CLINICAL TRIAL PROTOCOL

An Event-Driven,Phase3, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy, Safety, Immunogenicity,and Lot-to-Lot consistency of BBV152, a Whole-virion Inactivated SARS-CoV-2 Vaccine in Adults≥18Years of Age.

Protocol No: BBIL/BBV152-C/2020

Version No: 3.0; Date: 20-10-2020

Confidentiality Clause: The confidential information in this document is provided to you as an investigator for review by you, your staff, and the applicable Institutional Review Board/ Independent Ethics Committee member. By accepting this document, you agree that the information contained herein will not be disclosed to others, without written authorization from Bharat Biotech International Limited, Hyderabad, India.

Sponsored by:

Bharat Biotech International Limited (BBIL)
Genome Valley,Hyderabad, India.

Indian Council of Medical Research (ICMR)
Government of India, New-Delhi, India.

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Data Management
CRO – To be determined

Biostatistics
CRO – To be determined

Clinical Operations Management Unit (COM)
CRO – To be determined

Laboratories
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Declaration by Responsible Sponsor Representative(s)

An Event-Driven,Phase3, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy, Safety, Immunogenicity,and Lot-to-Lot consistency of BBV152, a Whole-virion Inactivated SARS-CoV-2 Vaccine in Adults≥18Years of Age.

This clinical study protocol version 2.0 was critically and scientifically reviewed and has been approved by, Bharat Biotech International Ltd., the Sponsor of this study. The information it contains is consistent with the current risk/benefit evaluation of the biological investigational medicinal product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, as amended in the 64th WMA General Assembly, Fortaleza, Brazil, October 2013 and national and international guidelines on Good Clinical Practice and applicable regulatory requirements.

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Date: Oct. 21, 2020

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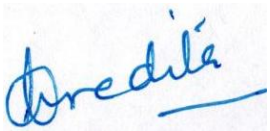
Signature: 

Date: 21-10-2020

SIGNATURE PAGE

By signing the protocol, the undersigned confirm our agreement with the contents of the protocol and our commitment to comply with the procedures contained in the protocol, with the conditions and principles of GCP, and with all relevant regulatory requirements.

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INVESTIGATOR PROTOCOL AGREEMENT

An Event-Driven,Phase3, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy, Safety, Immunogenicity,and Lot-to-Lot consistency of BBV152, a Whole-virion Inactivated SARS-CoV-2 Vaccine in Adults≥18 Years of Age.

Protocol Number:BBIL/BBV152-C/2020

By my signature, I confirm that my staff and I have carefully read and understood this protocol or protocol amendment, and agree to comply with the conduct and terms of the study specified herein.

I agree to conduct the study according to this protocol and the obligations and requirements of clinical investigators and all other requirements listed in ICH guidelines. I will not initiate this study without the approval of an Institutional Review Board (IRB) / Independent Ethics Committee (IEC).

I understand that should the decision be made by the sponsor to terminate prematurely or suspend the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from the execution of the study, I will communicate immediately such a decision in writing to the sponsor.

For protocol amendments, I agree not to implement the amendment without agreement from the sponsor and prior submission to and written approval (where required) from the IRB or IEC, except when necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).

_____ _____

Investigator's Signature Date

Investigator's Name

Address

CONTACT INFORMATION

An Event-Driven,Phase3, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy, Safety, Immunogenicity,and Lot-to-Lot consistency of BBV152, a Whole-virion Inactivated SARS-CoV-2 Vaccine in Adults≥18 Years of Age.

Protocol Number:BBIL/BBV152-C/2020

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Monitoring Team: Medical Affairs, Bharat Biotech International Limited & CRO

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term/ Abbreviation	Definition/ Full Form
Acute	A short-term, intense health effect
Active immunity	The production of antibodies against a specific disease by the immune system. Active immunity can be acquired in two ways, either by contracting the disease or through vaccination. Active immunity is usually permanent, meaning an individual is protected from the disease for the duration of their lives.
AE	Adverse event
AEFI	Adverse Event Following Immunization
Allergy	A condition in which the body has an exaggerated response to a substance (e.g. food or drug). Also known as hypersensitivity.
Anaphylaxis	An immediate and severe allergic reaction to a substance (e.g. food or drugs). Symptoms of anaphylaxis include breathing difficulties, loss of consciousness, and a drop in blood pressure. This condition can be fatal and requires immediate medical attention.
Antibody	A protein found in the blood that is produced in response to foreign substances (e.g. bacteria or viruses) invading the body. Antibodies protect the body from disease by binding to these organisms and destroying them.
Antigen	Foreign substances (e.g. bacteria or viruses) in the body that are capable of causing disease. The presence of antigens in the body triggers an immune response, usually the production of antibodies.
Asymptomatic COVID-19	A person with virologically confirmed (RT-PCR positive) SARS-CoV-2 infection without any symptoms of COVID-19 such as Fever or chills, Cough, Shortness of breath or difficulty breathing, Fatigue, Muscle or body aches, Headache, No loss of taste or smell, Sore throat, Congestion or runny nose, nausea or vomiting, Diarrhea.
BBIL	Bharat Biotech International Ltd.
B cells	Small white blood cells that help the body defend itself against infection. These cells are produced in the bone marrow and develop into plasma cells that produce antibodies. Also known as B lymphocytes.
BBV152	A Whole Virion Inactivated SARS-CoV-2 vaccine.
Brighton Collaboration Case Definition	Brighton Collaboration is an international voluntary collaboration to facilitate the development, evaluation, and dissemination of high-quality information about the safety of human vaccines. Brighton Collaboration case definitions are designed to identify cases and determine their diagnostic certainty.
Causal association	The presence or absence of a variable (e.g. smoking) is responsible for an increase or decrease in another variable (e.g. cancer). A change in exposure leads to a change in the outcome of interest.
CDC	Centers for Disease Control and Prevention, Atlanta, USA.
CDSCO	Central Drugs Standard Control Organisation.
CIOMS	Council for International Organizations of Medical Sciences.
Clinical Trial	A systematic study of pharmaceutical products on human subjects – (whether patients or

Term/ Abbreviation	Definition/ Full Form
	non-patient volunteers) –to discover or verify the clinical, pharmacological (including pharmacodynamics/ pharmacokinetics), and/ or adverse effects, with the object of determining their safety and/ or efficacy.
Confidentiality	Maintenance of privacy of study subjects including their identity and all medical information, from individuals other than those prescribed in the Protocol.
Community immunity	A situation in which a sufficient proportion of a population is immune to an infectious disease (through vaccination and/or prior illness) to make its spread from person to person unlikely. Even individuals not vaccinated (such as newborns and those with chronic illnesses) are offered some protection because the disease has little opportunity to spread within the community. Also known as herd immunity.
Contraindication	A condition in a recipient which is likely to result in a life-threatening problem if a vaccine were given.
Coordinating Investigator (per ICH E6)	An investigator assigned the responsibility for the coordination of investigators at different centers participating in a multicentre trial.
COVID-19	Corona Virus Disease 2019
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
Efficacy	The ability/ capacity/power to produce a desired or intended result
Efficacy rate	A measure used to describe how good a vaccine is at preventing disease.
ELISA	Enzyme-Linked Immunosorbent Assay
Endemic	Disease or condition regularly found among particular people or in a certain area
Epidemic	The occurrence of disease within a specific geographical area or population that is more than what is normally expected.
Exposure	Contact with infectious agents (bacteria or viruses) in a manner that promotes transmission and increases the likelihood of disease.
Essential Documents	The Documents that permit evaluation of the conduct of a study and the quality of the data generated
GCP	Good Clinical Practice
GACVS	Global Advisory Committee on Vaccine Safety
GMP	Good Manufacturing Practice
HCP	Health Care Profesional
Hypersensitivity	A condition in which the body has an exaggerated response to a substance (e.g. food or drug). Also known as an allergy.
IB	Investigator Brochure
IEC	Institutional Ethics Committee is also referred to as the Institutional Review Board. An independent review board or committee comprising of medical/scientific and non-medical/ non-scientific members, whose responsibility is to verify the protection of the rights, safety, and well-being of human subjects involved in a study. The independent review provides public reassurance by objectively, independently, and impartially reviewing and approving the “Protocol”, the suitability of the investigator(s), facilities, methods and

Term/ Abbreviation	Definition/ Full Form
	material to be used for obtaining and documenting "Informed Consent" of the study subjects and adequacy of confidentiality safeguards.
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IM	Intramuscular
IWRS	Interactive Web Response System
Immune system	The complex system in the body responsible for fighting disease. Its primary function is to identify foreign substances in the body (bacteria, viruses, fungi, or parasites) and develop a defense against them. This defense is known as the immune response. It involves the production of protein molecules called antibodies to eliminate foreign organisms that invade the body.
Immunity	Protection against a disease. There are two types of immunity, passive and active. Immunity is indicated by the presence of antibodies in the blood and can usually be determined with a laboratory test.
Impartial Witness	An impartial independent witness who will not be influenced in any way by those who are involved in the Clinical Trial, who assists at the informed consent process and documents the freely given oral consent by signing and dating the written confirmation of this consent.
Informed Consent	Voluntary written assent of a subject's willingness to participate in a particular study and its documentation. The confirmation is sought only after information about the trial including an explanation of its status as research, its objectives, potential benefits, risks and inconveniences, alternative treatment that may be available, and of the subject's rights and responsibilities have been provided to the potential subject.
Incidence	The number of new disease cases reported in a population over a certain period
Incubation period	The time from contact with infectious agents (bacteria or viruses) to onset of disease.
Investigator	ICH E6: A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and maybe called the principal investigator. CDSCO GCP: A person responsible for the conduct of the study at the trial site. The investigator is responsible for the rights, health, and welfare of the study subjects. In case the study is conducted by a team of investigators at the study site then the designated leader of the team should be the Principal Investigator
Investigator's Brochure	A collection of data (including the justification for the proposed study) for the Investigator consisting of all the clinical as well as non-clinical information available on the Investigational Product(s) known before the onset of the trial. There should be adequate data to justify the nature, scale, and duration of the proposed trial and to evaluate the potential safety and need for special precautions. If new substantially relevant data is generated during the trial, the information in the Investigator's Brochure must be updated
Investigational medicinal product (IP)	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form

Term/ Abbreviation	Definition/ Full Form
Investigational vaccine aka IP	Investigational vaccines are still in the testing and evaluation phase and are not licensed for use in the general public.
ITT	Intent-to-treat
LRTI	Lower Respiratory Tract Infection
MAAE	Medically Attended Adverse Event
MedDRA	Medical Dictionary for Regulatory Activities
Memory Cell	A group of cells that help the body defend itself against disease by remembering prior exposure to specific organisms (e.g. viruses or bacteria). Therefore, these cells can respond quickly when these organisms repeatedly threaten the body.
Monitor(Study)	A person appointed by the Sponsor or Contract Research Organisation (CRO) for monitoring and reporting the progress of the trial and for verification of data. The monitor ensures that the trial is conducted, recorded, and reported in accordance with the Protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirements.
Multi-Centre Study	A clinical trial conducted according to one single protocol in which the trial is taking place at different investigational sites, therefore carried out by more than one investigator.
NABL	National Accreditation Board for Testing and Calibration Laboratories
Outbreak	The sudden appearance of a disease in a specific geographic area (e.g. neighborhood or community) or population
Placebo	Placebois a treatment that looks like a regular treatment, but is made with inactive ingredients that have no real effect on patient health.
Passive immunity	Protection against disease through antibodies produced by another human being or animal. Passive immunity is effective, but protection is generally limited and diminishes over time (usually a few weeks or months). For example, maternal antibodies are passed to the infant before birth. These antibodies temporarily protect the baby for the first 4-6 months of life.
Prevalence	The number of disease cases (new and existing) within a population over a given period.
Risk	The likelihood that an individual will experience a certain event.
SAE	Serious Adverse Event
SAGE	Strategic Advisory Group of Experts
Seroconversion	Development of antibodies in the blood of an individual who previously did not have detectable antibodies
Serology	Measurement of antibodies, and other immunological properties, in the blood serum
SD	Standard Deviation
Source Data	Original documents (or their verified and certified copies) necessary for evaluation of the Clinical Trial. These documents may include Study Subjects' files, recordings from automated instruments, tracings, X-Ray, and other films, laboratory notes, photographic negatives, magnetic media, hospital records, clinical and office charts, diaries, check-lists, and pharmacy dispensing records
SARS-CoV-2	Severe acute Respiratory Syndrome Coronavirus 2
Sponsor	An individual or a company or an institution that takes the responsibility for the initiation, management, and/or financing of a Clinical Study

