formulations that overcome cold-chain limitations. Further details are provided in Appendix 5.

The purpose and goals of the hAd5-S-Fusion+N-ETSD vaccine are to:

1. **Reduce transmission** by viral clearance from lung and nasal airways. Data from NHP challenge studies showed that viral replication was undetectable within days of SARS-CoV-2 challenge (10E6 TCID50) in samples from both lung and nasal passages, following hAd5-S-Fusion+N-ETSD immunization.
2. **Induce innate and adaptive immunity** by selection of antigens with maximum epitopes for MHC-1 and MHC-2 presentation. Several studies have now shown that S and N proteins provide the opportunity for the broadest CD4+ and CD8+ T cell response. Preclinical immunogenicity data provide evidence for Th1 dominant cell immune response following hAd5-S-Fusion+N-ETSD immunization.
3. **Generate long-term durable immune protection**. By directing N to the lysosomal intracellular compartment, Th1 dominant CD4+ T helper cell and CD8+ T cells immune responses are enhanced. Both immune recall studies using T cells from patients previously infected with SARS-CoV-2 and preclinical studies in mice show CD4+ and CD8+ memory T cell responses are triggered by the hAd5-S-Fusion+N-ETSD antigens.
4. **Reduce incidence of mild-to-moderate infection** by stimulating an antibody, innate, adaptive and mucosal immune response. hAd5-S-Fusion+N-ETSD is designed to accomplish this response by both blocking entry of the virus and enabling rapid viral clearance via the innate and adaptive immune system. The Phase 2/3 randomized placebo controlled double-blind trial has been designed to test this hypothesis.
5. **Reduce severe disease, hospitalization time, admission to ICU, and mortality** by stimulating an antibody, innate, adaptive and mucosal immune responses. hAd5-S-Fusion+N-ETSD is designed to accomplish this response by both blocking entry of the virus and enabling rapid viral clearance via the innate and adaptive immune system. The Phase 2/3 randomized placebo controlled double-blind trial has been designed to test this hypothesis.
6. **Utilization of a platform with minimal side effects, scalability for rapid production, and that overcomes cold chain** distribution challenges. The second-generation adenovirus 5 vector has been administered in over 150 cancer patients without serious adverse events when administered repeatedly at doses as high as $5x10^{11}$. The Phase 1 study of hAd5-S-Fusion+N-

ETSD at doses of $5x10^{10}$ and $1x10^{10}$ were well tolerated in the first in human study with only grade 1 and grade 2 adverse events with no SAE reported. The vaccine is stable at 2-8 C and the oral formulation is stable at room temperature. Further details are provided in Appendix 4.

7. **Utilization of a platform that is able to deliver antigens in the presence of pre-existing Ad immunity.** Compared to current adenovirus vector platforms in Phase 3 clinical trials for COVID-19, ImmunityBio's hAd5 has four deletions, enabling delivery of the transgene COVID-19 proteins even in the presence of pre-existing adenovirus immunity. Clinical studies in cancer patients have shown the capability of hAd5-vectored cancer-related antigens (CEA, brachyury, etc.) to induce CD4+ and CD8+ T cell responses following multiple subcutaneous injections of hAd5 vaccine in patients with proven adenoviral immunity.

On October 13, 2020, FDA authorized a Phase 1 study of hAd5-S-Fusion+N-ETSD and both doses of 5×10^{10} VP/dose (n=10) and 1×10^{11} VP/dose (n=10) were administered subcutaneously without any SAEs or grade ≥3 AEs reported thus far. The most common AEs have been injection site redness, reaction, and pain, and fatigue, all of which were grade 1 or 2. The SRC met and confirmed the safety of the dose of 1×10^{11} VP/dose. The SRC report is attached in Appendix 4. On the basis of these safety findings, ImmunityBio will proceed with the 1×10^{11} VP/dose prime/boost in the phase 2/3 trial.

