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

In 1 collection

Chris Ockenhouse¹, Chris Gast¹, Renee Holt¹, Flores¹

¹Center for Vaccine Innovation and Access, PATH (Washington D.C. and Seattle, Washington)

Coronavirus Method Development Community

Chris Ockenhouse

DISCLAIMER

DISCLAIMER – FOR INFORMATIONAL PURPOSES ONLY; USE AT YOUR OWN RISK

The protocol content here is for informational purposes only and does not constitute legal, medical, clinical, or safety advice, or otherwise; content added to protocols.io is not peer reviewed and may not have undergone a formal approval of any kind. Information presented in this protocol should not substitute for independent professional judgment, advice, diagnosis, or treatment. Any action you take or refrain from taking using or relying upon the information presented here is strictly at your own risk. You agree that neither the Company nor any of the authors, contributors, administrators, or anyone else associated with protocols.io, can be held responsible for your use of the information contained in or linked to this protocol or any of our Sites/Apps and Services.

DOI: dx.doi.org/10.17504/protocols.io.bj5pkq5n

Collection Citation: Chris Ockenhouse, Chris Gast, Renee Holt, Jorge Flores 2020. Collection of Protocols and Guidelines for Phase 3 study of Vaccine Candidate for COVID-19. protocols.io https://dx.doi.org/10.17504/protocols.io.bj5pkq5n

License: This is an open access collection distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited

Protocol status: Working
We use this protocol and it's working

Created: Aug 22, 2020
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

GUIDELINES

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

Protocol Number
[XXX]

Trial Registration
[XXX]

Study Conducted By
[XXX]

<Regulatory/IND> Sponsor
[XXXX]

(Sponsor means an individual, pharmaceutical or medical device company, governmental agency, academic institution, private organization, or other organization that takes responsibility for and initiates a clinical investigation.)

Collaborating Partner/s (In Collaboration With)
[XXXX]
Pharmaceutical Support
[xxxx]

Source of funding
[SPONSOR, with funding from XXX]

Site Principal Investigator
[xxxx]

Protocol Version Number
[0.01]

Version Date
[_______2020]

Confidentiality Statement
(see example below)

“This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable regulatory authorities and independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from SPONSOR.”

---------------------

TABLE OF CONTENTS

1. BACKGROUND AND RATIONALE
   1.1. BACKGROUND
      ■ 1.1.1. Pathogen
      ■ 1.1.2. Clinical manifestations:
      ■ 1.1.3. Route of transmission:
      ■ 1.1.4. Risk factors:
      ■ 1.1.5. Clinical management:
      ■ 1.1.6. Site-specific epidemiolocal situation
   1.2. DESCRIPTION OF THE STUDY VACCINE
   1.3. SUMMARY OF PRE-CLINICAL STUDIES
      ■ 1.3.1. Immunogenicity studies in rodents
      ■ 1.3.2. Challenge and protection studies in non-human primates (macaques)
      ■ 1.3.3. GLP toxicology and developmental & reproductive toxicology (DART)
        studies
      ■ 1.3.4. Summary of candidate vaccine clinical studies (example)
   1.4. STUDY RATIONALE
1.5. POTENTIAL RISKS OF STUDY VACCINE

- 1.5.1. Risks of receipt of Vaccine Candidate
- 1.5.2. Vaccine-enhanced disease
- 1.5.3. Risk of pregnancy
- 1.5.4. Risks of accidental disclosure of private medical information
- 1.5.5. Risks of phlebotomy

1.6. POTENTIAL BENEFITS OF STUDY PARTICIPATION

1.7. CLINICAL DEVELOPMENT PLAN

2. HYPOTHESES, OBJECTIVES, ENDPOINTS, AND CASE DEFINITIONS

2.1. STUDY HYPOTHESES

2.2. STUDY OBJECTIVES AND ENDPOINTS

- 2.2.2. Secondary objectives:

2.3. CASE DEFINITIONS OF COVID-19-CONFIRMED CASES

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

3. STUDY DESIGN

3.1. SUCCESS CRITERIA

4. STUDY POPULATION

4.1. ENROLLMENT AND SAMPLE SIZE ADJUSTMENT

4.2. PARTICIPANT INCLUSION CRITERIA

4.3. PARTICIPANT EXCLUSION CRITERIA

4.4. DESCRIPTION OF STUDY POPULATION

4.5. COVID-19 CASE CAPTURE

4.6. COVID EVENT ADJUDICATION COMMITTEE

4.7. SAFETY ASSESSMENT STRATEGY

4.8. COVID-19 AES FOR ASSESSMENT OF VED

5. STUDY VACCINE

5.1. ACQUISITION

5.2. FORMULATION, APPEARANCE, PACKAGING, AND LABELING

5.3. PREPARATION

5.4. ROUTE OF ADMINISTRATION

5.5. VACCINATION SCHEDULE

5.6. TRACKING OF DOSE

5.7. STUDY VACCINE ACCOUNTABILITY AND DISPOSAL PROCEDURES

6. STUDY PROCEDURES

6.1. STUDY PROCEDURES AND EVALUATION

- 6.1.1. Screening visit – Day -7 to Day 0
- 6.1.2. Randomization
6.1.3. First vaccination visit (Day 1)
6.1.4. Second vaccination visit (Day 15 + 7-day window)
6.1.5. Day 28 (+5-day window)
6.1.6. Day XX (42-56; two-to-four weeks after final vaccination, depending on vaccine)
6.1.7. Day XX (42-56 to study end)
6.1.8. Day 180
6.1.9. Day 365/730
6.1.10. Interim contacts and visits
6.1.11. Withdrawal from study
6.1.12. Handling of participant withdrawals or termination
6.1.13. Premature termination or suspensions of study
6.1.15. Management of birth control and pregnancy during study

6.2. LABORATORY EVALUATIONS
6.2.1. Sample collection, distribution, and storage
6.2.2. Clinical laboratory tests
6.2.3. Immunological laboratory assays
6.2.4. Future use of stored samples; correlates analyses

7. SAFETY ASSESSMENT AND REPORTING
7.1. DEFINITIONS
7.1.1. Adverse event (AE)
7.1.2. Medically Attended Adverse Events
7.1.3. Serious adverse event (SAE)

7.2. GENERAL GUIDANCE ON RECORDING ADVERSE EVENTS
7.3. REPORTING OF SAEs
7.3.1. Investigator Reporting to Sponsor
7.3.2. Notification and Review of SAEs
7.3.3. Notification of LOCAL Ethical Review Committee (ERC)

7.4. NON-COMPLIANCE WITH THE REGULATIONS OR REQUIREMENTS
7.5. SAFETY OVERSIGHT

8. DATA HANDLING AND RECORDKEEPING
8.1. DETAILS OF DATA MANAGEMENT
8.1.1. Coding
8.1.2. Data validation
8.1.3. Source data verification
8.1.4. Definitions

8.2. DATA CAPTURE METHODS (CASE REPORT FORM DEVELOPMENT AND COMPLETION)
8.3. DATA STORAGE
8.4. DATABASE LOCKING PROCEDURES
8.5. RETENTION OF STUDY RECORDS
8.6. PROTOCOL DEVIATIONS

9. STATISTICAL CONSIDERATIONS
9.1. OVERVIEW AND GENERAL DESIGN
  9.1.1. Randomization procedures
9.2. SAMPLE SIZE
9.3. DEFINITIONS OF POPULATIONS TO BE ANALYZED
  9.3.1. Enrolled population
  9.3.2. Safety population
  9.3.3. Intention-to-Treat (ITT) population
  9.3.4. Reactogenicity population
  9.3.5. Per-protocol population (PP)
  9.3.6. Immunogenicity populations
9.4. INTERIM ANALYSIS, MONITORING FOR HARM
9.5. ANALYTICAL METHODOLOGY
  9.5.1. Descriptive methodology
  9.5.2. Changes in analysis plan
  9.5.3. Baseline and demographic characteristics, and participant disposition
  9.5.4. Analysis of the primary efficacy endpoint
  9.5.5. Analysis of the secondary endpoint(s)
9.6. SAFETY ANALYSIS
9.7. SEROLOGICAL ANALYSIS
9.8. HANDLING OF DROPOUTS AND MISSING DATA