Term/ Abbreviation	Definition/ Full Form
SOP	Standard Operating Procedures: Standard elaborate written instructions to achieve uniformity of performance in the management of a certain function and activities
Sub-Investigator (ICH E6)	Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows)
Symptomatic COVID-19 case	A person with virologically confirmed (RT-PCR) SARS-CoV-2 infection with one or more of the following symptoms such as fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, and headache.
UIP	Universal Immunisation Program
URTI	Upper Respiratory Tract Infection
Vaccination	Injection of a killed or weakened infectious organism to prevent the disease
Vaccine	A product that produces immunity therefore protecting the body from the disease. Vaccines are administered through needle injections, by mouth, and by aerosol
VAERD	Vaccine-associated enhanced respiratory disease
Vulnerable subject	Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of aretaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Othervulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.
Waning Immunity	The loss of protective antibodies over time
WBC	White Blood Cell
WHO	World Health Organization

2. PROTOCOL SYNOPSIS

Title	An Event-Driven, Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy, Safety, Immunogenicity,and Lot-to-Lot consistency of BBV152, a Whole-virion Inactivated SARS-CoV-2 Vaccine in Adults ≥18 Years of Age.
Short Title	AatmaNirbharCOVIDStudy
Selection of Formulation	BBV152 The candidates were formulated with two adjuvants: Algel (alum) and Algel-IMDG, an imidazoquinoline class molecule (TLR7/TLR8 agonist abbreviated as IMDG) adsorbed on alum. BBV152A: 3 µg-Algel-IMDG BBV152-B: 6 µg-Algel-IMDG BBV152-C: 6 µg-Algel Pre-clinical potency and live viral challenge studies (Non-Human Primates and Hamsters) of both formulations (BBV152A& B) reported favourable outcomes. BBV152A and B reported higher immunogencity in the Non-Human Primates Study. Phase 1 Interim results suggested comparable immunogencity across all three formualtions. T-cell responses were recorded only in the subjects that received Algel-IMDG. The safety profile of Algel-IMDG was found to be comparable to the control (Algel only) arm. A culmination of all these studies have led to the slection of the BBV152B (6µg-Algel-IMDG)for evaluation of Effiacy and Safety as part of a Phase 3 study.
Primary Objectives (Efficacy)	**Primary Endpoints (Efficacy)**
To evaluate the efficacy of BBV152 to prevent symptomatic COVID-19.	First occurrence of Virologically confirmed (RT-PCR positive) symptomatic cases of COVID-19.(The symptomatic COVID-19 cases include any participant who meets the Case Definitions for Symptomatic Endpoint and Severe Symptomatic COVID-19). [Time Frame: Day 42 to Month 12].
Secondary Objectives (Efficacy)	**Secondary Endpoints (Efficacy)**
To evaluate the efficacy of BBV152 to prevent COVID-19 based on the	First occurence of Virologically confirmed (RT-PCR positive) symptomatic cases of COVID-19 based on the case definition for the secondary efficacy symptomatic endpoint. [Time Frame: Day 42 to Month 12].

case definition for the secondary efficacy symptomatic endpoint.	
To evaluate the efficacy of BBV152 to prevent severe COVID-19	Virologically confirmed (RT-PCR positive) severe cases of COVID-19. [Time Frame: Day 42 to Month 12].
To evaluate the efficacy of BBV152 to prevent any severity COVID-19 by age.	Virologically confirmed COVID-19 cases of any severity occurring among participants 18 through 59 years of age and ≥60 years of age. [Time Frame: Day 42 to Month 12].
To evaluate the efficacy of BBV152 to prevent asymptomatic COVID-19.	Virologically confirmed COVID-19 asymptomatic cases. Excludes cases in which vaccination was incomplete, and cases detected among individuals who were positive by serology at the time of enrolment. [Time Frame: Month 2 to Month 12].
To evaluate the efficacy of BBV152 to prevent COVID-19 regardless of symptomatology or severity	Virologically confirmed COVID-19 asymptomatic and symptomatic cases occurring from two weeks after the second vaccination. Excludes cases in which vaccination was incomplete, and cases detected among individuals who were positive by serology at the time of enrolment. [Time Frame: Month 2 to Month 12].
To evaluate the efficacy of BBV152 to prevent COVID-19 related deaths	The number of participants with virologically confirmed COVID-19 deaths. [Time Frame: Day 42 to Month 12].
To evaluate the efficacy of BBV152 to prevent all cause deaths	The number of participants with all cause mortality.[Time Frame: Day 42 to Month 12].
To evaluate the efficacy of BBV152 to prevent symptomatic	The number of participants with virologically confirmed symptomatic COVID-19. Includes cases that were seropositive at baseline. Excludes cases in which vaccination was incomplete. [Time Frame: Day 42 to Month 12].

COVID-19, regardless of the previous infection.	
Secondary Objectives (Safety)	**Secondary Endpoints (Safety)**
To assess the safety of BBV152	Serious Adverse Events (SAEs) occurring at any time in all study participants; SAE rates will be analyzed tillprimary endpoint events have been confirmed in 130 study participants and at the study end. [Time Frame: Throughout the study period].
	Solicited local and systemic adverse events (AEs). [Time Frame: within 7 days post each vaccination]
	Unsolicited adverse events (AEs) occurring between the vaccination and 28 days after the final vaccination, among all study participants. [Time Frame: Within 28 days post vaccination]
	Immediate adverse events with 30 minutes of vaccination [Time Frame: within 30 minutes post each vaccination]
	Medically attended adverse events (MAAEs) or AEs leading to withdrawal through the entire study period.
	The occurrence of enhanced respiratory disease episodes reported by participant/documented in hospital records throughout the trial. [Time Frame: Throughout the study period]
	Adverse Event of Special Interest (AESI)[Time Frame: Throughout the study period]
Secondary Objectives (Immunogenicity)	**Secondary Endpoints (Immunogenicity)**
To evaluate the immunogenicity of BBV152	Geometric Mean Titer (GMT) of SARS-CoV-2 Specific Neutralizing Antibody (nAb) [Time Frame: Month 0 to Month 12]
	Geometric Mean Fold Rise (GMFR) of SARS-CoV-2 Neutralizing Antibody (nAb) at Month. [Time Frame: Month 0 to Month 12]
	Geometric Mean Titer (GMT) of SARS-CoV-2 S1 protein-specific Binding Antibody (bAb). [Time Frame: Month 0 to Month 12]
	Lot-to-Lot consistency will be assessed based on the neutralizing titer of the three consistent lots used in the trial. [Time Frame: Month 0 to Month 2]

Study Sites	Multicenter study
Population	A total sample size of 25,800 volunteers, ages ≥18 years and above will receive selected formulation of BBV152 vaccine and placebo in a 1:1 ratio. Recruitment should support the generalizability of results, including enrollment of healthy participants as well as participants at risk for severe COVID-19, such as persons ≥60 years of age and those individuals with stable co-morbid diseases such as hypertension, diabetes, obesity, chronic kidney disease, chronic obstructive pulmonary disease (COPD), and chronic heart disease.
Study Duration	~12 months
Investigational Vaccine (INV)	Whole-Virion Inactivated SARS-CoV-2 vaccine (BBV152) will be administered as a two-dose intramuscular injection 28 days apart.
Selection of INV	BBV152B (Based on Phase 1 trial interim report) The dose selected for this study (6 µg of Antigen & Adjuvant-IMDG) is based on the assessment of available safety and immunogenicity data from Phase 1 studies (**NCT04471519)** and animal studies.
Comparator (Control)	Phosphate buffered saline withAlum (without antigen) will be used as the control. There is no licensed SARS-CoV-2 vaccine currently available to serve as a reference control.
Blinding	The control is identical to the vaccine. The sponser, investigator and subject are blindes for investigational product.
Study Rationale	Bharat Biotech in partnership with ICMR and NIV has developed an indigenous whole virion inactivated COVID-19 vaccine and conducted a phase 1 clinical study with 375 volunteers to evaluate the safety and immunogenicity of the 3 vaccine formulations of BBV152A, BBV152B, BBV152C. The phase 2 study is currently on-going in 380 subjects with two selected formulations of BBV152 (BBV152A and BBV152B). Further, we plan to conduct a phase 3 study in 25,800 volunteers to evaluate the protective efficacy, immunogenicity, and safety of the selected formulation BBV152B, based on the Non-human primate challenge studies and phase 1 clinical study. The purpose of this Phase 3 study is to evaluate the protective efficacy, safety, and immunogenicity of the whole-virion inactivated SARS-CoV-2 vaccine, BBV152B. The Phase 3 study will follow randomized study participants for efficacy until virologically confirmed (RT-PCR positive) symptomatic COVID-19 participants will be eligible for the primary efficacy analysis. After reaching the target number (n=130) of symptomatic COVID-19 cases, the study will continue to assess safety until the completion of the study duration. The Lot-to-Lot consistency (Immunogenicity) study will be nested within the Phase 3 (Efficacy) study (in three selected sites). The Immunogenicity study will assess the immune response of a 2-dose regimen of BBV152 vaccine through geometric mean titers (GMTs) by neutralizing antibody, S-protein, and RBD specific anti-IgG binding titer in a subset of 600

	(450 vaccine: 150 control) participants, across three consecutive manufacturing Lots. Data generated through Day 56 (Month 2) will be unblinded only to the biostatistician for evaluation of immune responses in the Immunogenicity subset. This interim report containing safety and immunogenicity data will be submitted to CDSCO.
Study Design	This is a randomized, double-blind, phase 3 study to evaluate the Efficacy, Safety, and Immunogenicity of BBV152B, a Whole-Virion Inactivated SARS-CoV-2 Vaccine in Volunteers aged 18 years and above. A total of 25,800 subjects will be enrolled and randomized in a 1:1 ratio to receive BBV152Avaccine and control. All participants will be assessed for efficacy and safety endpoints and provide a NP swab and blood sample before the first dose of IP. The NP swab and blood collected will be subject to RT-PCR and Anti-SARS-CoV-2 IgG antibodies. The results of this will not affect enrollment of the participant. Particpants who are foind to be psostive for either RT-PCR Or Anti-SARS-CoV-2 IgG antibodies will be excluded from the primary efficacy anlysis. **In addition, sites will be segregated based on the study objectivies:** **Category 1 (Symptomatic)**: In addition to administering the IP, a series of post-dose telephonic follow-up visits will be scheduled to detect suspect symptomatic COVID-19 infections. If a suspect is identified, a nasopharyngeal sample will be collected from the participant for detecting the presence of COVID-19 infection. Telephonic follow-up will occur at 15 day intervals. **Category 2 (Symptomatic/Asymptomatic)**: In addition to administering the IP, a series of post-dose Nasopharyngeal samples for detecting incidence of Asymptomatic COVID-19 infection at 1-Month intervals will be collected. **Category 3 (Symptomatic/Asymptomatic+Immunogenicity)**: In addition to administering the IP, repeated NP swabs for asymptomatic, a series of blood samples will be collected for analyzing serum for immunological assessments. Efficacy assessments will include surveillance for COVID-19 with RT-PCR confirmation of SARS-CoV-2 infection after the first and second dose of IP. As noted above, this is a case-driven study: if the prespecified criterion for early efficacy is met at the time of interim analysis (IA) and the Data and Safety Monitoring Board (DSMB) recommends early

