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Hypotheses, Objectives, Endpoints, and Case Definitions (Part 2 of Phase 3 study of Vaccine Candidate for COVID-19)

In 1 collection

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1 Works for me dx.doi.org/10.17504/protocols.io.bj5vkq66

Coronavirus Method Development Community

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ABSTRACT

This is Part 2 of "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

DOI

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PROTOCOL CITATION

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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

2.1. Study hypotheses

- The Vaccine Candidate will provide protection against symptomatic COVID-19.
- The Vaccine Candidate will be safe and well-tolerated.
- The Vaccine Candidate will be immunogenic in the majority of participants tested.

2.2. Study objectives and endpoints

2.2.1. Primary objectives:

2.2.1.1. Efficacy:

1. To evaluate the efficacy of a full regimen of **Vaccine Candidate** against laboratory-confirmed COVID-19 of any severity.

2.2.1.2. Safety:

1. To assess **Vaccine Candidate** safety (i.e., SAEs or other medically attended AEs).
2. To assess **Vaccine Candidate** post-vaccination reactogenicity in a subset of participants.
3. To assess **Vaccine Candidate** post-vaccination safety in terms of AEs ≥ Grade 2 in all participants.

2.2.1.3. Immunogenicity:

1. To evaluate **Vaccine Candidate** immunogenicity among all study participants by ELISA-binding IgG antibodies against the **Vaccine Candidate** antigen(s).

2.2.2. Secondary objectives:

2.2.2.1. Efficacy:

1. To evaluate the efficacy of **Vaccine Candidate** against severe laboratory confirmed COVID-19.
2. To evaluate the overall efficacy of **Vaccine Candidate** against laboratory-confirmed COVID-19 of any severity.
3. To evaluate the efficacy of **Vaccine Candidate** against laboratory-confirmed COVID-19 of any severity among participants ≥60 years of age.
4. To evaluate the efficacy of **Vaccine Candidate** against asymptomatic SARS CoV-2 infections detected serologically.
5. To evaluate the efficacy of **Vaccine Candidate** against laboratory-confirmed COVID-19 deaths.
6. To evaluate the efficacy of **Vaccine Candidate** against deaths of any cause.

2.2.2.2. Safety:

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1. To assess **Vaccine Candidate** safety in terms of VED and AESI.

2.2.2.3. Immunogenicity:

1. To evaluate immunogenicity of **Vaccine Candidate** by neutralizing antibody (nAb) assay against SARS-CoV-2.
2. To evaluate persistence of vaccine-induced ELISA binding IgG antibodies against the vaccine antigen at 6 and 12 months after immunization in subsets of participants.

2.2.3. Exploratory objectives:

2.2.3.1. Efficacy:

1. To evaluate the efficacy of **Vaccine Candidate** against laboratory-confirmed COVID-19 of any severity categorized by sex.
2. To evaluate the efficacy of **Vaccine Candidate** against laboratory-confirmed COVID-19 of any severity stratified by disease severity grades.
3. To evaluate the efficacy of **Vaccine Candidate** against laboratory confirmed symptomatic cases among participants who were virologically or serologically positive for SARS-CoV-2 at time of enrollment.
4. To evaluate the efficacy of **Vaccine Candidate** against laboratory-confirmed COVID-19 of any severity among participants who were virologically and serologically negative for SARS-CoV-2 at time of enrollment.
5. To evaluate the efficacy of **Vaccine Candidate** against laboratory-confirmed COVID-19 of any severity among individuals who previously presented with a symptomatic COVID-19 infection of any severity.
6. To evaluate the efficacy of **Vaccine Candidate** against laboratory-confirmed COVID-19 of any severity within subgroups defined by randomization across sites.
7. To investigate disease severity as measured by hospitalization or mechanical ventilation.

2.2.3.2. Safety:

1. To evaluate COVID-19 cases of any severity with specialized assays to discern potential differences between breakthrough cases detected among **Vaccine Candidate** recipients vs. those in the placebo/control group.

2.2.3.3. Immunogenicity:

1. To evaluate early infection serum samples and convalescent serum samples (~15 days after infection resolution), as well as baseline and post-vaccination serum samples from COVID-19 cases.
2. To evaluate samples from COVID-19 cases (and appropriate controls) in additional serological assays in an effort to identify immune correlates of protection (e.g., antibody affinity, ADCC, complement fixation, novel assays to be developed).

2.2.3.4. Clinical:

1. To evaluate COVID-19 symptoms in **Vaccine Candidate** vs. placebo recipients; and, to investigate the relationship between COVID-19 symptoms and disease severity to develop a severity score for use in future COVID-19 studies.