10. QUALITY ASSURANCE AND QUALITY CONTROL
  10.1.1. General considerations
  10.1.2. Study monitoring
  10.1.3. Independent auditing
  10.1.4. Regulatory agency auditing
  10.5. Data and Safety Monitoring Board (DSMB) and Safety Monitoring Committee

11. ETHICAL CONSIDERATIONS (AND INFORMED CONSENT)
11.1. ETHICAL STANDARDS
11.2. ETHICAL REVIEW
11.3. INFORMED CONSENT PROCESS
11.4. PARTICIPANT CONFIDENTIALITY
11.5. REIMBURSEMENT
11.6. RISK AND BENEFITS
  11.6.1. Risk to study personnel
11.7. REPORTING OF COMMUNICABLE DISEASE
11.8. POLICY REGARDING STUDY-RELATED INJURY CARE AND COMPENSATION

12. FINANCING AND INSURANCE
13. PUBLICATION AND DATA SHARING POLICY

APPENDIX A: SCHEDULE OF STUDY VISITS AND EVALUATIONS - EXAMPLE PROVIDED; VACCINE DEPENDENT

APPENDIX B: SEVERITY GRADING TABLE

APPENDIX C. SAMPLE INFORMED CONSENT FORM TEMPLATE

--------------

Investigator’s Agreement Page

1. I have read the foregoing protocol and agree to conduct the study as outlined herein.
2. I agree to follow this protocol version as approved by the Ethics Review Committee/Institutional Review Board (ERC/IRB).
3. I agree this study will be conducted in accordance and in conformity with ICH GCP, the Declaration of Helsinki, and all applicable regulations.
4. I will conduct the study in accordance with applicable ERC/IRB requirements to maintain the protection of the rights and welfare of study participants.
5. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
6. I will not modify the protocol without first obtaining permission from the sponsor, an ERC/IRB approved amendment, and new protocol version, unless modification is necessary to protect the health and welfare of study participants.
7. I will ensure the data and/or specimens are maintained in accordance with the data and/or specimen disposition outlined in the protocol. Any modifications to this plan should first be reviewed and approved by the applicable ERC/IRB.
8. I will prepare and submit continuing review reports according to established timeframes at intervals established by the IRB and a study closure report when all research activities are completed.
9. I agree to maintain adequate and accurate records in accordance with institutional policies, local laws, and regulations as applicable.
10. I certify that the statements herein are true, complete, and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept the responsibility for the scientific conduct of the project.

_______________________________________             _____________________
XXX (PI)                                                                     DateXXX
## ABBREVIATIONS AND ACRONYMS