	stopping for demonstrated efficacy, or efficacy is established by the planned primary analysis after 130 primary endpoint events have accrued, a study report describing the efficacy and safety of BBV152Awill be prepared based on the data available at that time. Ten milliliter of blood will be collected from all the RT-PCR confirmed symptomatic COVID-19 participants. If success criteria are met either at the time of the interim analyses or when the total number of cases toward the primary endpoint has accrued, participants will continue to be followed in a blinded fashion until Month 12, to enable assessment of long-term safety (all category sites) and immunogenicity (only for category 3 [immunogenicity] sites). The design and focus of the study are dependent on the current COVID-19 pandemic, requiring identification of participant candidates at high risk of SARS-CoV-2 infection. The Sponsor may adjust the size of the study or duration of follow-up based on the blinded review of the total number ofcases of COVID-19 (based on approapriatequantams of symptomatic or severe cases) accrued during the study, in addition to estimated percentages of study participants with immunologic evidence of SARS-CoV-2 infection at baseline. If achieving 130 cases of COVID-19 is manifestly unattainable based on plausible expansions of sample size or increased follow-up, an analysis of blinded data may be performed and change of the study design such as changing the required lower bound for the primary analysis may be proposed.
Eligibility Criteria	**Inclusion** 1. Ability to provide written informed consent and availability to fulfill the study requirements. 2. Participants of either gender of aged 18 years and above. 3. Participants with good general health as determined by the discretion of the investigator, or participants with stable medical conditions. A stable medical condition is defined as a disease not requiring significant change in therapy or hospitalization or worsening disease during the 3 months before enrolment. 4. For a female participant of child-bearing potential, planning to avoid becoming pregnant (use of an effective method of contraception or abstinence) from the time of study enrolment until at least eight weeks after the last vaccination. 5. Male subjects of reproductive potential: Use of condoms to ensure effective contraception with the female partner and to refrain from sperm donation from first vaccination until at least 3 months after the last vaccination. 6. Agrees not to participate in another clinical trial at any time during the study period. 7. Agrees not to take any COVID-19 licensed vaccination for the entire duration of the study.

	8. Agrees to remain in the study area for the entire duration of the study. 9. Willing to allow storage and future use of biological samples for future research. **Exclusion** 1. History of any other COVID-19 investigational or licensed vaccination. 2. Known history of SARS-CoV-2 infection, as declared by the subject. 3. For women, positive urine pregnancy test before the first dose of vaccination, or any time during the study period. 4. Temperature >38.0°C (100.4°F) or symptoms of an acute self-limited illness such as an upper respiratory infection or gastroenteritis within three days prior to each dose of vaccine. 5. Resident of COVID-19 infection in same household. 6. Known case of HIV, hepatitis B, or hepatitis C infection. 7. Receipt of any licensed/experimental vaccine within four weeks before enrolment in this study. 8. Receipt of immunoglobulin or other blood products within the three months before vaccination in this study. 9. Immunosuppression as a result of an underlying illness or treatment with immunosuppressive or cytotoxic drugs, or use of anticancer chemotherapy or radiation therapy within the preceding 36 months. 10. Immunoglobulins, anti-cytokine antibodies and blood products within 6 months prior to study vaccination, during and 21 days following last dose of vaccination. 11. Pregnancy, lactation, or willingness/intention to become pregnant during the first 6 months after enrolment. 12. Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder,, and neurological illness (mild/moderate well-controlled comorbidities are allowed) Re-Vaccination Exclusion Criteria 13. Pregnancy. 14. History of virologically (RT-PCR) confirmed SARS-CoV-2 infection 15. Anaphylactic reaction following administration of the investigational vaccine.
Case Definition of Asymptomatic COVID-19	Virologically confirmed (RT-PCR positive) COVID-19 infection without any reported symptoms.

<table>
<tr>
<td>Criteria for identifying a suspect symptomatic COVID-19 case.

(If criteria is met, a NP swab must be collected within 72 hours of reporting)</td>
<td>Participants with any one symptom of COVID-19 lasting at least 48 hours (except for fever and/or respiratory symptoms) will visit the clinic or will be visited at home by medically qualified site staff within 72 hours (an “Illness Visit”) to collect an NP swab sample for RT-PCR testing for SARS-CoV-2.
<table>
<tr><th>Symptom</th><th>Minimum time since symptom onset to identify a suspect case of COVID-19, which will trigger NP swab collection.</th></tr>
<tr><td>Fever</td><td>>24 hours</td></tr>
<tr><td>New or increased Cough</td><td>>24 hours</td></tr>
<tr><td>Shortness of breath/Difficulty in breathing</td><td>>24 hours</td></tr>
<tr><td colspan="2"></td></tr>
<tr><td>Chills</td><td>>48 hours</td></tr>
<tr><td>Congestion/Runny nose</td><td>>48 hours</td></tr>
<tr><td>Sore throat</td><td>>48 hours</td></tr>
<tr><td>Myalgia/Fatigue</td><td>>48 hours</td></tr>
<tr><td>Headache</td><td>>48 hours</td></tr>
<tr><td>New onset Anosmia/Ageusia</td><td>>48 hours</td></tr>
<tr><td>Diarrhea</td><td>>48 hours</td></tr>
<tr><td>Nausea/Vomiting</td><td>>48 hours</td></tr>
</table>
</td>
</tr>
<tr>
<td>Case Definition of symptomatic COVID-19 Endpoint</td>
<td>The study is designed to accrue 130 symptomatic COVID-19 cases.

This includes any participant who meets any of the two below following criteria:

Case Definition for Primary Efficacy Symptomatic Endpoint
Case Definition for Severe Symptomatic COVID-19

Any one of the below mentioned criteria (A or B) must be met, along with a positive SARS-CoV-2 RT-PCR confirmation to be a confirmed symptomatic case.
<table>
<tr><th>Criteria A: One or More</th><td>OR</td><th>Criteria B: Two or More</th></tr>
<tr><td>1. Shortness of Breath/Difficulty in breathing
2. New onset Anosmia/Aguesia
3. Oxygen saturation of <94% or escalation by requiring supplemental Oxygen.
4. Pneumonia: diagnosed by chest X ray or CT scan
5. Evidence of Shock</td><td></td><td>1. Fever
2. Chills
3. New cough
4. Myalgia/Fatigue
5. Headache
6. Sore throat
7. Nausea/Vomiting
8. Diarrhea
9. Congestion/ Runny Nose</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><td colspan="2">6. ICU Admission/Death</td><td></td></tr>
<tr><td colspan="3">AND</td></tr>
<tr><td colspan="3">Positive SARS-CoV-2 RT-PCR test</td></tr>
</table>
</td></tr>
<tr><td>Case Definition of symptomatic COVID-19 (Severe)</td><td>Virologically confirmed (RT-PCR positive) SARS-CoV-2 Severe Respiratory tract infection with one or more of the following symptoms:
<table>
<tr><td>1. Clinical signs at rest indicative of severe systemic illness (respiratory rate >30/min, heart rate >125/min, SpO2<93%)</td></tr>
<tr><td>2. Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO)</td></tr>
<tr><td>3. Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)</td></tr>
<tr><td>4. Significant acute renal, hepatic, or neurologic dysfunction</td></tr>
<tr><td>5. Admission to an ICU</td></tr>
<tr><td>6. Death</td></tr>
</table>
</td></tr>
<tr><td>Case Definition of Symptomaitc COVID-19 Case</td><td>The study is designed to accrue 130 symptomatic COVID-19 cases.

This includes any participant who meets the following criteria:
• Case Definition for Primary Efficacy Symptomatic Endpoint
• Case Definition for Severe Symptomatic COVID-19</td></tr>
</table>

<table>
<tr><td>Case Definition of symptomatic COVID-19 for the Secondary Efficacy symptomatic Endpoint</td><td>If a suspect COVID-19 case is identified and does not meet the primary efficacy symptomatic endpoint, they will then be eligible for inclusion into the seoncdary efficacy symptomatic endpoint.

Participants with any one symptom of COVID-19 lasting at least 48 hours (except for fever) with positive RT-PCR test for SARS-CoV-2 will be considered as a COVID-19 symptomatic case for the secondary efficacy symptomatic endpoint.

The following two criteria must be met for a participant to be confirmed as a symptomatic case of COVID-19 for the secondary efficacy symptomatic endpoint; Criteria C OR Criteria D and Positive RT-PCR COVID-19 test with Nasopharyngeal Swab:

<table>
<tr><td rowspan="2"><u>Criteria C</u>
At least one of the symptoms lasting > 24 hours</td><td rowspan="2">Fever</td><td rowspan="8">OR</td><td rowspan="8"><u>Criteria D</u>
At least one of the symptoms lasting > 48 hours</td><td>Chills</td></tr>
<tr><td>Congestion/Runny nose</td></tr>
<tr><td colspan="2"></td><td>Sore throat</td></tr>
<tr><td colspan="2"></td><td>Myalgia/Fatigue</td></tr>
<tr><td colspan="2"></td><td>Headache</td></tr>
<tr><td colspan="2"></td><td>Nausea/Vomiting</td></tr>
<tr><td colspan="2"></td><td>Diarrhea</td></tr>
<tr><td colspan="5">AND</td></tr>
<tr><td colspan="5">Criteria 2: Positive RT-PCR COVID-19 test with Nasopharyngeal Swab</td></tr>
</table>
</td></tr>
<tr><td>Adverse Events of Special Interest (AESI)</td><td>The following AESIs (if any) will be evaluated during the study period.

1. Anaphylaxis
2. Vaccine-associated enhanced respiratory disease (VAERD)
3. Generalized convulsion

An AESI can be either serious or non-serious. All AESIs will be recorded. Serious AESIs will be recorded and reported as per reporting guidelines for SAEs.</td></tr>
<tr><td>Statistical Analysis Plan</td><td>Estimation of vaccine efficacy (VE) in this study is based on person-time incidence rates: VE = 1 – (nv/Fv) / (np/Fp) = 1 – R, where R = (nv/Fv) / (np/Fp); nv and np are the numbers of participants who develop PCR-confirmed symptomatic COVID-19 among BBV152 vaccine and placebo recipients, respectively, and Fv and Fp are the corresponding total lengths of follow-up in years in the two groups, with follow-up in years defined as a follow-up in days divided by 365.25. VE will typically be expressed as a percentage. We assume that nv and np follow Poisson distributions with respective parameters λvFv and λpFp; the true (unknown) VE is 1 – λv / λp. Then, conditional on n = nv + np, the total number of participants who develop symptomatic COVID-19, the number nv in the vaccine group follows a binomial distribution with n trials and probability parameter λvFv / (λvFv +</td></tr>
</table>

	λpFp), estimated by P = nv / (nv+np). Hypotheses about VE can also be stated in terms of P and the ratio h = Fp/Fv, which is expected to be very close to 1, since by the above definitions R = hP / (1-P) and thus VE = 1 – hP / (1-P). A two-sided confidence interval (CI) around the estimated VE will be obtained by converting an exact CI for the probability parameter P, using the observed Fp/Fv, to a CI for VE.
Sample Size	The study is designed to obtain a two-sided 95% CI for vaccine efficacy with a lower bound ≥ 30%. (A slight adjustment, to a 95.3% CI, will be necessary at the final analysis if there is an interim analysis with possible early stopping for demonstrated efficacy.) For assumed true efficacy of 60%, the required number of cases for 85% power is 130. The total number of participants required depends on the assumed incidence during the follow-up period. We assume an average incidence among placebo recipients of 1% during follow-up beginning 14 days after the second dose; thus the expected number of participants required to accrue 130 cases is approximately 18,572. Allowing for baseline seropositivity and RT-PCR confirmed COVID-19 cases as exclusions (20%) and other losses (loss to follow-up, etc.) of 10%, the number becomes 25,794. It is planned to randomize approximately 25,800 study participants. The assumption of Vaccine Efficacy of 60% is for sample size estimation only. The intended success criteria for vaccine efficacy is 50% (in agreement with the minimum requirement given in the WHO Target Product Profile). Based on approapriate accrual of symptomatic or severe cases, the Sponsor may increase the sample size or increase the follow-up time. These changes will be reflected in future amendments. The null hypothesis Vaccine Efficacy value may be adaptively modified to below 30% during the trial, based on a lower-than-projected COVID-19 attack rate or case accrual rate, with collaborative decision-making by DSMB. Starting with a 30% null hypothesis VE value rather than a lower value helps assure that vaccine efficacy is estimated with sufficient precision to support decision-making about a vaccine, which may include regulatory approval and acceptance of the vaccine for manufacturing and widespread use.
Assessment of asymptomatic COVID-19 Case	In addition to administering the IP, a series of post-dose Nasopharyngeal (NP) samples for detecting an incidence of Asymptomatic COVID-19 infection at 1-Month intervals will be collected. (only in a subset of subjects (n=10,000).
Data Documentation	Electronic/Paper Case Report Form and Subject Diary Card.