2.2.3.5. Virological:

1. To evaluate and compare sequences of breakthrough infection viruses in **Vaccine Candidate** vs. placebo recipients, and vs. the strain source of the vaccine antigen.
2. To confirm SARS-CoV-2 infection either by virologic or serologic methods, or by evaluating antibodies to SARS-CoV-2 antigens not included in the vaccine.

2.2.4. Primary endpoints:

2.2.4.1. Efficacy:

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1. Virologically confirmed COVID-19 of any severity occurring from two weeks after completion of the vaccination regimen until the time the targeted number of cases (n = **XXX**) has accrued.

2.2.4.2. Safety:

1. SAEs or other medically attended AEs occurring at any time in all study participants; SAE and medically attended AE rates will be analyzed when the primary efficacy endpoint (**XXX** cases) is reached and at study end.
2. Solicited local and systemic reactions for seven days after each study vaccination in a subset of study participants (e.g. **X,XXX**). Local reactions include pain at the injection site, redness, induration, and swelling as self-reported in diaries. Systemic reactions include fever, fatigue, headache, chills, vomiting, and diarrhea. The number and proportion of participants reporting such symptoms will be recorded.
3. Unsolicited vaccine-related ≥ Grade 2 AEs occurring between vaccinations and 28 days after the final vaccination, among all study participants. The number and proportion of participants reporting such symptoms will be recorded.

2.2.4.3. Immunogenicity:

1. IgG ELISA bAb in specimens collected before vaccination and XX days after each immunization, and at 6 and 12, months after completion of all study vaccinations. Geometric mean ELISA units, geometric mean fold rise, and seroconversion rates (proportion of participants with ≥4-fold rises in ELISA units between pre-vaccination and **XX** days after final vaccination) will be reported.

2.2.5. Secondary endpoints:

2.2.5.1. Efficacy:

1. Virologically confirmed severe COVID-19 cases occurring from two weeks after completion of first vaccination through 12 months of follow-up. Includes cases in which vaccination was incomplete or occurred out of allowable windows, and cases detected among individuals who were positive by serology or RT PCR at the time of enrollment.
2. Virologically confirmed COVID-19 cases of any severity occurring from two weeks after first vaccination through 12 months of follow-up.Includes cases in which vaccination was incomplete or occurred out of allowable windows, and cases detected among individuals who were positive by serology or RT PCR at the time of enrollment.
3. Virologically confirmed COVID-19 cases of any severity occurring among participants 18 through 59 years of age and ≥60 years of age from two weeks after first vaccination through 12 months of follow-up. Includes cases in which vaccination was incomplete or occurred out of allowable windows.
4. Serologically confirmed SARS-CoV-2 asymptomatic infections occurring from two weeks after first vaccination through 12 months of follow-up. Includes cases in which vaccination was incomplete or occurred out of allowable windows. Excludes cases detected among individuals who were positive by serology or RT PCR at the time of enrollment.
5. Virologically confirmed COVID-19 deaths occurring from two weeks after first vaccination through 12 months of follow-up. Includes cases in which vaccination was incomplete or occurred out of allowable windows, and cases detected among individuals who were positive by serology or RT PCR at the time of enrollment.
6. Deaths occurring during the study, independently of their association with COVID-19/SARS-CoV-2 infection, occurring from two weeks after first vaccination through 12 months of follow-up. Includes cases in which vaccination was incomplete or occurred out of allowable windows, and cases detected among individuals who were positive by serology or RT PCR at the time of enrollment.

2.2.5.2. Safety:

1. VED events occurring among participants with symptomatic virologically confirmed COVID-19 over the entire duration of the study; AESI events observed among all study participants over the entire duration of the study. Frequency count and proportion of participants reporting VEDs and AESIs will be reported.

2.2.5.3. Immunogenicity:

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1. nAb titers measured by neutralization assay against SARS-CoV-2 will be measured in a random subset of participants in specimens collected before the first and **XX** weeks after the final immunization. The geometric mean nAb titers, geometric mean fold rise, and seroconversion rate will be reported. Seroconversion rate will be defined as a baseline titer below the limit of detection (LOD) or lower level of quantitation (LLOQ) with the post-baseline titer above LOD/LLOQ. The overall seroresponse rate (*e.g., negative-to-positive or ≥4-fold rise among those initially positive)* will be summarized separately. The frequency of **XX**-fold rise or greater among those initially positive will also be summarized.
2. IgG ELISA bAb in specimens collected at 6 and 12 months after vaccination in a random subset of participants. Geometric mean ELISA units will be reported