**TO BE UPDATED DEPENDING UPON PRODUCT**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADE</td>
<td>Antibody-Dependent Enhancement</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>AESI</td>
<td>Adverse Event of Special Interest</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine Transaminase</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate Transaminase</td>
</tr>
<tr>
<td>bAb</td>
<td>Binding Antibody</td>
</tr>
<tr>
<td>BSC</td>
<td>Biological Safety Cabinet</td>
</tr>
<tr>
<td>CAPA</td>
<td>Corrective and Preventive Action</td>
</tr>
<tr>
<td>CBC</td>
<td>Complete Blood Count</td>
</tr>
<tr>
<td>CDC</td>
<td>Center for Disease Control</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CIOMS</td>
<td>Council for International Organization of Medical Sciences</td>
</tr>
<tr>
<td>CONSORT</td>
<td>Consolidated Standards of Reporting Trials</td>
</tr>
<tr>
<td>CoV</td>
<td>Coronavirus</td>
</tr>
<tr>
<td>COVID-19</td>
<td>Coronavirus Disease 19</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CRO</td>
<td>Contract Research Organization</td>
</tr>
<tr>
<td>CSR</td>
<td>Clinical Study Report</td>
</tr>
<tr>
<td>DART</td>
<td>Developmental &amp; Reproductive Toxicology</td>
</tr>
<tr>
<td>DMP</td>
<td>Data Management Plan</td>
</tr>
<tr>
<td>DRM</td>
<td>Data Review Meeting</td>
</tr>
<tr>
<td>DSMB</td>
<td>Data and Safety Monitoring Board</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic Case Report Form</td>
</tr>
<tr>
<td>EDC</td>
<td>Electronic Data Capture</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme-linked Adsorbent Assay</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>ERC</td>
<td>Ethical Review Committee</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GMC</td>
<td>Geometric Mean Concentration</td>
</tr>
<tr>
<td>GMT</td>
<td>Geometric Mean Titre</td>
</tr>
<tr>
<td>HCW</td>
<td>Healthcare Worker</td>
</tr>
<tr>
<td>IAP</td>
<td>Interim Analysis Plan</td>
</tr>
<tr>
<td>IB</td>
<td>Investigator’s Brochure</td>
</tr>
<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
</tr>
<tr>
<td>ICH</td>
<td>International Council for Harmonisation</td>
</tr>
<tr>
<td>ID</td>
<td>Identification Number</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>Interferon-gamma</td>
</tr>
<tr>
<td>IgG</td>
<td>Immunoglobulin G</td>
</tr>
<tr>
<td>IP</td>
<td>Investigational Product</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention-to-Treat</td>
</tr>
<tr>
<td>IWRS</td>
<td>Interactive Web Response System</td>
</tr>
<tr>
<td>Kg</td>
<td>Kilogram</td>
</tr>
<tr>
<td>MERS</td>
<td>Middle East Respiratory Syndrome</td>
</tr>
<tr>
<td>MERS-CoV</td>
<td>Middle East Respiratory Syndrome Coronavirus</td>
</tr>
<tr>
<td>mL</td>
<td>Milliliter</td>
</tr>
<tr>
<td>μg</td>
<td>Microgram</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>MM</td>
<td>Medical Monitor</td>
</tr>
<tr>
<td>mm</td>
<td>Millimeter</td>
</tr>
<tr>
<td>nAb</td>
<td>Neutralizing Antibodies</td>
</tr>
<tr>
<td>NP</td>
<td>Nasopharyngeal</td>
</tr>
<tr>
<td>PBS</td>
<td>Phosphate-buffered Saline</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>PP</td>
<td>Per Protocol</td>
</tr>
<tr>
<td>PSRT</td>
<td>Protocol Safety Review Team</td>
</tr>
<tr>
<td>术语</td>
<td>英文</td>
</tr>
<tr>
<td>-------</td>
<td>---------</td>
</tr>
<tr>
<td>PT</td>
<td>Preferred Term</td>
</tr>
<tr>
<td>PTID</td>
<td>Participants Identification Number</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic Acid</td>
</tr>
<tr>
<td>rRT-PCR</td>
<td>Real Time Reverse Transcription Polymerase Chain Reaction</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical and Analysis Plan</td>
</tr>
<tr>
<td>SARS-CoV-2</td>
<td>Severe Acute Respiratory Syndrome Coronavirus 2</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SDMC</td>
<td>Statistical and Data Management Center</td>
</tr>
<tr>
<td>SOC</td>
<td>System Organ Class</td>
</tr>
<tr>
<td>SDV</td>
<td>Source Data Verification</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operational Procedure</td>
</tr>
<tr>
<td>SDMC</td>
<td>Statistical &amp; Data Management Center</td>
</tr>
<tr>
<td>SPEAC</td>
<td>Safety Platform for Emergency Vaccines</td>
</tr>
<tr>
<td>VED</td>
<td>Vaccine-Enhanced Disease</td>
</tr>
<tr>
<td>VAERD</td>
<td>Vaccine-Associated Enhanced Respiratory Disease</td>
</tr>
<tr>
<td>VE</td>
<td>Vaccine Efficacy</td>
</tr>
<tr>
<td>VTM</td>
<td>Viral Transport Media</td>
</tr>
<tr>
<td>WBC</td>
<td>White Blood Cell</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>