Table 1: Study Flow Chart of Phase 3 study **Category 1 Site (Symptomatic)**:

Parameters	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13
	Month 0	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Informed consent	✓												
Inclusion/ exclusion criteria	✓												
Screening number	✓												
Demography	✓												
Urine pregnancy test	✓	✓	✓										
Blood sample for Immunogenicity	✓												
Nasopharyngel Swab	✓												
Randomization	✓												
Vitals (Including pulse Oximetry) & General & Systemic Examination	✓	✓											
Investigational vaccine administration	✓	✓											
Subject Diary distribution	✓	✓											
Concomitant medication	✓	✓	As applicable for treatment of SAE and MAAE										
Current Health Status	✓	✓											
COVID-19 Symptoms examination	✓	✓											
Adverse event recording	✓	✓	✓	SAEs and MAAEs									
Telephonic follow-up (2 times/month) [Current health, General History, COVID-19 Symptom history, Adverse Event recording]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 2: Study Flow Chart of Phase 3 study **Category 2Site (Symptomatic/Asymptomatic)**:

Parameters	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13
	Month 0	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Informed consent	✓												
Inclusion/ exclusion criteria	✓												
Screening number	✓												
Demography	✓												
Randomization	✓												
Vitals (Including pulse Oximetry) & General & Systemic Examination	✓	✓	✓	✓	✓	✓	✓	✓					
Urine pregnancy test	✓	✓	✓										
Blood sample for Immunogenicity	✓												
Nasopharyngeal Swab (asymptomatic participants only)	✓		✓	✓	✓	✓	✓	✓					
Investigational vaccine administration	✓	✓											
Subject Diary distribution	✓	✓											
Concomitant medication	✓	✓	✓	✓	✓	✓	✓	✓	As applicable for treatment of SAE and MAAEs				
Current Health Status	✓	✓	✓	✓	✓	✓	✓	✓					
COVID-19 Symptoms examination	✓	✓	✓	✓	✓	✓	✓	✓					
Adverse event recording	✓	✓	✓	✓	✓	✓	✓	✓	SAE and MAAEs				
Telephonic follow-up (2 times/month) [Current health, General History, COVID-19 Symptom history, Adverse Event recording]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 3: Study Flow Chart of Phase 3 study **Category 3Site (Symptomatic/Asymptomatic+Immunogenicity)**:

Parameters	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13
	Month 0	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Informed consent	✓												
Inclusion/ exclusion criteria	✓												
Screening number	✓												
Demography	✓												
Randomization	✓												
Vitals (Including pulse Oximetry) & General & Systemic Examination	✓	✓	✓	✓	✓	✓	✓	✓					
Urine pregnancy test	✓	✓	✓										
Blood sample for Immunogenicity	✓	✓*	✓*	✓*			✓*			✓*			✓*
Nasopharyngeal Swab (asymptomatic participants only)	✓		✓	✓	✓	✓	✓	✓					
Investigational vaccine administration	✓	✓											
Subject Diary distribution	✓	✓											
Concomitant medication	✓	✓	✓	✓	✓	✓	✓	✓	As applicable for treatment of SAE and MAAEs				
Current Health Status	✓	✓	✓	✓	✓	✓	✓	✓					
COVID-19 Symptoms examination	✓	✓	✓	✓	✓	✓	✓	✓					
Adverse event recording	✓	✓	✓	✓	✓	✓	✓	✓	SAEs and MAAEs				
Telephonic follow-up (2 times/month) [Current health, General History, COVID-19 Symptom history, Adverse Event recording]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

*** Blood sample for subset 600 subjects in the immunogenicity cohort will be collected to assess immunogenicity (Only 3 sites).**

3. INTRODUCTION

The outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2/COVID-19) has, as on September 12th,2020, spread to over 216 countries across the globe, with a total of ~30 Million confirmed cases and ~900,000 deaths. The number of reported SARS-CoV-2 cases in India is also on an increase with ~5 Million confirmed cases and ~77,000 deaths **(1)**. Coronaviruses are a severe threat to the humans and other animals, earlier other members of the same family coronaviridae, SARS-CoV infected ~8000 people with a death rate of 10% and another member Middle East Respiratory Syndrome (MERS) virus was out-broken in the Middle East region and infected ~2000 people with 35% fatality rate **(2)**. Porcine epidemic diarrhea coronavirus (PEDV) has swept throughout the United States of America, causing an almost 100% fatality rate in piglets and wiping out more than 10% of America's pig population in less than a year **(2)**.

Coronaviruses are the enveloped positive-stranded RNA viruses which have the largest genome among all RNA viruses with approximately 27 to 32 kb^2. The viral genome is packed inside a helical capsid formed by the nucleocapsid protein (N) which is surrounded by an envelope. SARS-CoV viral envelope is associated with at least three structural proteins: The membrane protein (M) and the envelope protein (E) are involved in virus assembly, whereas the spike protein (S) mediates virus entry into host cells. Among these structural proteins, the spike forms large protrusions from the virus surface, giving coronaviruses the appearance of having crowns **(2)**. The SARS-CoV-2 virus transmits from person to person mainly through respiratory droplets **(3)**.

The inhaled virus SARS-CoV-2 likely binds to epithelial cells in the nasal cavity and starts replicating. ACE2 is the main receptor for both SARS-CoV-2 and SARS-CoV **(4,5)**. There is local propagation of the virus but a limited innate immune response. At this stage, the virus can be detected by nasal swabs. Although the viral burden may be low, these individuals are infectious. The RT-PCR value for the viral RNA might be useful to predict the viral load and the subsequent infectivity and clinical course. The virus propagates and migrates down the respiratory tract along the conducting airways, and a more robust innate immune response is triggered. Nasal swabs or sputum should yield the virus (SARS-CoV-2) as well as early markers of the innate immune response **(6)**. The symptoms of SARS-CoV-2 infection appear after an incubation period of ~5 days **(7)**. The period from the onset of SARS-CoV-2 symptoms to death ranged from 6 to 41 days with a median of 14 days. This period is dependent on the age of the patient and the status of the patient's immune system. It was shorter among patients >70 years old compared with those under the age of 70 **(8)**. The most common symptoms at the onset of SARS-CoV-2 illness are fever, cough, and fatigue, while other symptoms include sputum production, headache, hemoptysis, diarrhea, dyspnoea, and lymphopenia **(9,10)**.

As per the European Centre for Disease Prevention and Control, an observational study of 1,420 patients with mild or moderate disease indicated that the most common symptoms were headache (70.3%), loss of smell (70.2%), nasal obstruction (67.8%), cough (63.2%), asthenia (63.3%), myalgia (62.5%), rhinorrhoea (60.1%), gustatory dysfunction (54.2%) and sore throat (52.9%). Fever was reported by on 45.4% **(11)**. The latest International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) reported on 25,849 hospitalised cases of COVID-19 across a broad clinical spectrum. The five most common symptoms at admission were history of fever, shortness of breath, cough, fatigue/malaise, and confusion **(12)**.

In another study conducted between 24 March and 21 April 2020, 2,450,569 UK and 168,293 US individuals reported symptoms through the smartphone app. Of the 2,450,569 participants in the United Kingdom, 789,083 (32.2%) indicated having one or more potential symptoms of COVID-19. The symptoms reported were fever, loss of smell or taste, fatigue, persistent cough, shortness of breath, diarrhea, delirium, abdominal pain, chest pain, and hoarse voice **(13)**.

A study was conducted to quantify how individual COVID-19 symptoms contribute to COVID-19 'case' finding. The results of the study were presented in the webinar for COVAX workshop for "COVID-19 Efficacy Trial Design Considerations & Early Learnings from Ongoing Studies" conducted by World Health Organization (WHO), Coalition for Epidemic Preparedness Innovations (CEPI), and Gavi, The Vaccine Alliance.

The COVID Symptom Study App was launched in the UK on the 24th of March, and in the US and Sweden on the following weeks together with KCL, MGH Harvard and Lund University

- Users can log up to 20 distinct symptoms on a daily basis and enter COVID test results
- 4+ million users have joined, 170+ millions health reports have been logged and 1+ million test results have been entered
- 800,000+ users have signed up to the vaccine registry allowing to contact them about potential studies involving vaccines and other preventive treatments

The inclusion criteria were as follows:

- UK 18+ users active from 24th of March to 15th of September 2020 ○ Users who have regularly logged feeling healthy and then got sick (i.e. newly symptomatic) or kept feeling healthy (i.e. healthy).
- Included health reports that were logged any time after they got sick (i.e. symptoms onset) until 14 days after the onset - regular analysis - or until 3 days after the onset - 72 hours analysis.
- Included PCR test results that were logged any time from symptoms onset to 7 days after the onset.
- Included only first episode of PCR positive.
- Excluded users who signed up in the App and had already had COVID-19

Study Results:

The symptoms were classified into two types:

- Classic symptoms:Fever, cough, dyspnea, tachypnea, anosmia & ageusia.
- Extended symptoms:Classic symptoms + Fatigue + Headache

It was found that 14% of the positive cases showed no classic symptom during the two first weeks.

Symptoms	Tested positive	Recall (or Sensitivity)	Tested negative	Precision (or PPV)
Fatigue	1068	84.0	63138	1.7
Headache	1021	80.3	65038	1.5
Sore throat	744	58.5	55383	1.3
Loss of taste and smell *	730	57.4	5856	11.1
Persistent cough *	671	52.8	16648	3.9
Fever *	618	48.6	19576	3.1
Unusual muscle pains	592	46.5	20253	2.8
Shortness of breath *	527	41.4	15441	3.3
Chest pain	522	41.0	16274	3.1
Skipped meals	513	40.3	16017	3.1

Total num positive tests	1272
Total num negative tests	121347

Symptoms	Tested positive	Recall (or Sensitivity)	Tested negative	Precision (or PPV)
* Any classic symptom	1092	85.8	42292	2.5

Total number of tests
43,384

This percentage reduces to 3% if we include fatigue and headache into the triggering symptoms.

Symptoms	Tested positive	Recall (or Sensitivity)	Tested negative	Precision (or PPV)
Fatigue	111	61.7	34243	0.32
Headache	106	58.9	39391	0.27
Sore throat	83	46.1	33685	0.25
Diarrhoea	44	24.4	15588	0.28
Unusual muscle pains	43	23.9	9483	0.45
Dizzy light headed	43	23.9	16695	0.26
Typical hayfever	43	23.9	18917	0.23
Nausea	42	23.3	16683	0.25
Abdominal pain	36	20.0	14371	0.25
Eye soreness	33	18.3	11732	0.28

Total num positive tests	180
Total num negative tests	79055

Extended symptoms = classic symptoms + fatigue + headache

Symptoms	Tested positive	Recall (or Sensitivity)	Tested negative	Precision (or PPV)
Any extended symptom	1236	97.2	95073	1.3

Total number of tests
96,309

Classic symptoms are less likely to occur in the first 72 hours, but fatigue+headache might help case finding.