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
1. To evaluate the efficacy of prophylactic hAd5-S-Fusion+N-ETSD against confirmed COVID-19 in subjects without serological or virological evidence of infection before vaccination	In subjects complying with the key protocol criteria (evaluable efficacy population) at least 14 days after receipt of the last dose of study intervention: Vaccine Efficacy (VE) defined as 100% × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence based on central laboratory or locally confirmed nucleic acid amplification test (NAAT) in subjects with no serological or virological evidence (up to 14 days after receipt of the last dose) of past SARS-CoV-2 infection
2. To evaluate the efficacy of prophylactic hAd5-S-Fusion+N-ETSD against confirmed COVID-19 in subjects with and without serological or virological evidence of infection before vaccination	In subjects complying with the key protocol criteria (evaluable efficacy population) at least 14 days after receipt of the last dose of study intervention: VE = 100% × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence based on central laboratory or locally confirmed NAAT in subjects with and without serological or virological evidence of infection before vaccination

Primary Safety		
1. To define the safety profile of prophylactic hAd5-S-Fusion+N-ETSD in the first 200 subjects randomized (Phase 2)	In subjects receiving at least 1 dose of study intervention (safety analysis population), the percentage of subjects reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the last dose • SAEs from Dose 1 to 7 days after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
2. To define the safety profile of prophylactic hAd5-S-Fusion+N-ETSD in all subjects randomized in Phase 2/3	In subjects receiving at least 1 dose of study intervention (safety analysis population), the percentage of subjects reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 6 months after the last dose	• AEs • SAEs • In a subset of at least 1,000 subjects: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
Secondary Efficacy		
1. To evaluate the efficacy of prophylactic hAd5-S-Fusion+N-ETSD against confirmed severe COVID-19 in subjects without serological or virological evidence of infection before vaccination	In subjects complying with the key protocol criteria (evaluable efficacy population) at least 14 days after receipt of the last dose of study intervention: VE = 100% × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed NAAT severe COVID-19 incidence in subjects with no serological or virological evidence of past SARS-CoV-2 infection
2. To evaluate the efficacy of prophylactic hAd5-S-Fusion+N-ETSD against confirmed severe COVID-19 in subjects with and without serological or	In subjects complying with the key protocol criteria (evaluable efficacy population) at least 14 days after receipt of the last dose of study intervention: VE = 100% × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed NAAT severe COVID-19 incidence in subjects with and without serological or virological evidence of infection before vaccination

virological evidence of infection before vaccination		
3. To describe the efficacy of prophylactic hAd5-S-Fusion+N-ETSD against confirmed COVID-19 (according to the CDC-defined symptoms) in subjects without serological or virological evidence of infection before vaccination	In subjects complying with the key protocol criteria (evaluable efficacy population) at least 14 days after receipt of the last dose of study intervention: VE = 100% × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence based on central laboratory or locally confirmed (according to the CDC-defined symptoms) in subjects with no serological or virological evidence (up to 14 days after receipt of the last dose) of past SARS-CoV-2 infection
4. To describe the efficacy of prophylactic hAd5-S-Fusion+N-ETSD against confirmed COVID-19 (according to the CDC-defined symptoms) in subjects with and without serological or virological evidence of infection before vaccination	In subjects complying with the key protocol criteria (evaluable efficacy population) at least 14 days after receipt of the last dose of study intervention: VE = 100% × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence based on central laboratory or locally confirmed (according to the CDC-defined symptoms) in subjects with and without serological or virological evidence of infection before vaccination
Exploratory (up to 500 subjects)		
1. To evaluate the humoral immune response over time to prophylactic hAd5-S-Fusion+N-ETSD and persistence of immune response in subjects with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC, GMT, GMFR, percentage of subjects with titers greater than defined threshold(s), and neutralizing antibody titer demonstrated by ACE2 inhibition at baseline and specific times during the study, as noted in the Schedule of Events	• S-binding IgG levels • N-binding IgG levels • SARS-CoV-2 neutralizing antibody by cPass assay in subjects with and without serological or virological evidence of infection before vaccination
2. To evaluate the humoral immune response over time to prophylactic hAd5-S-Fusion+N-ETSD and persistence of immune response in subjects with serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC, GMT, GMFR, percentage of subjects with titers greater than defined threshold(s), and neutralizing antibody titer demonstrated by ACE2 inhibition at baseline and specific times during the study, as noted in the Schedule of Events	• S-binding IgG levels • N-binding IgG levels • SARS-CoV-2 neutralizing antibody by cPass assay • in subjects with serological or virological evidence of SARS-CoV-2 infection
3. To evaluate the cellular immune stimulatory efficacy, persistence, and duration of prophylactic hAd5-S-Fusion+N-ETSD cellular immunity against	Memory immune $CD4^+$ and $CD8^+$ T cell stimulation from baseline to specific times during the study, as noted in the Schedule of Events	• SARS-CoV-2 specific memory $CD4^+$ and $CD8^+$ T-cell stimulation to N and S proteins based on central laboratory or locally confirmed NAAT in