KEY ROLES AND CONTACT INFORMATION

---

<table>
<thead>
<tr>
<th>Principal Investigator</th>
<th>NAME</th>
<th>INSTITUTION</th>
<th>ADDRESS</th>
<th>TEL:</th>
<th>MOBILE:</th>
<th>FAX:</th>
<th>EMAIL:</th>
</tr>
</thead>
</table>

protocol.io | [https://dx.doi.org/10.17504/protocols.io.bj5pkq5n](https://dx.doi.org/10.17504/protocols.io.bj5pkq5n) | Oct 25 2020 | 10
<table>
<thead>
<tr>
<th>Role</th>
<th>Name</th>
<th>Institution</th>
<th>Address</th>
<th>Tel</th>
<th>Mobile</th>
<th>Fax</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Associate Investigators</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Site Data Manager</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pharmacist</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Study Coordinator</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Medical Monitor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vaccine Manufacturer Representative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Statistical and Data Management Center</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Research Manager (for each participating institution)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## PROTOCOL SUMMARY

| **Title** | 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 |

---

**Clinical Laboratory**

| NAME | INSTITUTION | ADDRESS | TEL: | MOBILE: | FAX: | EMAIL: |

**Research Laboratory**

| NAME (Principal) | INSTITUTION | ADDRESS | TEL: | MOBILE: | FAX: | EMAIL: |

**Contract Research Organizations**

| NAME (Principal) | INSTITUTION | ADDRESS | TEL: | MOBILE: | FAX: | EMAIL: |

**Safety Monitoring and Data Management**

| NAME (Principal) | INSTITUTION | ADDRESS | TEL: | MOBILE: | FAX: | EMAIL: |

**Site Monitoring**

| NAME | INSTITUTION | ADDRESS | TEL: | MOBILE: | FAX: | EMAIL: |

**Ethics Review Committee / Institutional Review Boards (for each participating institution)**

| NAME | INSTITUTION | ADDRESS | TEL: | MOBILE: | FAX: | EMAIL: |

| ADDITIONAL REVIEW BOARDS/ETHICS COMMITTEES TO BE ADDED |

**Local Regulatory Authority (for each participating country)**

| NAME | INSTITUTION | ADDRESS | TEL: | MOBILE: | FAX: | EMAIL: |

---

**REFERENCES**

- protocols.io | https://dx.doi.org/10.17504/protocols.io.bj5pkq5n
- Oct 25 2020
<table>
<thead>
<tr>
<th>Short Title</th>
<th>Phase 3 study of [Vaccine Candidate] for COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol Number</td>
<td>[XXX]</td>
</tr>
<tr>
<td>Trial Phase</td>
<td>Phase 3</td>
</tr>
</tbody>
</table>

**Rationale**

The 2019 outbreak of coronavirus disease (COVID-19)—caused by a novel coronavirus, SARS-CoV-2—has now spread to more than 210 countries and territories globally. There are no specific therapies or vaccines to prevent COVID-19 and the numbers of new cases and deaths continue to increase daily. Fast-tracked vaccine development is urgently needed. Phase 1/2 clinical trials of Vaccine Candidate, the SARS-CoV-2 vaccine candidate manufactured by Sponsor, are now being conducted in location to evaluate the vaccine candidate’s safety and immunogenicity among healthy adults (Clinical Trial Registry #). Preliminary analysis from Phase 1/2 trials indicate Vaccine Candidate has an acceptable safety and immunogenicity profile. We propose to conduct a Phase 3, individually randomized, double-blind, placebo-controlled trial in location to determine the safety and efficacy of the vaccine candidate among healthy adults > 18 years of age.