Symptoms	Tested positive	Recall (or Sensitivity)	Tested negative	Precision (or PPV)
Headache	845	66.4	57798	1.4
Fatigue	828	65.1	56176	1.5
Sore throat	598	47.0	49526	1.2
Persistent cough *	469	36.9	13411	3.4
Fever *	467	36.7	16567	2.7
Unusual muscle pains	374	29.4	16737	2.2
Hoarse voice	311	24.4	12126	2.5
Skipped meals	293	23.0	13386	2.1
Chest pain	293	23.0	13248	2.2
Loss of taste and smell	284	22.3	4673	5.7

Total num positive tests	1272
Total num negative tests	121340

Extended symptoms = classic symptoms + fatigue + headache

Symptoms	Tested positive	Recall (or Sensitivity)	Tested negative	Precision (or PPV)	Total number of tests
Any classic symptom *	865	68.2	36523	2.3	37,388
Any extended symptom	1160	91.2	89725	1.3	90,885

Summary:

- Inclusion of fatigue and headache to the triggering symptoms (classic symptoms), the proportion of the positive cases will increase from 68.2% to 91.2% (an increase of 23%) during the first 3 days of symptoms onset.

		Recall	Tests per positive case
14 days	Classic symptoms	85.8%	40
	Extended symptoms	97.2%	77
3 days	Classic symptoms	68.2%	43
	Extended symptoms	91.2%	78

Study conclusion:

- The COVID Symptom Study App has created a large prospective community-based cohort to understand how symptoms that may trigger PCR contribute to case finding. Based on data from the COVID Symptom Study App:
- 14% of the positive cases show no classic symptoms (Fever, cough, dyspnea, tachypnea, anosmia & ageusia) during the first two weeks of symptoms.

- By including fatigue and headache to the triggering symptoms, one would double the number of tests performed but 97.2% of the positive cases could be found.
- This is even more important during the first three days of symptoms, in which classic symptoms would only find 68.2% of the positive cases and the extended symptoms, 91.2%

The attack rate of the COVID-19 is high among the age group 20 to 40 years **(14)**. Among the infected patients, 1 in 6 is severely ill and, 1 in 5 needs hospitalization **(15)**. To date, no specific treatment was recommended for SARS-CoV-2 infection hence, there is a necessity to develop a vaccine to prevent the SARS-CoV-2 infection. Various types of COVID-19 vaccines, such as DNA-, RNA based formulations, Recombinant subunit vaccines containing the viral protein (Spike) epitopes, vector-based formulations (eg: Adenovirus), and traditional inactivated vaccines are under development **(16–19)** .

R0, pronounced "R naught," is a mathematical term that indicates how contagious an infectious disease is. R0, which is also referred to as the reproduction number, indicates how many other people will catch the disease from a single infected person, in a population that hasn't been exposed to the disease before.In April, the R0 for the SARS-CoV-2 infection is somewhere between 1.5 and 4, as per ICMR **(20)**.

As of 04th August 2020, the R0 in India remains steady at 1.16. For Delhi, the value of R0 has declined to 0.66 from 0.68 last week. For Mumbai and Chennai, the value of R0 has declined from 1 to 0.81 and 0.86, respectively. Kolkata's R0 reduced to 1.06 from 1.30 last week, while for Bengaluru, the value has reduced from 1.40 last week to 1.15 this week. Andhra Pradesh has an R0 value at 1.48 and has the highest R0 among the 12 worst-affected states. Bihar had an R0 value of 1.32. For Kerala, the R0 value was 1.12. For Rajasthan, it has fallen to 1.19. Uttar Pradesh and Telangana have witnessed an increase in R0 value, which now stands at 1.33 and 1.18, respectively. West Bengal, Gujarat, and Maharashtra have not seen much change in their R0 values and are at 1.34, 1.09, and 1.14, respectively **(21)**.

4. STUDY RATIONALE

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is accelerating globally leading to an increase in morbidity and mortality. The high-risk group includes the health care workers (HCW) (physicians and paramedical staff), working amid SARS-CoV-2 infected patients, all other people including household contacts of COVID-19 confirmed patients, people currently residing or working in COVID-19 hotspots/outbreak areas where there is a high risk of transmission of SARS-CoV-2 infection and especially the elderly people (age >70 Years). Though SARS-CoV-2 infection may cause mild symptoms in many, nearly 14% develop a severe disease that requires hospitalization and oxygen support, and 5% require admission to an intensive care unit (ICU). In severe cases, COVID-19 can becomplicated by acute respiratory distress syndrome, sepsis, septic shock, and multiorgan failure with an estimated case fatality of 3.4% as of March 10, 2020 **(3,22)**.

The COVID-19 pandemic is rapidly worsening in all parts of the world, overwhelming health systems. There is a serious threat to a densely populated country like India. Also, reports from all over the world demonstrate that the disease takes a severe course in elderly people and people with co-morbid conditions leading to higher mortality rates. Thus, there is an urgent need to ensure the safety and health of existing people living in COVID-19 affected areas where there is a high risk of disease transmission and find strategies to prevent the SARS-CoV-2 infection among such populations.

To date, no specific anti-viral drug has been approved for COVID-19 although Remdesivir has been given Emergency Use Authorization approval is approved. Hence, there is a necessity to develop a vaccine to prevent SARS-CoV-2 infection. Various types of COVID-19 vaccines, such as DNA, RNA based formulations, recombinant subunit vaccines containing the viral protein (Spike) epitopes, vector-based formulations (eg: Adenovirus), and traditional inactivated vaccines are under development **(16–19)**. A Chinese based vaccine manufacturing company (Sinovac Biotech Ltd.) has developed an inactivated vaccine formulation against the SARS-CoV-2 virus and proved its safety and immunogenicity in animals such as mice, rats, and non-primate mammal, *Rhesus macaque* monkeys **(19)**.

Bharat Biotech in partnership with ICMR and NIV has developed an indigenous whole virion inactivated COVID-19 vaccine and conducting a phase 1 clinical study with 375 volunteers to evaluate the safety and immunogenicity of the 3 vaccine formulations of the BBV152 vaccine. Further, we plan to conduct a phase 3 study in 25,800 healthy volunteers to evaluate the protective efficacy, immunogenicity, and safety of the selected formulation (BBV152B) from the phase 1 clinical study based on the objectives.

The purpose of this Phase 3 study is to evaluate the protective efficacy, safety, and immunogenicity of the whole-virion inactivated SARS-CoV-2 vaccine, BBV152B.

The subset (Immunogenicity) cohort will be nested within the Phase 3 (Efficacy) study. The immunogenicity cohort will assess the immune response of a 2-dose regimen of BBV152B vaccine through Geometric Mean Titers by neutralizing antibody, RBD specific anti-IgG binding titer in a subset of 600 (450 vaccine: 150 control) participants.

Data generated on Month 2, will be un-blinded only to the biostatistician for evaluation of immune responses in the immunogenicity cohort. This interim report containing safety and immunogenicity data will be submitted to CDSCO.

The Phase 3 study will continue to recruit individuals until virologically confirmed (RT-PCR positive) symptomatic SARS-CoV-2 infection, eligible for the primary efficacy analysis, has occurred in 130 study

participants. After reaching the target number of primary endpoint events, the study will continue to assess safety until the completion of the study duration.

5. RISK/BENEFIT ASSESSMENT

POTENTIAL BENEFITS OF STUDY PARTICIPATION

The target study population for this study is adults with no known history of SARS-CoV-2 infection but whose locations or circumstances put them at high risk of COVID-19. The following benefits may accrue to participants.

- The BBV152 vaccine may be an effective vaccine against COVID-19.
- Contributing to the development of a vaccine against COVID-19, a current pandemic disease.

RISKS FROM STUDY PARTICIPATION

Vaccination with corona virus vaccine, BBV152 is the first ever vaccine used in clinical trials. Based on experiences with other similar vaccines you may experience the following symptoms after vaccination:

- Anaphylaxis
- Pain
- Redness
- Swelling at injection site
- Systemic symptoms like raised temperature or fever, chills, fatigue, nausea, myalgia, vomiting, headache, and
- You may experience some pain and/or swelling of your arm from having blood drawn the number of times specified in the study procedures above. Drawing of blood can cause local bruising and reactions at the site of injection such as redness, swelling, and heat sensation.

6. STUDY OBJECTIVES/ENDPOINTS

Primary Objectives (Efficacy)	**Primary Endpoints (Efficacy)**
To evaluate the efficacy of BBV152 to prevent symptomatic COVID-19.	First occurrence of Virologically confirmed (RT-PCR positive) symptomatic cases of COVID-19. (The symptomatic COVID-19 cases include any participant who meets the Case Definitions for Symptomatic Endpoint and Severe Symptomatic COVID-19). [Time Frame: Day 42 to Month 12].
Secondary Objectives (Efficacy)	**Secondary Endpoints(Efficacy)**

To evaluate the efficacy of BBV152 to prevent COVID-19 based on the case definition for the secondary efficacy symptomatic endpoint.	First occurrence of Virologically confirmed (RT-PCR positive) symptomatic cases of COVID-19 based on the case definition for the secondary efficacy symptomatic endpoint. [Time Frame: Day 42 to Month 12].
To evaluate the efficacy of BBV152 to prevent severe COVID-19	Virologically confirmed (RT-PCR positive) severe cases of COVID-19. [Time Frame: Day 42 to Month 12].
To evaluate the efficacy of BBV152 to prevent any severity COVID-19 by age.	Virologically confirmed COVID-19 cases of any severity occurring among participants 18 through 59 years of age and ≥60 years of age. [Time Frame: Day 42 to Month 12].
To evaluate the efficacy of BBV152 to prevent asymptomatic COVID-19.	Virologically confirmed COVID-19 asymptomatic cases. Excludes cases in which vaccination was incomplete, and cases detected among individuals who were positive by serology at the time of enrolment. [Time Frame: Month 2 to Month 12].
To evaluate the efficacy of BBV152 to prevent COVID-19 regardless of symptomatology or severity	Virologically confirmed COVID-19 asymptomatic and symptomatic cases occurring from two weeks after the second vaccination. Excludes cases in which vaccination was incomplete, and cases detected among individuals who were positive by serology at the time of enrolment. [Time Frame: Day 42 to Month 12].
To evaluate the efficacy of BBV152 to prevent COVID-19 related deaths	The number of participants with virologically confirmed COVID-19 deaths. [Time Frame: Day 42 to Month 12].
To evaluate the efficacy of BBV152 to prevent symptomatic COVID-19, regardless of the previous infection.	The number of participants with virologically confirmed symptomatic COVID-19. Includes cases that were seropositive at baseline. Excludes cases in which vaccination was incomplete. [Time Frame: Day 42 to Month 12].
Secondary Objectives (Safety)	**Secondary Endpoints (Safety)**
To assess the safety of BBV152	Serious Adverse Events (SAEs) occurring at any time in all study participants; SAE rates will be analyzed when the primary efficacy endpoint (130 cases) is reached and at the study end. [Time Frame: Throughout the study period].
	Solicited local and systemic adverse events (AEs). [Time Frame: within 7 days post each vaccination]

	Unsolicited adverse events (AEs) occurring between the vaccination and 28 days after the final vaccination, among all study participants. [Time Frame: Within 28 days post vaccination]
	Immediate adverse events with 30 minutes of vaccination [Time Frame: within 30 minutes post each vaccination]
	Medically attended adverse events (MAAEs) or AEs leading to withdrawal through the entire study period.
	The occurrence of enhanced respiratory disease episodes reported by participant/documented in hospital records throughout the trial. [Time Frame: Throughout the study period]
	Adverse Event of Special Interest (AESI). [Time Frame: Throughout the study period]
Secondary Objectives (Immunogenicity)	**Secondary Endpoints (Immunogenicity)**
To evaluate the immunogenicity of BBV152	Geometric Mean Titer (GMT) of SARS-CoV-2 Specific Neutralizing Antibody (nAb) [Time Frame: Month 0 to Month 12]
	Geometric Mean Fold Rise (GMFR) of SARS-CoV-2 Neutralizing Antibody (nAb) at Month. [Time Frame: Month 0 to Month 12]
	Geometric Mean Titer (GMT) of SARS-CoV-2 S1 protein-specific Binding Antibody (bAb). [Time Frame: Month 0 to Month 12]
	Lot-to-Lot consistency will be assessed based on the neutralizing titer of the three consistent lots used in the trial. [Time Frame: Month 0 to Month 2]

7. STUDY DESIGN

The study will be an endpoint-driven, randomized, double-blind, placebo-controlled, in which participating adults will be randomized 1:1 to receive 2 doses of either Vaccine Candidate or a control normal saline plus aluminum hydroxide] on Month 0 and Month 1. Participants will be followed for efficacy, safety, and immunogenicity.