confirmed SARS-CoV-2 in subjects with and without serological or virological evidence of infection before vaccination		subjects with and without serological or virological evidence of infection before vaccination
4. To evaluate the cellular immune stimulatory efficacy, persistence, and duration of prophylactic hAd5-S-Fusion+N-ETSD cellular immunity against confirmed SARS-CoV-2 in subjects with serological or virological evidence of infection before vaccination	Memory immune $CD4^+$ and $CD8^+$ T cell stimulation from baseline to specific times during the study, as noted in the Schedule of Events	• SARS-CoV-2 specific memory $CD4^+$ and $CD8^+$ T-cell stimulation to N and S proteins based on central laboratory or locally confirmed NAAT in subjects with serological or virological evidence of SARS-CoV-2 infection
5. To describe the safety, immunogenicity, and efficacy of prophylactic hAd5-S-Fusion+N-ETSD in individuals with confirmed stable HIV disease		• All safety, immunogenicity, and efficacy endpoints described above
[a] HIV-positive and participants who develop immunosuppressive related diseases (eg, cancer, autoimmune disease) in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.		

Study Design:

This is a phase 2/3, multicenter, randomized, placebo-controlled, observer-blind study assessing the safety, tolerability, immunogenicity, and efficacy of prophylactic hAd5-S-Fusion+N-ETSD against COVID-19. The study schema is shown in Figure 1. Subjects will be ≥ 16 years of age who are healthy or have medically-stable chronic diseases and are at increased risk for SARS-CoV-2 infection and COVID-19. Approximately 20,700 subjects will be randomized in a 1:1 ratio to receive 2 subcutaneous (SC) doses of either 1×10^{11} viral particles (VP)/dose hAd5-S-Fusion+N-ETSD or placebo 3 weeks apart, on Days 1 and 22. Randomization will be stratified by age (16 to 55 years or >55 years). It is intended that a minimum of 25% of subjects will be in the >55-year stratum. Safety, immunogenicity, and efficacy assessments will be conducted per the Schedule of Events (SoE) and subjects are expected to participate for up to a maximum of approximately 2 years.

The first 200 subjects randomized will comprise the phase 2 portion of the study. Safety data through 7 days after Dose 2 from these 200 subjects will be analyzed by an independent statistical team and reviewed by the DMC. Enrollment may continue during this period and these subjects would be included in the phase 3 portion of the study.

Enrollment (planned):
Approximately 20,700 subjects will be randomized in this study.

Eligibility Criteria:

Inclusion Criteria:

Subjects are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants ≥16 years of age, at randomization.
   - Refer to Appendix 2 for reproductive criteria for male and female participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled assessments, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.
3. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

   Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for Phase 3 participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV) can be found in Appendix 3.
4. Participants who, in the judgment of the investigator, are at higher risk for SARS-CoV-2 infection and subsequent development of COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, and frontline essential workers).