**Study Products**

- Study vaccines:
  - Vaccine Candidate (volume mL contains xx amount of antigen and xx amount of adjuvant)
  - Control (placebo or licensed vaccine) - (i.e., no SARS-CoV-2 antigen)

**Primary Study Hypotheses**

- **Efficacy**: Vaccine Candidate will provide protection against laboratory-confirmed COVID-19 of any severity.
- **Safety**: Vaccine Candidate will be safe and well-tolerated.
- **Immunogenicity**: Vaccine Candidate will be immunogenic.

**Primary Objectives**

<table>
<thead>
<tr>
<th>Primary endpoints</th>
</tr>
</thead>
</table>

**Efficacy**

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

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.

**Safety**

1. To assess Vaccine Candidate safety (i.e., severe adverse events [SAEs] or other medically attended adverse events [AEs]).

1. SAEs or other medically attended AEs occurring at any time in all study participants; SAE and medically attended AE rates will be analyzed at when the primary efficacy endpoint (XXX cases) is reached and at study end.
<table>
<thead>
<tr>
<th>Immunogenicity</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. To evaluate [Vaccine Candidate] immunogenicity among all study participants</td>
<td>1. To evaluate the efficacy of [Vaccine Candidate] against severe laboratory-confirmed COVID-19.</td>
</tr>
<tr>
<td>by ELISA-binding IgG antibodies against the [Vaccine Candidate] antigen(s).</td>
<td>1. Virologically confirmed severe COVID-19 cases occurring from two weeks after first vaccination through 12 months of follow-up.</td>
</tr>
<tr>
<td>2. Solicited local and systemic reactions for seven days after each study vaccination in a subset of study participants (e.g., XXXX).</td>
<td>2. To evaluate the efficacy of [Vaccine Candidate] against laboratory-confirmed COVID-19 of any severity.</td>
</tr>
<tr>
<td>3. Vaccine related unsolicited AEs &gt; Grade 2 occurring between vaccinations and 28 days after the final vaccination, among all study participants.</td>
<td>3. Virologically confirmed COVID-19 cases of any severity occurring from two weeks after first vaccination through 12 months of follow-up.</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>Efficacy</td>
</tr>
<tr>
<td>1. To evaluate [Vaccine Candidate] immunogenicity among all study participants by ELISA-binding IgG antibodies against the [Vaccine Candidate] antigen(s).</td>
<td>1. To evaluate the efficacy of [Vaccine Candidate] against laboratory-confirmed COVID-19 of any severity among participants by age cohort.</td>
</tr>
<tr>
<td>2. Solicited local and systemic reactions for seven days after each study vaccination in a subset of study participants (e.g., XXXX).</td>
<td>2. Virologically confirmed COVID-19 cases of any severity occurring from two weeks after first vaccination through 12 months of follow-up.</td>
</tr>
<tr>
<td>3. Vaccine related unsolicited AEs &gt; Grade 2 occurring between vaccinations and 28 days after the final vaccination, among all study participants.</td>
<td>3. Virologically confirmed COVID-19 cases of any severity occurring from two weeks after first vaccination through 12 months of follow-up.</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>Efficacy</td>
</tr>
<tr>
<td>1. To evaluate [Vaccine Candidate] immunogenicity among all study participants by ELISA-binding IgG antibodies against the [Vaccine Candidate] antigen(s).</td>
<td>1. To evaluate the efficacy of [Vaccine Candidate] against laboratory-confirmed COVID-19 of any severity among participants by age cohort.</td>
</tr>
<tr>
<td>2. Solicited local and systemic reactions for seven days after each study vaccination in a subset of study participants (e.g., XXXX).</td>
<td>2. Virologically confirmed COVID-19 cases of any severity occurring from two weeks after first vaccination through 12 months of follow-up.</td>
</tr>
<tr>
<td>3. Vaccine related unsolicited AEs &gt; Grade 2 occurring between vaccinations and 28 days after the final vaccination, among all study participants.</td>
<td>3. Virologically confirmed COVID-19 cases of any severity occurring from two weeks after first vaccination through 12 months of follow-up.</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>Efficacy</td>
</tr>
<tr>
<td>1. To evaluate [Vaccine Candidate] immunogenicity among all study participants by ELISA-binding IgG antibodies against the [Vaccine Candidate] antigen(s).</td>
<td>1. To evaluate the efficacy of [Vaccine Candidate] against laboratory-confirmed COVID-19 of any severity among participants by age cohort.</td>
</tr>
<tr>
<td>2. Solicited local and systemic reactions for seven days after each study vaccination in a subset of study participants (e.g., XXXX).</td>
<td>2. Virologically confirmed COVID-19 cases of any severity occurring from two weeks after first vaccination through 12 months of follow-up.</td>
</tr>
<tr>
<td>3. Vaccine related unsolicited AEs &gt; Grade 2 occurring between vaccinations and 28 days after the final vaccination, among all study participants.</td>
<td>3. Virologically confirmed COVID-19 cases of any severity occurring from two weeks after first vaccination through 12 months of follow-up.</td>
</tr>
</tbody>
</table>

