EXAMPLE

IDCRC – Initial Concept Proposal

Name	Anna Wald
Institution/Organization	University of Washington
Address	Harborview Medical Center 325 9th Ave., Box #359928 WA 98104
Phone	(xxx) xxx-xxxxx
Email	name@xxxx.edu
IDCRC Network Affiliation	_____VTEU
Expert Working Group	Respiratory Diseases
Study Title	Phase 1 Dose Escalation Study To Evaluate the Safety of NewVac, an Attenuated ABC Virus SARS-CoV-2 Vaccine, in Healthy Adult Volunteers
Study Description	This Phase 1 dose escalation study will evaluate safety of NewVac, an attenuated ABC virus that expresses SARS-CoV-2 antigens. The study will be performed in healthy volunteers with no sign of prior or current SARS-CoV-2 infection. The primary endpoint is safety and tolerability, and secondary endpoints include the evaluation of immunogenicity: antibody and T cell responses specific to the vaccine insert antigens. A maximum of 15 research subjects will be enrolled at each of the 3 dose levels and will receive 2 intramuscular (IM) injections of NewVac, 28 days apart. The dose escalation plan will follow a modified queue-based version of a 3+3 design based on the incidence of moderate toxicity (MOD) events (details in the Design section). The proposed analysis of the immune responses is comprehensive, since parenteral administration of NewVac can be effective in inducing both protective mucosal and systemic immune responses. As viral antigens generate humoral and T-cell responses, both types of immunity will be investigated. As an exploratory objective, we will record any incidental COVID-19 infections and describe the characteristics of infected and non-infected subjects.

Background & Significance

A novel coronavirus jumped from animal species to humans (zoonosis) in December 2019 in Hubei, China. The rapidly spreading virus, named SARS-CoV-2 after the samples were sequenced by Chinese investigators, was shown to be 96.2% identical to a bat coronavirus. Despite extended quarantine of individuals in China, the cases continued to mount with accompanying hospitalizations, need for ventilators and death in some cases. The virus continued to spread to other regions of the world, including the United States (US) because of the interconnectedness of modern society. The spread is similar to that of the so-called "Spanish flu" in 1918. The penetrance of the virus worldwide suggested that therapeutics would not suffice to stem the outbreak, and two starkly different options for containment arose.

One option is that "herd immunity" will eventually lessen the impact of a new pathogen, but the consequence of that strategy is the 1% mortality estimated worldwide from COVID-19; while mortality has reached ~10% in areas such as Northern Italy, Spain and France. In the US, ~3.3 million people could die as we establish herd immunity, even if done slowly to avoid overwhelming the medical system.

The alternative is a vaccine that will provide protective immunity to the recipient and with the hope for long-lived immunity, eliminating the need for repeated annual vaccination campaigns.

To urgently end the COVID-19 pandemic, an organization like the VTEU can provide crucial support to investigate the properties of a potentially protective vaccine to guard against the SARS-CoV-2 pathogen. The VTEU's broad experience with vaccinating healthy subjects and patients with viral-based vaccines makes VTEU best fit for this vaccine campaign.

Objectives

The primary objectives of the study are to evaluate the safety and tolerability of NewVac vaccine in healthy volunteers. Secondary objectives include the evaluation of: humoral immunity (IgG, IgM, and IgA in serum and saliva), quality and properties of antibodies elicited as a result of the vaccination, T-cell responses in the peripheral blood, T-cell memory markers, durability of immune responses, and maintenance of immunity that can be associated with protection over the study period.

Design

Study population: adult healthy volunteers will be screened based on eligibility criteria similar to those from the ongoing Moderna study (NCT04283451). Eligible subjects will show no sign of prior or current SARS-Cov-2 infection, as assessed by both antibody and nucleic acid diagnostic tests.
Recruitment/enrollment site: 2 VTEU sites
Statistical plan: The main objective of the study is to evaluate the safety of the NewVac vaccine in research subjects treated at one of 3 dose levels: Dosage 1, Dosage 2, and Dosage 3. The low dose level (DL) was chosen based on experiences with similar vaccines. To establish safety of the vaccine, a maximum of 15 subjects will be treated at each of the 3 DLs, for a maximum of 45 subjects overall. Subjects will receive two IM injections in the upper arm, 4-weeks apart. Health criteria will be assessed, and any adverse event (AE) (any grade) and any dose-limiting toxicity (DLT) will be evaluated through 2 weeks post-vaccination. The assessments will collect any grade of 3 or higher AE through 365-days post-vaccination, consisting of 12 in-person and/or telehealth visits.

Each subject will receive 2 injections at the assigned DL on days 0 and 28 (2nd administration requires no DLT and no persistent AEs), and will be followed for 365 days. DLT in a given subject is defined as any grade 3 or higher toxicity possibly, probably or definitely attributable to the research treatment in the first 42 days, and a moderate toxicity (MOD) is a grade 2 event that lasts for 1 week or longer. Toxicity will be graded according to standard DMID adult toxicity tables. To be evaluable for safety, a subject must receive at least 1 vaccine injection. To be evaluable for dose escalation, all subjects in a cohort who do not experience a DLT or MOD must have received 2 injections and be followed for at least 2 weeks after the second injection (42-day window). Any subject not evaluable for dose escalation will be replaced if prior to the completion of the dose escalation portion of the study. All subjects receiving any amount of vaccine will be followed for AEs and accounted for in the final data summary. Any grade 4 toxicity possibly, probably, or definitely attributable to the research treatment will be considered a DLT, and will temporarily suspend the vaccine administration, pending review and approval of resumption of treatment by the PI, DSMC, IRB and in consultation with the FDA. Thus, dose escalation and accrual will depend on toxicity observed including MOD, DLT and Grade 4. The basic design follows a modified 3+3 design based on incidence of MOD, while one DLT will mandate at least 7 non-DLT non-MOD patients on that DL to consider opening a higher DL, and any grade 4 or higher AE will hold accrual.

Laboratory testing: We will assess humoral immunity (IgA, IgG, and IgM) in

	serum and saliva by ELISA. Statistical power is based on positive IgG after the second evaluation. The neutralizing capability of the antibodies to prevent infection of a susceptible cell line will be evaluated using a pseudo-type of the SARS-CoV-2 virus. We will evaluate: a) antigen-specific T cell responses using overlapping peptide library specific for SARS-CoV-2 at all time points in the 365-day observation period; and b) memory marker evolution on the surface of antigen specific T cells elicited as a result of the vaccination.
Intervention	The NewVac vaccine is an attenuated ABC virus that expresses the SARS-CoV-2 antigens. The vaccine is delivered by IM injection (1.0 mL max. volume) in the upper non-dominant arm at one of the three dose levels: 1.0x10e7 PFU/dose, 1.0x10e8 PFU/dose, and 5.0x10e8 PFU/dose. Subjects remain in the study for a follow-up period of 365 days. The GMP lot of NewVac will be manufactured early in Q3 of financial year (FY) 2020 in sufficient amounts for the study, which is estimated to treat 45 subjects. The cGMP laboratory will be responsible for conducting basic safety tests, while the release testing done at manufacture will be carried out by BioReliance CRO.
Planned Duration of Study (months)	18
Study Location	Two VTEU sites
Sites	Two
Timeline for availability of product	The proposed Phase I trial is anticipated to start at in Q4 of FY 2020, based on safety of similar vaccines and a rapid approval of the IND. A delay to Q1 FY 2021 might occur if the FDA has more stringent requirements upon IND review. Study duration is estimated to be 12-18 months, ending in Q2 FY2022.
Estimated Costs	The cost of this clinical trial is estimated to be approximately $1M.