Informed Consent:

5. Capable of giving personal signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and in this protocol.

Exclusion Criteria:

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.
2. **Phase 2 only:** Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).
3. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).
4. Receipt of medications intended to prevent COVID-19.
5. Previous clinical or microbiological diagnosis of COVID-19.
6. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

7. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate subcutaneous injection.
8. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

9. Previous vaccination with any coronavirus vaccine.
10. Individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.
11. Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

12. Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation.

Other Exclusions

13. Investigator site staff or Sponsor employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator.

Investigational Product, Dosage, and Mode of Administration:
hAd5-S-Fusion+N-ETSD, 1×10^{11} VP/dose, SC

Comparator: Placebo, SC

Duration of Treatment:

Subjects will be treated with hAd5-S-Fusion+N-ETSD or placebo on Days 1 and 22 (ie, 2 doses total of assigned intervention).

Duration of Follow-up:

Subjects are expected to participate for up to a maximum of approximately 2 years.

Evaluation of Endpoints:

Safety: Safety endpoints include assessments of reactogenicity events, AEs, and SAEs.

Efficacy: The first primary efficacy endpoint is COVID-19 incidence based on central laboratory or locally confirmed NAAT in subjects with no serological or virological evidence (up to 14 days after receipt of the last dose) of past SARS-CoV-2 infection.

The secondary primary endpoint is COVID-19 incidence based on central laboratory or locally confirmed NAAT in subjects with and without evidence of infection before vaccination.

Immunogenicity: Humoral immune response will be evaluated by S-binding IgG levels, N-binding IgG levels, and SARS-CoV-2 neutralizing antibody by cPass assay. Cellular immune response will be evaluated by SARS-CoV-2 specific memory $CD4^+$ and $CD8^+$ T-cell stimulation to N and S proteins.

Statistical Methods:

Primary Efficacy Endpoints: The first primary efficacy endpoint is COVID-19 incidence based on central laboratory or locally confirmed NAAT in subjects with no serological or virological evidence (up to 14 days after receipt of the last dose) of past SARS-CoV-2 infection and will be summarized in terms of VE = 100% × (1 – IRR) [ratio of active vaccine to placebo].

After the above first primary endpoint is met, the second primary endpoint will be evaluated.

The second primary endpoint COVID-19 incidence based on central laboratory or locally confirmed NAAT in subjects with and without evidence of infection before vaccination.

Sample Size: The first 200 subjects randomized in the study will be included in phase 2. Phase 2 subjects will be included in the phase 3 portion of the study.

For phase 3, ~20,700 subjects will be randomized in a 1:1 ratio to either the hAd5-S-Fusion+N-ETSD or placebo. All randomized subjects who received at least one dose of study intervention will included in the all-available efficacy population. The primary efficacy analysis will be based on the evaluable efficacy population which will include subjects in the all-available efficacy population who receive all planned doses of vaccine per schedule and have no major protocol deviations judged to effect efficacy.

The phase 3 sample size calculation is based on the primary efficacy endpoints and derived from the exact conditional test under the Poisson assumption which is appropriate for large trials where the illness rate is very low and hypothesis testing is based on a non-zero lower bound (Chan 1998). The null and alternative hypotheses for the primary efficacy analyses are:

Ho: VE ≤ 30%

Ha: VE > 30%

Under the assumption that the true VE is 60%, the primary efficacy analysis will require ~160 confirmed COVID-19 illness cases which will provide 90% power to conclude the true VE is > 30%. Assuming the placebo illness rate is 1.3%, ~17,600 subjects will be required in the evaluable efficacy population for the primary efficacy analyses. These calculations are based a one-sided Type I error rate of 0.025. Assuming 15% of the all-available efficacy population will be unevaluable for the evaluable efficacy population, ~20,700 subjects will be sufficient to accrue ~17,600 subjects in the evaluable efficacy population.