---

**Secondary Objectives**

**Secondary Endpoints**
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.

Exploratory Objectives

<table>
<thead>
<tr>
<th>Exploratory Endpoints</th>
</tr>
</thead>
</table>

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 COVID-19 of any severity 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 evaluate the efficacy of [Vaccine Candidate] against laboratory-confirmed COVID-19 of any severity within subgroups defined by randomization across sites.

Safety

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.

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.

1. Virologically confirmed COVID-19 cases of any severity occurring from two weeks after first vaccination through study end categorized by sex.

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.

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 that require hospitalization or mechanical ventilation.
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.

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.

### 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.

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. Acute and convalescent sera will also be collected. Geometric mean ELISA units, geometric mean fold rise, and seroconversion rates (proportion of participants with XX-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. To evaluate additional serological assays in samples from COVID-19 cases (and appropriate controls) in an effort to identify immune correlates of protection or risk (e.g., antibody affinity, ADCC, complement fixation, novel assays to be developed).

2. Test results, positivity rates, and mean titers will be reported.

### 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, in an effort to develop a severity score that can be used in future COVID-19 studies.

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.

### 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.

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. 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. Frequency 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.
Study Design

A case-driven, randomized, double-blind, placebo-controlled, adaptive, group-sequential Phase 3 clinical trial will be conducted to assess the efficacy, safety, and immunogenicity of [Vaccine Candidate]. Men and women 18 years and older will be enrolled and stratified by age (<60 years and ≥ 60 years). Note: Pregnant and breastfeeding women, as well as those intending to become pregnant within the three months after vaccination, will not be permitted to participate, unless data from developmental and reproductive toxicology (DART) and Phase 1/2 studies and a benefit/risk analysis are supportive. No pre-screening at time of enrollment to exclude seropositive or RT-PCR positive participants will be conducted. Participants will be randomized among X number of sites in X countries. Solicited AEs will be recorded in a subset of participants for seven days following each immunization and unsolicited AEs grade ≥ 2 will be recorded for all participants in between vaccinations and 28 days following the last vaccination. SAEs and medically attended AEs will be monitored throughout the study duration. For immunogenicity evaluations, blood samples will be taken from all participants before and XX weeks after each vaccination, and at 6 and 12 months. Antibody titers of IgG against SARS-CoV-2 will be measured in all participants pre-vaccination and XX days following the last vaccination. Neutralizing antibody titers will be measured in a subset of participants, with samples retained from all participants for future use to identify immune correlates of protection and/or risk. Attempts will be made to obtain acute (i.e., obtained at time of diagnosis) and convalescent (~2 weeks after recovery) serum from any participant that develops COVID-19 during the follow-up period. Participants will be monitored over 12 months for signs of COVID-19 infection. The study is end point driven. If the rate of detection of primary COVID-19 endpoints indicates that XX number of primary endpoints (i.e., laboratory-confirmed COVID-19 of any severity) has been accrued among fully vaccinated participants eligible for the primary analysis are not likely to be detected within 6 months of initiating surveillance, additional sites and/or countries may be enrolled. Enrollment at some sites may be closed due to low disease incidence, and total sample size may be increased or decreased based on blinded data. For safety determination for AESI or VED, whether Vaccine-Associated Enhanced Respiratory Disease (VAERD) or Antibody-Dependent Enhancement (ADE), an extended follow-up period may be necessary. The study will include interim analyses for safety, as well as formal early efficacy or futility analysis.

