Background and Rationale (Part 1 of Phase 3 study of Vaccine Candidate for COVID-19)

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In 1 collection

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Coronavirus Method Development Community

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ABSTRACT

This is a collection of protocols for: "Phase 3 randomized, double-blinded, placebo-controlled trial to evaluate the safety, immunogenicity, and efficacy of **Vaccine Candidate** against COVID-19 in adults ≥ 18 years of age"

This generic Phase 3 protocol was developed by the PATH team with support of the Bill and Melinda Gates Foundation. The aim of the collection is to share recommended best practices in designing and implementing a Phase 3 study of a COVID-19 vaccine candidate. As Phase 3 trials of different Vaccine Candidates proceed around the world, following the same protocols will ensure consistency and comparability of the Phase 3 trial results.

Please note that this is an evolving document, to be versioned and updated, based on community feedback and new data.

ATTACHMENTS

Generic Phase 3 Protocol COVID-19 Vaccine - 25AUG2020-version 1.docx

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COLLECTIONS

Collection of Protocols and Guidelines for Phase 3 study of Vaccine Candidate for COVID-19

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Collection of Protocols and Guidelines for Phase 3 study of Vaccine Candidate for COVID-19

GUIDELINES

1.1. Background

COVID-19, the infectious disease caused by SARS-CoV-2, was first detected in December 2019 in Wuhan City, Hubei Province, China [1]. Several cases of pneumonia of unknown cause were reported to the Chinese Center for Disease Control and Prevention (CDC), which detected the novel coronavirus in patient nasal swabs. Because the virus is capable of human-to-human transmission, the epidemic escalated and COVID-19 has since spread across more than 210 countries and territories globally. In January 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a public health emergency of international concern, followed by the declaration of a world-wide pandemic in March 2020.

1.1.1. Pathogen

The novel β-coronavirus, SARS-CoV-2, belongs to the Nidovirales family of Coronavirinae and has the typical features of the coronavirus family. Evolutionary analysis shows that SARS-CoV-2 is most similar to the bat severe acute respiratory syndrome-related coronaviruses to which it has a nucleotide homology of 84 percent. SARS-CoV-2 has 50 percent homology with MERS-CoV [2].

SARS-CoV-2 has a lipid envelope and its granules are round or oval, often polymorphic, with a diameter of 60-140 nm. To date, there have been limited mutations in the positive stranded RNA; however, single point mutations may increase or decrease host infection and pathogenicity. The understanding of the physical and chemical characteristics of coronavirus mostly comes from the study of SARS-CoV and MERS-CoV.

1.1.2. Clinical manifestations:

Based on current epidemiological studies, the incubation period of the disease is one to 14 days, with an average of 5.68 days [3]. Signs and symptoms of the infection have been evolving since it was first identified and range from asymptomatic to severe manifestations that can result in COVID-19-related death [4]. While fever, shortness of breath, and dry cough are the most common initial manifestations, additional symptoms include fatigue, bluish lips or face, sore throat, nausea or vomiting, diarrhea, new loss of taste or smell, myalgia, headache, congestion, or runny nose. Severe patients often develop dyspnea and/or hypoxemia five to seven days after the onset of initial symptoms and can rapidly progress to acute respiratory distress syndrome, septic shock, metabolic acidosis, coagulopathies, and multi-organ failure. While most patients have a favorable prognosis, approximately 15 percent progress to moderate or severe disease that requires hospitalization. The prognosis for the elderly and those with co-morbidities is often poor.

Laboratory testing in severe disease patients indicate lymphopenia with elevated ALT, lactate dehydrogenase, cardiac troponin I, creatine kinase, d-dimer greater than 1 µg/mL, serum ferritin, IL-6, creatinine, and prolonged prothrombin time.

1.1.3. Route of transmission:

SARS-CoV-2 is spread from person-to-person, primarily by respiratory droplets, aerosols, and contact transmission. Fecal-oral transmission may contribute to spread as well. Public health measures to control infection include hand washing, physical distancing, and wearing face coverings or masks.

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1.1.4. Risk factors:

Based on currently available information and clinical expertise, the documented risk factors include but are not limited to: age >65 years, asthma, chronic kidney disease, chronic lung disease, hypertension, diabetes, being immunocompromised, living in nursing homes or long-term care facilities, and severe obesity.