Dependent upon the evolution of the pandemic, it is possible that the COVID-19 illness rate may change as the study progresses. An increase in illness rate could accelerate case accrual allowing the primary endpoints to be evaluated sooner, whereas a decrease in illness rate could slow down case accrual delaying the evaluation. At the time of the first interim efficacy analysis, the independent statistical team and DMC will evaluate the placebo illness rate. If the upper bound of the two-sided 95% CI for the observed placebo illness rate is less than the assumed placebo illness rate, then the sample size will be re-estimated by the independent statistician and DMC based on the observed placebo illness rate, and recommendations made to the Sponsor for final decision by the Sponsor.

Primary Efficacy Analysis: The primary efficacy endpoints will be analyzed at 2 interim analyses and the final analysis. The interim analyses will be conducted by the independent statistical team and reviewed by the independent DMC. The Lan-DeMets/O'Brien-Fleming alpha(α)-spending function (Lan 1983, O'Brien 1979) will be used to control the overall Type I error at one-sided 0.025 level. At each analysis, VE will be summarized by the one-sided (1-α)100% CI. The table below summarizes the

information fraction (ie, % of total cases), nominal α, criterion for success, and cumulative probability of success if the true VE is 60% for each analysis:

Analysis	Information Fraction (% of Total Cases)	α	Success Criterion	Cumulative Probability of Success (if true VE=60%)
Interim #1	40% (64 cases)	0.0004	Point estimate of VE ≥ 50% and lower bound of the one-sided 99.96% CI for VE is > 30%	9.9%
Interim #2	70% (112 cases)	0.0073	Point estimate of VE ≥ 50% and lower bound of the one-sided 99.27% CI for VE is > 30%	61.5%
Final	100% (160 cases)	0.0227	Point estimate of VE ≥ 50% and lower bound of the one-sided 97.73% CI for VE is > 30%	90.0%

Should the primary endpoint(s) show success at either interim analysis, the Sponsor will decide after discussion with FDA to explore the options to expedite submission of the data for approval and possible early closure of the trial, with long-term follow up of patients already enrolled.

The study may be stopped early for futility (lack of benefit) at either interim analysis if the conditional power for the first primary endpoint is less than 5% (Jennison 2000).

A Poisson regression model with robust error variance will be used to estimate VE and its one-sided (1-α)100% CI (Zou 2004).

Safety Analyses: Safety analyses will be based on the safety analysis population and subjects will be analyzed according to the actual study intervention received. Descriptive statistics will be provided for each reactogenicity endpoint for the active vaccine group and the placebo group. Local reactions and systemic events from Day 1 through Day 7 after each vaccination will be presented overall and by severity.

AEs and SAEs will be categorized according to the MedDRA terms. Descriptive statistics will be provided for each AE for the active vaccine group and the placebo group. For phase 2, AEs and SAEs will be presented for first vaccination through 7 days after last vaccination overall and by severity. For phase 3, AEs will be presented for first vaccination through 1 month after last vaccination and SAEs will be presented for first vaccination through 6 months after last vaccination overall and by severity.

Immunogenicity Analyses: Immunogenicity analyses will be based on the immunogenicity analysis population and subjects will be analyzed according to the actual study intervention received. Humoral immune response endpoints will be summarized descriptively for the vaccine and placebo groups by GMT, GMC, GMFR, percentage of subjects with titers greater than defined threshold(s), and neutralizing antibody titer demonstrated by ACE2 inhibition at baseline and specific times during the study, as noted in the Schedule of Events. Cellular immune response endpoints will be summarized

descriptively for the vaccine and placebo groups at baseline and specific times during the study, as noted in the Schedule of Events.