Each site participating in the study will have a site-specific protocol addendum that will allow for site-specific guidelines and variance (such as Ethics Council requirements and local case surveillance and clinical management guidelines). Endpoint definitions and data collection instruments will be common across sites.

In addition, sites will be segregated based on the study objectives:

Category 1 (Symptomatic): In addition to administering the IP, a series of post-dose telephonic follow-up visits will be scheduled to detect suspect symptomatic COVID-19 infections. If a suspect is identified, a nasopharyngeal sample will be collected from the participant for detecting the presence of COVID-19 infection. Telephonic follow-up will occur at 15 Day intervals.

Category 2 (Symptomatic/Asymptomatic): In addition to administering the IP, a series of post-dose Nasopharyngeal samples for detecting incidence of asymptomatic COVID-19 infection at 1-Month intervals will be collected.

Category 3 (Symptomatic/Asymptomatic+Immunogenicity): In addition to administering the IPandcollecting NP samples, a series of blood samples will be collected for analyzing serum for immunological assessments.

Efficacy assessments will include surveillance for COVID-19 with RT-PCR confirmation of SARS-CoV-2 infection after the first and second dose of IP. As noted above, this is a case-driven study: if the prespecified criterion for early efficacy is met at the time of interim analysis (IA) and the Data and Safety Monitoring Board (DSMB) recommends early stopping for demonstrated efficacy, or efficacy is established by the planned primary analysis after 130 primary endpoint events have accrued, a study report describing the efficacy and safety of BBV152B will be prepared based on the data available at that time.
If success criteria are met either at the time of the interim analyses or when the total number of cases toward the primary endpoint has accrued, participants will continue to be followed in a blinded fashion until Month 12, to enable assessment of long-term safety (all category sites) and immunogenicity (only for category 3 [immunogenicity] sites).

The design and focus of the study are dependent on the current COVID-19 pandemic, requiring identification of participant candidates at high risk of SARS-CoV-2 infection. The Sponsor may adjust the size of the study or duration of follow-up based on the blinded review of the total number of cases of COVID-19 accrued during the study, in addition to estimated percentages of study participants with immunologic evidence of SARS-CoV-2 infection at baseline. If achieving 130 cases of COVID-19 is manifestly unattainable based on plausible expansions of sample size or increased follow-up, an analysis of blinded data may be performed and change of the study design such as changing the required lower bound for the primary analysis may be proposed.

The study is adaptive, in that the total sample size may be increased at an early time point depending upon the rate of confirmed primary efficacy endpoint events and/or the observed vaccine efficacy. An Adjudication Committee will be constituted to review and confirm each case determined to be an endpoint. In addition, a DSMB will be established to provide periodic independent monitoring of vaccine safety and

operational quality, as well as to evaluate an interim efficacy analysis. The DSMB will review unblinded efficacy data and make recommendations regarding sample size adjustment or extension of follow-up according to predefined criteria, as well as recommendations for closing/opening sites to target enrollment in places where cases are accruing most rapidly. The DSMB will evaluate unblinded safety data periodically and additionally upon sponsor requests.

In addition, the study will include interim analyses to allow the DSMB to review interim unblinded efficacy data and determine whether there is overwhelming evidence of early efficacy or futility, and thus make recommendations in light of data accrued and predefined stopping criteria.

The DSMB risk/benefit evaluation will include additional vaccine-specific information from similar studies or other vaccines based on the same platform (inactivated vaccines).

Blinding

The control is identical to the vaccine. Sufficient measures will be taken to assure that blinding of participants and evaluation staff is maintained. Study product assignments will be accessible to the data coordinating center staff and others who are required to know this information to ensure proper trial conduct. The DSMB members may also be unblinded to treatment assignment as required to review vaccine safety and efficacy. Emergency unblinding decisions are expected to be rare and justified only when that information is needed for the future clinical management of that participant.

If in the opinion of the investigator, the event the health and safety of the participant will benefit from knowing the treatment code, efforts will be made to contact the medical monitor as long as patient safety is not at imminent risk. If the subject is at imminent risk, the investigator should have the ability to unblind although should notify the Medical Monitor (MM) and Sponsor as soon as possible thereafter.

8. SUCCESS CRITERIA

Success will be defined by a two-sided 95% CI for vaccine efficacy (adjusted as necessary for interim monitoring) with a lower bound ≥ 30%. The International Coalition of Medicines Regulatory Authorities noted that “a specific numeric value to be used for the lower bound and vaccine efficacy point estimate was not agreed upon at this stage”. It was also reflected that efficacy estimates crossing a certain pre-specified lower bound for efficacy, due to factors such as epidemiological evolution of the pandemic, would not preclude the possibility of a positive benefit-risk conclusion if there also were other data supportive of efficacy.

It is anticipated that the 6-month COVID-19 attack rate in the control arm will be approximately 1 percent. The trial is endpoint driven; the primary efficacy analysis is triggered by the accrual of 130 primary endpoint events across the two arms, at which point the results will be analyzed and reported. In the event overwhelming efficacy is detected during the interim analysis, placebo participants may be provided with closeout vaccinations.

All sites will monitor the incidence of severe COVID-19 and death attributable to COVID-19. Although the study may lack power for formal statistical inference about vaccine efficacy against severe disease and death, this secondary endpoint will be calculated and reported.

9. SUBJECT ELIGIBILITY

Inclusion

1. Ability to provide written informed consent and availability to fulfill the study requirements.
2. Participants of either gender of aged 18 years and above.
3. Participants with good general health as determined by the discretion of the investigator, or participants with stable medical conditions. A stable medical condition is defined as a disease not requiring significant change in therapy or hospitalization or worsening disease during the 3 months before enrolment.
4. For a female participant of child-bearing potential, planning to avoid becoming pregnant (use of an effective method of contraception or abstinence) from the time of study enrolment until at least eight weeks after the last vaccination.
5. Male subjects of reproductive potential: Use of condoms to ensure effective contraception with the female partner and to refrain from sperm donation from first vaccination until at least 3 months after the last vaccination.
6. Agrees not to participate in another clinical trial at any time during the study period.
7. Agrees not to take any COVID-19 licensed vaccination for the entire duration of the study.
8. Agrees to remain in the study area for the entire duration of the study.
9. Willing to allow storage and future use of biological samples for future research.

Exclusion

1. History of any other COVID-19 investigational or licensed vaccination.
2. Known history of SARS-CoV-2 infection, as declared by the subject.
3. For women, positive urine pregnancy test before the first dose of vaccination, or any time during the study period.
4. Temperature >38.0°C (100.4°F) or symptoms of an acute self-limited illness such as an upper respiratory infection or gastroenteritis within three days prior to each dose of vaccine.

5. Resident of COVID-19 infection in same household.
6. Known case of HIV, hepatitis B, or hepatitis C infection.
7. Receipt of any licensed/experimental vaccine within four weeks before enrolment in this study.
8. Receipt of immunoglobulin or other blood products within the three months before vaccination in this study.
9. Immunosuppression as a result of an underlying illness or treatment with immunosuppressive or cytotoxic drugs, or use of anticancer chemotherapy or radiation therapy within the preceding 36 months.
10. Immunoglobulins, anti-cytokine antibodies and blood products within 6 months prior to study vaccination, during and 21 days following last dose of vaccination.
11. Pregnancy, lactation, or willingness/intention to become pregnant during the first 6 months after enrolment.
12. Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder,, and neurological illness (mild/moderate well-controlled comorbidities are allowed)

Re-Vaccination Exclusion Criteria

13. Pregnancy.
14. History of virologically (RT-PCR) confirmed SARS-CoV-2 infection
15. Anaphylactic reaction following administration of the investigational vaccine.

10. COVID-19 CASE CAPTURE

COVID-19-confirmed cases will be captured by enhanced active surveillance. Participants will receive a card containing investigator contact information and locations to receive a SARS-CoV-2 RT-PCR test if they have any of the following signs or symptoms at any time up to study end:
A 24/7 healthcare communication service will be established to connect with the enrolled participants. Participants will be instructed to call this service for any illness that develops.

- Participants will be contacted by study staff approximately once every two weeks (or more frequently without restriction) by phone, SMS text message, or other means of communication to inquire whether the participant has experienced any signs/symptoms consistent with COVID-19 and to remind the participant about the vaccine trial.
- Those with any COVID-19 suspected symptoms that last more than one day will have a nasopharyngeal swab collected and tested by RT-PCR at a designated laboratory.
- Surveillance will be supplemented by the following:

- Participant communication via SMS text or telephone call, about whether they developed an illness during the past two week.
- Reporting via the 24/7 study healthcare communication service maintained by the study and staffed by doctors and nurses.
- Notation in the health report about whether participants experienced any illnesses in the past two week.
- Follow-up calls from the study center to participants who do not submit the bi-weekly health report.

All participants will receive clinical care.

Symptomatic participants not requiring hospitalization will be assessed regularly over the telephonic call until the symptoms abate. A detailed case report form (CRF) will be completed describing the clinical course and outcome for all hospitalized and non-hospitalized COVID-19 confirmed participants.

Criteria for collecting a swab:

Participants with any one symptoms of COVID-19 lasting at least 48 hours (except for fever and/or respiratory symptoms) will visit the clinic or will be visited at home by medically qualified site staff within 72 hours (an "Illness Visit") to collect an NP swab sample for RT-PCR testing for SARS-CoV-2.

Symptom	**Minimum time since symptom onset to identify a suspect case of COVID-19, which will trigger NP swab collection.**
Fever	>24 hours
New or increased Cough	>24 hours
Shortness of breath/Difficulty in breathing	>24 hours
Chills	>48 hours
Congestion/Runny nose	>48 hours
Sore throat	>48 hours
Myalgia/Fatigue	>48 hours
Headache	>48 hours
New onset Anosmia/Ageusia	>48 hours
Diarrhea	>48 hours
Nausea/Vomiting	>48 hours

- Once a suspect case is confirmed, the Case Adjudication Committee will evaluate the clinical information to classify it as a symptomatic case. Classification will be based on the following criteria.
-
- Any one of the below mentioned criteria (A or B) must be met, along with a positive SARS-CoV-2 RT-PCR confirmation to be a confirmed symptomatic case.