2.2.6. Exploratory endpoints:

2.2.6.1. Efficacy:

1. Virologically confirmed COVID-19 cases of any severity occurring from two weeks after first vaccination through study end categorized by sex. Includes cases in which vaccination was incomplete or occurred out of allowable windows, or cases detected among individuals who were positive by serology or RT PCR at the time of enrollment.
2. Virologically confirmed COVID-19 cases of any severity occurring from two weeks after first vaccination through study end stratified by disease severity according to WHO Clinical Progression Scale. Includes cases in which vaccination was incomplete or occurred out of allowable windows, and cases detected among individuals who were positive by serology or RT PCR at the time of enrollment.
3. Virologically confirmed COVID-19 cases of any severity occurring from two weeks after first vaccination through study end in participants who were virologically or serologically SARS-CoV-2 positive at the time of enrollment.
4. Virologically confirmed COVID-19 cases of any severity occurring from two weeks after first vaccination through study end in participants who were virologically and serologically SARS-CoV-2 negative at the time of enrollment.
5. Virologically confirmed COVID-19 cases of any severity occurring from two weeks after first vaccination through study end. Includes only participants who were virologically or serologically positive at enrollment as well as participants who developed symptomatic SARS-CoV-2 infection of any severity during the follow-up.
6. Virologically confirmed COVID-19 of any severity occurring from two weeks after completion of the vaccination regimen through study end for each clinical site independently.
7. Count and frequency of COVID-19 cases occurring at any time during the study that require hospitalization or mechanical ventilation.

2.2.6.2. Safety:

1. Exploratory tests to be defined, e.g., IL-6, inflammation markers, Th1/Th2 markers (IgG subclasses, cytokines), etc. Frequency count and rate of positive tests will be reported.

2.2.6.3. Immunogenicity:

1. IgG ELISA bAb in specimens collected before vaccination and **XX** days after each immunization, as well as at 6 and 12 months after vaccination from participants who develop COVID-19 of any severity. Geometric mean ELISA units, geometric mean fold rise, and seroconversion rates (proportion of participants with ≥4-fold rises in ELISA units between pre-vaccination and **XX** days after final vaccination) will be reported. Geometric mean ELISA units for sera collected at 6 and 12 months will be reported.
2. Test results, positivity rates, and mean titers will be reported.

2.2.6.4. Clinical:

1. Tabulate the range of symptoms presented among COVID-19 cases in Vaccine Candidate vs. placebo recipients and examine the relationship of symptoms with disease severity. Counts and rate of individual systems will be presented categorized by vaccine / placebo treatment and by disease severity according to the WHO Clinical Progression Scale.

2.2.6.5. Virological:

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1. Attempt to isolate/cultivate viruses from COVID-19 cases. Viral sequence comparisons between strains isolated from study participants and the vaccine strain from which the vaccine was derived.
2. Frequnecy and counts of seroresponses to non-vaccine SARS-CoV-2 antigens that may be indicative of infection in samples collected at the time of infection and after a COVID-19 infection.

2.3. Case definitions of COVID-19-confirmed cases

The case definition for participants that meet the primary endpoint of this Phase 3 trial is defined as, *RT-PCR confirmed (PCR+) COVID-19 (i.e., symptomatic SARS-CoV-2 infection) of any severity*.

COVID-19 positive status includes participants with A) mild, or B) severe signs/ symptoms [17].

This includes the following:

2.3.1. Mild COVID-19: Respiratory tract infection with or without general systemic symptoms including one or more of the following:

- Fever or chills
- Cough
- Shortness of breath or difficulty breathing
- Fatigue
- Muscle or body aches
- Headache
- New loss of taste or smell
- Sore throat
- Congestion or runny nose
- Nausea or vomiting
- Diarrhea

2.3.1. Severe COVID-19:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93 percent on room air at sea level or PaO2/FiO2 < 300 mm Hg)
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or ECMO)
- Evidence of shock (SBP < 90 mm Hg, DBP < 60 mm Hg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurologic dysfunction
- Admission to an ICU
- Death

Severe COVID-19 cases are a subset of all cases, and participants may present initially to health care providers as a mild case. All participants will be followed until resolution of their disease, even if the initial presentation is classified as mild. Upon resolution of the COVID-19 episode, participants will continue to be followed through study end in the same manner as those who have not presented disease. Reinfections occurring in individuals who were infected earlier will not be counted towards the primary objective, however they will be considered for secondary analysis (see analysis section).

LITERATURE CITED

17. Development and Licensure of Vaccines to Prevent COVID-19. FDA guidance.https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19

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