Figure 1: Study Schema

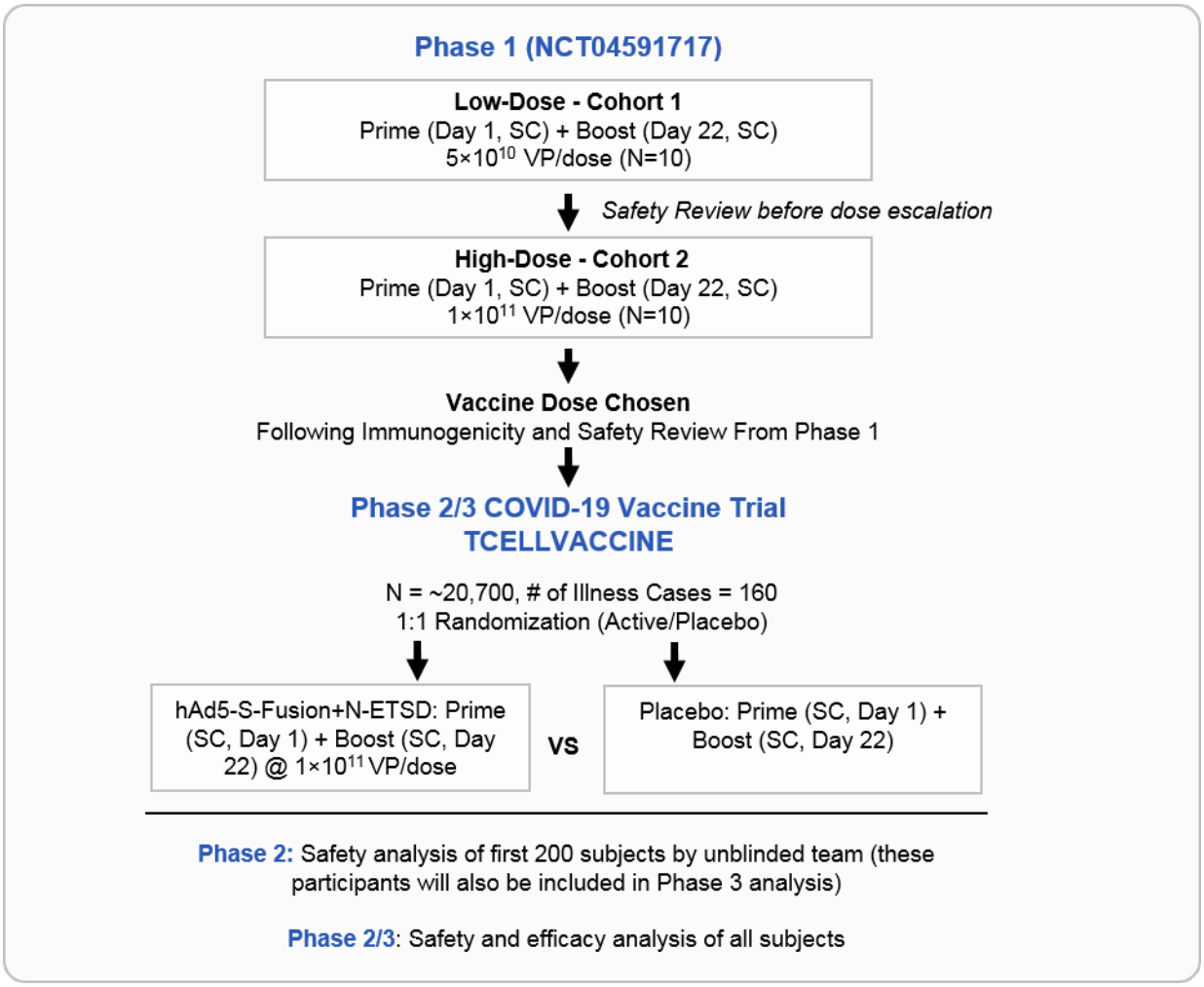

Table 8: Schedule of Events

Patient Assessment Number	**1**	**2**	**3**	**4**	**5**	**6**	**Unplanned**	**Unplanned**
Activity Description	**First Vaccination**	**Second Vaccination**	**1-Month Follow-up Assessment**	**6-Month Follow-up Assessment**	**12-Month Follow-up Assessment**	**24-Month Follow-Up Assessment**	**Potential COVID-19 Illness Assessment**	**Potential COVID-19 Convalescent Assessment**
Assessment Window (Days)	**Day 1[a]**	**19 to 23 Days After Assessment 1**	**28 to 35 Days After Assessment 2**	**175 to 189 Days After Assessment 2**	**350 to 378 Days After Assessment 2**	**714 to 742 Days After Assessment 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Assessment**
Informed consent	X							
Assign subject number	X							
Demographics	X							
Medical history	X							
Perform clinical assessment[b]	X							
Measure height/weight	X							
Measure temperature (body)	X	X						
Perform pregnancy test (if appropriate)	X	X						
Confirm use of contraceptives (if appropriate)	X	X	X					
Collect nonstudy vaccine information	X	X	X	X				
Collect prohibited medication use		X	X	X	X	X	X	X
Confirm eligibility	X	X						

Patient Assessment Number	**1**	**2**	**3**	**4**	**5**	**6**	**Unplanned**	**Unplanned**
Activity Description	**First Vaccination**	**Second Vaccination**	**1-Month Follow-up Assessment**	**6-Month Follow-up Assessment**	**12-Month Follow-up Assessment**	**24-Month Follow-Up Assessment**	**Potential COVID-19 Illness Assessment**	**Potential COVID-19 Convalescent Assessment**
Assessment Window (Days)	**Day 1[a]**	**19 to 23 Days After Assessment 1**	**28 to 35 Days After Assessment 2**	**175 to 189 Days After Assessment 2**	**350 to 378 Days After Assessment 2**	**714 to 742 Days After Assessment 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Assessment**
Review temporary delay criteria	X	X						
Serum sample for SARS-CoV-2 serology testing	X							X