Criteria A: One or More		**Criteria B: Two or More**
1. Shortness of Breath/Difficulty in breathing 2. New onset Anosmia/Aguesia 3. Oxygen saturation of <94% or escalation by requiring supplemental Oxygen. 4. Pneumonia: diagnosed by chest X ray or CT scan 5. Evidence of Shock 6. ICU Admission/Death	OR	1. Fever 2. Chills 3. New cough 4. Myalgia/Fatigue 5. Headache 6. Sore throat 7. Nausea/Vomiting 8. Diarrhea 9. Congestion/ Runny Nose
AND		
Positive SARS-CoV-2 RT-PCR test from NP swab		

- In case participant does not report to the site, expertnal hospital files or discharge summaries can be coleected for data capture.

11. DATA AND SAFETY MONITORING BOARD (DSMB)

An external DSMB, composed of independent vaccine and infectious disease experts and a biostatistician, will be established to periodically review cumulative data. DSMB responsibilities and procedures will be defined in the DSMB charter.

The DSMB will be responsible for safeguarding the interests of trial participants, assessing safety during the trial, and monitoring the overall conduct of the clinical trial. The DSMB will provide recommendations to BBIL about continuing, modifying, or stopping the trial. Items reviewed by the DSMB will include study participant accrual and demographic information; interim/cumulative safety data; discontinuations of study injections; factors that might affect the study outcome or compromise the confidentiality of the trial data (such as treatment and endpoint unblinding); data quality, completeness, and timeliness; and factors external to the study, such as scientific or therapeutic developments that may impact participant safety or the ethics of the study, in addition to making recommendations based on interim analyses for possible

sample size or study duration adjustment, early stopping for demonstrated efficacy, or early stopping for futility.

The DSMB will convene before study initiation and then at least every 2 months. In addition to routinely scheduled calls, if the protocol team has serious safety concerns the DSMB will convene by teleconference to review the data. DSMB reviews will be summarized with recommendations to the study Sponsor as to whether there are safety concerns and whether the study should continue without change, be modified, or be terminated.

12. ADJUDICATION COMMITTEE

Anonymized electronic CRFs (eCRFs) and other source data for each RT-PCR positive case will be submitted to the COVID-19 Event Adjudication Committee, an expert panel consisting of experts in infectious diseases, internal medicine, and pulmonology, for cases suspected, but not clinically or laboratory-confirmed to be COVID-19. It is possible that there will be suspected cases where the RT-PCR result is equivocal, or the symptomatology is suspect and not recorded correctly.

In addition, the COVID-19 Event Adjudication Committee will review any participant deaths that occur to assess whether they were COVID-19-related. The sponsor will develop a charter for the COVID Event Adjudication. The committee chair will attend DSMB sessions as an ad hoc member.

13. SAFETY ASSESSMENT STRATEGY

Safety assessment is a critical component and a secondary endpoint of this trial. Two separate safety components will be monitored:

1. Safety related to vaccine administration will capture local and systemic *solicited* AEs for seven days following each of the two immunizations using the diary card. *Unsolicited* AEs will be captured for 28 days following each immunization. SAEs and medically attended AEs (MAAEs) will be captured during the entire study period.

2. Safety related to risk of vaccine associated enhanced respiratory disease (VAERD) will be captured throughout the follow-up period beginning after participants have received at least one vaccine dose AND have a confirmed RT-PCR for SARS-CoV-2 infection. The specific likelihood of enhanced respiratory disease is unknown but is theoretically related to an aberrant and exaggerated immunological type II response observed in animal studies with other coronavirus infections such as SARS-CoV or MERS-CoV, but which has not been observed in human infection. As such, study staff will follow up with all participants who experience severe infection to capture data including but not limited tothetype of oxygen

support requirement (if any), organ system dysfunction, specific therapies initiated, time to resolution, and outcome (survival or death).

14. ASSESSMENT OF VACCINE-ASSOCIATED ENHANCED RESPIRATORY DISEASE (VAERD)

Study staff will compare clinical features observed among both placebo and vaccine recipients who become infected with COVID-19 to explore the occurrence of VAERD. If a svere COVID-19 and suspect VAERD epidose is identidied the PI, along with the CRO and Sponsor will investigate further. The Case Adjudication Committee will be the final authority on confirming if an episode of VAERD has occurred.

Following vaccination, enhanced respiratory disease episodes will be monitored based on the investigator's judgment, and detailed clinical parameters will be collected from medical records. These parameters would likely include but are not limited to, oxygen saturation, need for oxygen therapy, respiratory rate, need for ventilator support, imaging, blood test results, and other clinically relevant assessments. The potential vaccine-associated enhanced respiratory disease cases will be evaluated by regular reviews of COVID-19 cases.

Once a participant is a virologically-confirmed case of COVID-19, the participant will be followed in a manner that captures the patient outcome according to the WHO Clinical Progression Scale (as shown below). The “score” of the worst outcome will be entered into the CRF.

WHO Clinical Progression scale for COVID-19

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy*	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe diseases	Hospitalised; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, pO_2/FiO_2 ≥150 or SpO_2/FiO_2 ≥200	7
	Mechanical ventilation pO_2/FIO_2 <150 (SpO_2/FiO_2 <200) or vasopressors	8
	Mechanical ventilation pO_2/FiO_2 <150 and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

ECMO=extracorporeal membrane oxygenation. FiO_2=fraction of inspired oxygen. NIV=non-invasive ventilation pO_2=partial pressure of oxygen. SpO_2=oxygen saturation. *If hospitalised for isolation only, record status as for ambulatory patient.

The study will assess for enhanced respiratory disease (ERD) progression based on the WHO scale.

Safety follow-up will include follow-up with COVID-19-presenting participants to examine the possible progression of ERD, requirement for hospitalization, and/or admission to intensive care units.

The severity of enhanced respiratory disease in both the placebo and vaccine arms will be assessed for each clinical case of COVID-19 and categorized.

Case definitions will be harmonized across all participating sites and case adjudication for each disease endpoint will be determined by a central independent committee blinded to the participant vaccine group.

Close clinical monitoring of participants is critical, and staff and clinicians should be available at all times. Units chosen for SARS-CoV-2 vaccine candidate studies should have access to a hospital or other facilities that can provide access to oxygen, pulse oximetry, and emergency CPR equipment. Clinical management protocols must be in place for initiating care at the clinical site or the referral hospital. The referral hospitals

should have the clinical staff and capability to evaluate and manage complications of SARS-CoV-2 infection.

Should a treatment shown to prevent or arrest the progression from mild and moderate clinical COVID-19 illness to severe clinical illness become available, treatment will be initiated once a case definition has been achieved. The sponsor and the study teams should make all possible attempts to acquire and provide to study participants novel drugs proven to be efficacious and approved for an emergency, in accordance with their licensed and recommended use.

Given the study will not be screening out participants with SARS-CoV-2 at the time of first vaccination, it is possible some participants may be unknowingly infected at the time of vaccination. Therefore, the safety review team needs to maintain awareness and ensure appropriate questioning of the participant. A physical examination should be conducted to explore that possibility.

Safety procedures to apply during the assessment of suspected cases may, depending on severity, include the following:

- Physical examination including but not limited to nose, throat, pulmonary, cardiovascular, neurological, and skin exam, conducted at least twice during the event (at the initial visit and two to three days later). The frequency of physical exams would be increased if the volunteer develops clinical signs and symptoms.
- Vital signs at least every 8-12 hours for severe cases.
- Pulse oximetry
- Cardiac monitoring
- Chest X-rays. Should an abnormality be noted
- EKG
- Safety laboratory studies, including metabolic panel, CBC with differential (to document lymphopenia), CRP, and PT/PTT/INR.
- Availability of a full crash cart and prompt access to ventilatory support.

All AEs of any grade associated with a known or suspected case of COVID-19 will be captured and entered into the CRF from the time of first participant encounter with the health system and continuing until final disposition (release to home or discharge from health care facility) or end of the study. The rationale for this rigorous follow-up is to assess AEs of any grade severity due to the potential for VAERD. As there are no specific disease processes or symptoms specific for VAERD, the investigators will depend upon the

participant's history and health care provider to provide an overall assessment of clinical course, organ systems affected, and grade severity.

15. STUDY PROCEDURES

Visit 1 Baseline (Month 0):

- The participant will be screened for eligibility based on medical history, vitals and physical examination.
- If the participant is eligible (in good general health or stable pre-existing disease as per the discretion of the Principal investigator), a blood sample will be withdrawn prior to vaccination for all 25,800 participants, regardless of site.
- A study vaccine/placebo will be administered. Following vaccination, participants will remain at the study site for at least 30 minutes of observation to record any immediate adverse event.
- A nasopharyngeal swab will be collected (For all three categories).

Visit 2 (Month 1+2 days):

- Study participants will return to the OPD for vitals and physical examination (general and systemic examination), and specific symptoms for COVID-19.
- Blood sample (5 mL) will be withdrawn prior to vaccination (for category 3 sites).
- A study vaccine /placebo will be administered.
- Following vaccination, participants will remain at the study site for at least 30 minutes of observation to record any adverse event.

Visit 3 (Month 2±1 week):(for category 2 & 3 sites).

- Study participants will return to the OPD for physical examination (general and systemic examination), and specific symptoms for COVID-19.
- Blood sample (5 mL) will be collected(for category 3 [immunogenicity] sites).
- A nasopharyngeal swab will be collected (for category 2 & 3 sites).
- Telephonic followup for all categories.

Visit 4 (Month 3±1 week):(for category 2 & 3 sites).

- Study participants will return to the OPD for physical examination (general and systemic examination), and specific symptoms for COVID-19.
- Blood sample (5 mL) will be collected(for category 3 sites).
- A nasopharyngeal swab will be collected (for category 2 & 3 sites).
- Telephonic followup for all categories.

Visit 5 (Month 4±1 week):(for category 2 & 3 sites).

- Study participants will return to the OPD for physical examination (general and systemic examination), and specific symptoms for COVID-19.
- A nasopharyngeal swab will be collected (for category 2 &3 sites).
- Telephonic followup for all categories.

Visit 6 (Month 5±1 week):(for category 2 & 3sites).

- Study participants will return to the OPD for physical examination (general and systemic examination), and specific symptoms for COVID-19.
- A nasopharyngeal swab will be collected (for category 2 & 3 sites).
- Telephonic followup for all categories.

Visit 7 (Month 6±1 week):(for category 2 & 3 sites).

- Study participants will return to the OPD for physical examination (general and systemic examination), and specific symptoms for COVID-19.
- Blood sample (5 mL) will be collected(for category 3sites).
- A nasopharyngeal swab will be collected (for category 2 & 3 sites).
- Telephonic followup for all categories.

Visit 8 (Month 7±1 week):(for category 2 & 3sites).

- Study participants will return to the OPD for physical examination (general and systemic examination), and specific symptoms for COVID-19.
- A nasopharyngeal swab will be collected (for category 2 & 3 sites).

- Telephonic followup for all categories.

Visit 9 (Month 8±1 week):(for category 2 & 3 sites).

- Study participants will return to the OPD for physical examination (general and systemic examination), and specific symptoms for COVID-19.
- Telephonic followup for all categories.

Visit 10 (Month 9±1 week):(for category 2 & 3 sites).

- Study participants will return to the OPD for physical examination (general and systemic examination), and specific symptoms for COVID-19.
- Blood sample (5 mL) will be collected(for category 3 sites).
- Telephonic followup for all categories.

Visit 11 (Month 10±1 week):(for category 2 & 3 sites).

- Study participants will return to the OPD for physical examination (general and systemic examination), and specific symptoms for COVID-19.
- Telephonic followup for all categories.

Visit 12 (Month 11±1 week):(for category 2 & 3 sites).

- Study participants will return to the OPD for physical examination (general and systemic examination), and specific symptoms for COVID-19.
- Telephonic followup for all categories.

Visit 13 (Month 12±1 week):(for category 2 & 3 sites).

- Study participants will return to the OPD for physical examination (general and systemic examination), and specific symptoms for COVID-19.
- Blood sample (5 mL) will be collected(for category 3 sites).
- Telephonic followup for all categories.