1.1.5. Clinical management:

There are no specific curative treatments available for COVID-19, although remdesivir has shortened hospitalization in a randomized trial [5, 6], and dexamethasone has reduced mortality in moderate-to-severe patients receiving respiratory support [7]. Careful home-based monitoring for clinical deterioration is recommended for patients with mild symptoms [8-10]. Severe disease necessitates hospitalization, especially if patients require either supplemental oxygenation or advanced support including high flow oxygen, CPAP, mechanical ventilation, dialysis, etc. Many countries around the globe have developed local clinical management guidance that match their resources.

1.1.6. Site-specific epidemiolocal situation

TO BE INSERTED BY SPONSOR.

1.2. Description of the study vaccine

TO BE INSERTED BY SPONSOR. Description should include:

- **The vaccine candidate Vaccine Candidate is ….**
- **What is it?**
- **How is it made/manufactured?**
- **Bulk material details**
- **Formulation details**
- **Stability details**

The lot intended for use in this Phase 3 trial is a single lot # **XXXXX**. Details are provided in the Investigator's Brochure.

1.3. Summary of pre-clinical studies

1.3.1. Immunogenicity studies in rodents

TO BE INSERTED BY SPONSOR
Refer to Investigator's Brochure for details.

1.3.2. Challenge and protection studies in non-human primates (macaques)

TO BE INSERTED BY SPONSOR
Refer to Investigator's Brochure for details.

1.3.3. GLP toxicology and developmental & reproductive toxicology (DART) studies

TO BE INSERTED BY SPONSOR
Refer to Investigator's Brochure for details.

1.3.4. Summary of candidate vaccine clinical studies (<example>)

Two Phase 1/2 clinical trials have been and are currently being conducted in **Location** to evaluate the safety and immunogenicity of **Vaccine Candidate**—one in adults 18-59 years of age and one in adults 60 years of age and older. **Sponsor** will commit to performing parallel clinical studies in children and high-risk persons with multiple co-morbidities, as well as developmental and reproductive toxicology (DART) preclinical studies, followed by studies in pregnant women to ensure prompt availability of vaccines to critical populations.

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1.3.4.1 Phase 1/2 safety
TO BE INSERTED BY SPONSOR

1.3.4.2 Phase 1/2 immunogenicity
TO BE INSERTED BY SPONSOR

1.4. Study rationale

This study is designed to provide data in support of ***biological license application (BLA or equivalent)*** for regulatory approval of **Vaccine Candidate** to prevent COVID-19. Data will also support the application for WHO prequalification (PQ). The study site(s) selected for this study are located in areas where populations are at increased risk for COVID-19.

1.5. Potential risks of study vaccine

1.5.1. Risks of receipt of <Vaccine Candidate>

As with any vaccination, there is the potential for an anaphylactic reaction. To identify and address this potential problem, medical staff experienced in the management of anaphylactic reaction will observe patients for at least 30 minutes following each vaccination. Recipients of any of the investigational products (IPs) in this study may experience pain, tenderness, erythema, induration or swelling, pruritis at the injection site, fever, headache, fatigue, chills, myalgia, and arthralgia. Additionally, there may be other side effects to **Vaccine Candidate** that at this time are not known.

1.5.2. Vaccine-enhanced disease

There is a theoretical concern of enhanced pathology in immunized participants subsequently exposed to live SARS-CoV-2, as was seen when some animals that received SARS or MERS-CoV candidate vaccines were subsequently challenged with live virus. The pathology has been described as primarily a lymphocytic and eosinophilic infiltrate in the lungs, similar to that observed in infants that experienced enhanced Respiratory Syncytial Virus (RSV) disease following immunization with formalin-inactivated RSV vaccine. This immunopathology was considered by some investigators to be the consequence of a dominant Th2-type response to the vaccine antigens [11], however no direct proof of that is available. Although no similar histopathology was found in pre-clinical studies of **Vaccine Candidate**-immunized **non-human primates** subsequently challenged with SARS-CoV-2, the concern for enhanced respiratory disease—termed Vaccine-Associated Enhanced Respiratory Disease (VAERD)—will necessitate close monitoring and follow-up of all participants for SAEs that may occur during or following confirmed COVID-19 infection and that are consistent with the pathogenesis of severe COVID-19, including non-respiratory consequences.