Study Population

Adults (male and female) ≥ 18 years old at enrollment

Participating Sites

[Sponsor] will initiate a Phase 3 trial in the following location(s): XXX.
### Study Duration

Participants will be followed for 12 months following first vaccination. Time until primary efficacy analysis will be based on accumulation of primary endpoints which is expected to be approximately 6-12 months duration. With an anticipated enrolment period per site of 6 months, the study is anticipated to last for ~18 months.

### LITERATURE CITED

7. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell


16. Considerations for study design for Phase 3 clinical trial. International Coalition of


**Additional Resources:**

**COVID-19 specific:**

- The Brighton Collaboration standardized template for collection of key information for benefit-risk assessment of protein vaccines. [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7343648/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7343648/)

**General:**

**Code of Federal Regulations (CFR)**
- 21 CFR Part 11: Electronic Records, Electronic Signatures
- 21 CFR Part 50: Protection of Human Subjects
- 21 CFR Part 312: Investigational New Drug Application

**Food and Drug Administration (FDA)**
- FDA Regulations Relating to Good Clinical Practice and Clinical Trials
- Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs – Improving Human Subject Protection
- Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees
- Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance
DISCLAIMER

DISCLAIMER – FOR INFORMATIONAL PURPOSES ONLY; USE AT YOUR OWN RISK

The protocol content here is for informational purposes only and does not constitute legal, medical, clinical, or safety advice, or otherwise; content added to protocols.io is not peer reviewed and may not have undergone a formal approval of any kind. Information presented in this protocol should not substitute for independent professional judgment, advice, diagnosis, or treatment. Any action you take or refrain from taking using or relying upon the information presented here is strictly at your own risk. You agree that neither the Company nor any of the authors, contributors, administrators, or anyone else associated with protocols.io, can be held responsible for your use of the information contained in or linked to this protocol or any of our Sites/Apps and Services.

ATTACHMENTS

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

FILES

Protocol

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

VERSION 1
CREATED BY
Chris Ockenhouse

protocol.s.io | https://dx.doi.org/10.17504/protocols.io.bj5pkq5n

Oct 25 2020
Protocol

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

Protocol

Study Design (Part 3 of Phase 3 study of Vaccine Candidate for COVID-19)

Protocol

Study Population (Part 4 of Phase 3 study of Vaccine Candidate for COVID-19)

Protocol

Study Vaccine (Part 5 of Phase 3 study of Vaccine Candidate for COVID-19)

Protocol

Study Procedures (Part 6 of Phase 3 study of Vaccine Candidate for COVID-19)
Severity Grading Table (Appendix B of Phase 3 study of Vaccine Candidate for COVID-19)

VERSION 1
CREATED BY
Chris Ockenhouse

Sample Informed Consent Form Template (Appendix C of Phase 3 study of Vaccine Candidate for COVID-19)

VERSION 1
CREATED BY
Chris Ockenhouse