Collect biospecimen (eg, nasal [midturbinate] swab) for SARS-CoV-2 testing	X	X					X	
Obtain randomization number and study intervention allocation	X							
Administer study intervention	X	X						
Assess acute reactions for at least 30 minutes after study intervention administration	X	X						
Explain subject communication methods (including for e-diary completion)	X							

Patient Assessment Number	**1**	**2**	**3**	**4**	**5**	**6**	**Unplanned**	**Unplanned**
Activity Description	**First Vaccination**	**Second Vaccination**	**1-Month Follow-up Assessment**	**6-Month Follow-up Assessment**	**12-Month Follow-up Assessment**	**24-Month Follow-Up Assessment**	**Potential COVID-19 Illness Assessment**	**Potential COVID-19 Convalescent Assessment**
Assessment Window (Days)	**Day 1[a]**	**19 to 23 Days After Assessment 1**	**28 to 35 Days After Assessment 2**	**175 to 189 Days After Assessment 2**	**350 to 378 Days After Assessment 2**	**714 to 742 Days After Assessment 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Assessment**
Provide/ensure the subject has a thermometer (all subjects) and measuring device[c]	X	X						
Review reactogenicity e-diary data[c]	←→	←→						
Review ongoing reactogenicity e-diary symptoms[c]		X	X					
Collect AEs and SAEs as appropriate	X	X	X	X[d]	X[d]	X[d]	X	X[d]
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X	X

[a] The assessment may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
[b] Including, if indicated, a physical examination.
[c] Reactogenicity subset subjects only.
[d] Any AEs occurring up to 48 hours after the blood draw must be recorded.

APPENDIX 6. SPONSOR SIGNATURE

Study Title:	A Phase 2/3, Placebo-Controlled, Randomized, Observer-Blind Study To Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of a 2nd Generation E1/E2B/E3-Deleted Adenoviral COVID-19 Vaccine: The TCELLVACCINE TRIAL
Study Number:	COVID-3.001
Version Number:	1
Final Date:	16 November 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: 11/16/2020

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