In addition to the possible risk associated with VAERD, antibody-dependent enhancement (ADE) of disease has been highlighted as another mechanism of VED, whereby antibodies elicited after vaccination may result in increased viral uptake into host cells and result in immune responses that promote rather than prevent disease [12-15].

<The sponsor will develop and provide Clinical Management Guidance across all sites to ensure consistency in participant evaluation, treatment, case identification, management, and infection prevention. This guidance will also define protection measures to be instituted for non-study participants exposed to hospital participants in a hospital setting and to staff participating in the study.>

1.5.3. Risk of pregnancy

<Pregnant women should be excluded from participating in the vaccination portion of this study unless the sponsor has completed DART and Phase 1/2 safety trials.

Vaccine Candidate has not been previously evaluated in nonclinical reproductive toxicology studies by Sponsor and therefore, the study will not be able to enroll pregnant women or women of child-bearing age seeking to become pregnant. Sponsor has committed to promptly conduct

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the preclinical and clinical studies required to make this vaccine available to pregnant women [16].>

1.5.4. Risks of accidental disclosure of private medical information

To ensure all information collected on study participants is kept confidential, the following safeguards will be applied: 1) access to study files and personal information will be limited to study personnel, ethics committees, regulatory authorities, and **Sponsor**; 2) study information will be kept in locked rooms when not in use; and 3) all information or samples will be labeled with a unique study identification number and have no personal identifying information (PII).

1.5.5. Risks of phlebotomy

Venipuncture is a routine clinical procedure the medical community commonly uses to obtain blood samples. Immediate complications may include slight pain during puncture of the skin, and, rarely, dizziness and syncope. Additionally, a hematoma may result from the venipuncture, but this has minimal risk. Infection of the skin/soft tissue at the puncture site, vein, or blood stream can all occur, though are very rare with both finger sticks and venous blood draws. Participant monitoring and aseptic techniques such as using sterile disposable blood collection apparatuses and adhering to standard medical precautions reduce any risk to a minimum. The amount of blood to be taken for sampling will not be harmful to the participant's health.

1.6. Potential benefits of study participation

All study participants will receive the following benefits:

- All volunteers will undergo a medical examination at screening free of charge. All volunteers, whether accepted for enrollment into the trial (participant) or not, will benefit from this free health check-up. The results of all tests will be communicated to all volunteers. Where illnesses are newly diagnosed, a referral to an appropriate health provider will be made for the volunteer.
- Should **Vaccine Candidate** be found to be efficacious after either the interim analysis or at study end, and meet regulatory approval, participants in the placebo group will be offered **Vaccine Candidate** free-of-charge.
- Participation in the study will contribute to a better understanding about COVID-19 disease and development of better prevention measures. If **Vaccine Candidate** is successful in preventing COVID-19, then participations will have made a major contribution to public health advancement.

1.7. Clinical development plan

The clinical development plan (CDP) comprises Phase 1, 2, and 3 clinical studies meant to lead to initial regulatory approval for the indication, "To prevent laboratory-confirmed COVID-19 in population >18 years of age." Phase 1/2 clinical trials have been conducted in **location** to evaluate the safety and immunogenicity of **<Vaccine Candidate—DEFINE AGE GROUPS/POPULATIONS, INCLUDING ELDERLY, CHILDREN, AND PREGNANT WOMEN>**.

Sponsor will commit to:

- Parallel pediatric Phase 1/2 clinical studies in children. Studies will be conducted as early as possible in children 3-17 years of age.
- Parallel clinical studies in high-risk persons with multiple co-morbidities and in older adults ≥ 60 years old.
- Lot-consistency clinical studies using three consecutive lots of commercial scale.
- DART studies, which are required before assessing the vaccine in pregnant women.
- Making Vaccine Candidate available for pre-licensure through WHO's Emergency Use Listing Procedure (EUL) and meeting all requirements for WHO PQ.

Meetings will be arranged with the WHO Vaccines PQ Team to discuss data requirements and timing. In addition, meetings will be considered with the national regulatory authorities of the potential technology transfer recipient country and other target countries. Options for fast track approvals will be explored to achieve global supply demands.

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