Unscheduled Illness Visit: This visit may be at any time during the course of the study and will include a

screening of suspect COVID-19 cases, regardless of the category of the site.

If any subject develops a fever or is concerned about his/her health, he/she will be advised to visit the study site during the study follow-up period. All unscheduled visits and details of adverse events, if any will be documented in the source document. Concomitant medications, if any, will also be recorded.

If scheduled, a study site Illness Visit (Unscheduled visit) may include assessments such as medical history, physical examination, and NP swab sampling for viral PCR to evaluate the severity of the clinical case. Radiologic imaging studies may be conducted. Blood samples will be collectedfor potential future immunologic assessment of SARS-CoV-2 infection.

16. STUDY CLOSE OUT

After completing the required number of 130 virologically confirmed (RT-PCR positive) COVID-19 symptomatic cases for the primary analysis, further recruitment will be terminated if recruitment is still ongoing. However, study participants will be followed up throughout the study period for safety.

17. PREMATURE DISCONTINUATION OF THE TRIAL

Premature termination or temporary suspension of the study may be done if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party. If the study is prematurely terminated or suspended, the Investigator will promptly inform the Ethics Committee (EC) and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected significant, and unacceptable risk to subjects
- Due to protocol non-compliance and/or any other reason, data generated is insufficient and is non-evaluable
- Plans to modify, suspend or discontinue the development of the investigational vaccine

If the study is temporarily suspended it may resume once concerns about safety, protocol compliance, data quality, etc. are addressed and satisfy the Sponsor, IEC, and/or regulatory authority.

18. EARLY DISCONTINUATION FROM OF THE STUDY

Failure of the subject to comply with the requirements of the protocol will lead to early discontinuation from the study. The discontinuation from the study will be considered by the investigator if it is in the

subject or legally acceptable representative's best interest. A subject whose data is complete for all the observations is considered to have completed the study.

It will be specified on the study conclusion page of the CRF as to which of the following reasons were responsible for the withdrawal of the subject from the study.

- Serious adverse event
- Protocol violation
- Consent withdrawal, not due to an adverse event
- Migration from the study site
- Lost to follow-up
- Others

Lost to follow up or early withdrawal is taken into sample size calculation and hence such subjects will not be replaced. However, all enrolled subjects will be followed up for 28±2 days post-vaccination for AE assessment.

All subjects who withdraw early from the study for any reason are encouraged to complete 3rd-month visit assessments.

19. LOST TO FOLLOW-UP SUBJECTS

Even though subjects may be withdrawn prematurely from the study, it is imperative to collect at least safety data on such subjects as possible. Such data is important to the integrity of the final study analysis since early withdrawal could be related to the safety profile of the study product. If a subject withdraws consent, attempts should be made to obtain at least safety data until the end of the studyperiod. A subject who withdraws from the study should be contacted regularly with extensive efforts (i.e., documented phone calls or registered post or home visits)for safety follow up. The subject is considered lost to follow up only after 3 documented attempts to contact have been made.

20. MONITORING SUBJECT COMPLIANCE

Site study staff will maintain contact via telephone or visit the subject's parent/caregivers for AE assessment and will remind them about the next study visit. All study-related questions and queries will be answered and all attempts will be made to make study participants complete all study-related procedures as per the currently approved protocol.

21. INVESTIGATIONAL VACCINE (INV)

21.1 STUDY VACCINES

Whole Virion Inactivated SARS-CoV-2 vaccine (BBV152-B)will be administered as an intramuscular injection.

Active Ingredient	Quantity
Whole Virion, Inactivated Corona Virus Antigen (Strain: NIV-2020-770)	BBV152B 6µg
Inactive Ingredients	
Aluminium Hydroxide Gel equivalent to Al^{+++}	250 mcg
TLR7/8 Agonist	15 mcg
2-Phenoxyethanol (2PE) I.P.	2.5 mg
Phosphate Buffered Saline	q.s. to 0.5 mL

21.2 DOSAGE FORM AND ROUTE OF ADMINISTRATION

- COVID-19 Vaccine (BBV152-B), is a liquid 0.5 mL Vero cell-derived inactivated vaccine containing NLT 6µgand administered as a two-dose regimen intramuscularly (IM) 4 weeks apart.

21.3 DOSE REGIMEN

- Vaccine is administered as two doses, on Day 0 and Day 28.

21.4 PACKAGING

The study vaccines will be provided by the sponsor, Bharat Biotech International Limited.

21.5 LABELLING

The label of the INV will also state the following:

- Protocol Number
- Manufacturer’s name, address, and telephone number
- Vial Number
- ‘To be stored at +2°C and +8°C’

- 'Vaccine for Clinical Trial Use Only'

21.6 Supplies and Handling of Materials

All the study vaccines will be supplied by Bharat Biotech/CRO. The study vaccines will be delivered to the study site within 48 hrs from the dispatch time. The designated site staff will examine the shipping container and contents for damage during transport and immediately place the vaccine in the refrigerator between 2°C and 8°C. All discrepancies in shipment conditions, shipment receipt times, and conditions of the vaccines must be reported to the sponsor.

21.7 Accountability procedures for the Investigational Vaccines

INV supplies must be received by a designated person at the trial site, handled, stored, temperature maintained & documented, and kept under controlled access. The INV is to be stored at +2°C and +8°C. Upon receipt of the study treatment supplies, an inventory must be performed and an INV accountability log filled out and signed by the person accepting the shipment. It is important that the designated study staff should count and verify the shipment contains all the items noted in the shipment inventory or not. Any damage or unusable study vaccine in a given shipment will be documented in the study files. The investigator must notify the Sponsor of any damage or unusable study vaccines that were supplied to the Investigator's Site. The investigational vaccine will not be delivered to the site until all required documentation (Ethics Committee Approval, signed contract, and protocol, authority approval where required) are reviewed by the sponsor.

All INV's must be stored in a safe and locked place with no access for unauthorized personnel. If any discrepancy in the package arises, this should be communicated immediately to the sponsor, and the storage temperature of vaccines will be monitored and recorded daily. Any temperature deviation, i.e. temperature outside the defined range will be reported within 24 hours to the sponsor (i.e. Study Monitor/Sponsor Contact). Following exposure to a temperature deviation, vaccines will not be used until written approval is obtained from the sponsor. An appropriate cold chain will be maintained for all vaccines that would be used in the study.

21.8 Dispensing study vaccine

Either the investigator or the designated staff should reconcile the investigational vaccines at the site. This reconciliation should be logged on the INV accountability log and signed and dated by the study team.

The Investigator must maintain 100% accountability for all study vaccines received and dispensed during his or her entire participation in the study. Proper INV accountability includes, but is not limited to:
Frequently verifying that actual inventory matches documented inventory
Verifying that the INV accountability log is completed for each participant
Verifying that all the INV shipments are documented accurately on the relevant log
Verifying that required fields of the INV accountability log are completed accurately and legibly

If any dispensing errors or discrepancies are discovered, the sponsor/CRO must be notified immediately. The investigator must maintain a current inventory (INV accountability log) of all INV delivered to the site, inventory at the site, and participants' use records. This log must accurately reflect the accountability of the INV at all times. The following information will be recorded at a minimum: protocol number, name of the investigator, site identifier and subject number, date and amount dispensed, initials of the person dispensing. The log should include all required information as a separate entry for each participant who is dispensed INV.

Prior to site closure or at appropriate monitoring intervals, a representative from the Sponsor or its designee will perform INV accountability and reconciliation before INV are returned to the Sponsor or its designee for destruction. The investigator will retain the original documentation regarding the INV accountability log and return, and copies will be sent to the sponsor.

21.9 Return or Destruction of Investigational Vaccine

After the completion of the study or at the last patient's last visit, there will be a final reconciliation of the investigational vaccine shipped, INV consumed, and INV remaining. This reconciliation will be logged on the INV accountability form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to the return. A list of INV (used and unused) returned to the sponsor will be documented in the study files.

22. MEDICATIONS DURING TRIAL PARTICIPATION

22.1 Drug Interactions

Chloroquines and Corticosteroids are known to depress antibody response.

Contraindications to subsequent doses of the study vaccines

- Anaphylaxis or other indications of an allergic reaction after a previous dose.
- Presence of any illness requiring hospitalization. The dose will be given when the condition improves.

Concomitant Medications and Co-interventions

Any concomitant medication received by the subject will be recorded in the CRF.

Details of dose, dosage, date, and route of administration, the period of use and reason for use, etc will be recorded.

All other interventions and procedures that the subject may undergo for any medical condition will be duly recorded in the appropriate fields in CRF.

22.2 PROHIBITED MEDICATION PRIOR AND DURING STUDY

- Immunoglobulin within 3 months prior to study vaccination, during, and 21 days following the last dose of study vaccination.
- Anti-cytokine anti-bodies within 3 months prior to study vaccination, during, and 21 days following the last dose of study vaccination.
- Any kind of blood product within 3 months prior to study vaccination and 21 days following the last dose of study vaccination.
- Immunosuppressants and immune modifying agents within 6 months prior to study vaccination and 21 days following the last dose of study vaccination.

23. MANAGEMENT OF SPECIMENS

BBV152 vaccine must be stored at 2°C to 8°C in a secure area with limited access and protected from moisture and light until it is prepared for administration. The refrigerator should have automated temperature recording and a 24-hour alert system in place that allows for rapid response in case of refrigerator malfunction. There must be an available backup refrigerator. The refrigerators must be connected to a backup generator.

Blood samples for screening will be obtained and processed at the clinical trial site and transported to the site's designated laboratory for clinical testing. Samples will be stored in monitored, controlled-temperature freezers, with a backup power supply to assure proper sample storage. A laboratory manual documents the procedures for obtaining and managing samples.

Samples will be prepared, handled, and stored according to site-specific SOPs. All samples will be labeled with the subject ID number, date/time of collection, study designator, and bar code. No personal identifiers will be included on sample labels. A chain of custody will be maintained both at the sending lab and the receiving lab.

Serum samples for immunological endpoints will be obtained and processed at the clinical trial and site and

transported to the immunology lab(s).

Nasopharyngeal specimens will be collected from all participants. Nasopharyngeal flocked swabs will be collected and placed into viral transport medium (VTM). The VTM with swab stick will be placed in Ziploc bags and carried in a cooler box with an ice pack (maintaining 2 to 8˚C) for transportation to the site freezer (Figure 1.) Nasopharyngeal samples will be processed in a certified Class II biological safety cabinet (BSC). Once a clinical sample has been treated with lysis buffer for RNA extraction, the samples can be moved to a less restrictive environment to complete the RNA extraction and real-time RT-PCR.

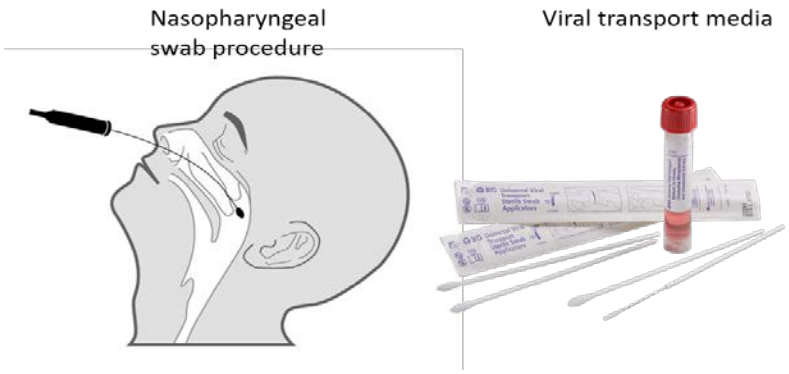

Figure 1. Swab procedures

23.1 CLINICAL LABORATORY TESTS

COVID-19 case-mandated laboratory tests will be conducted by the site laboratory, which is accredited according to country-specific guidelines. Laboratory results will be reviewed promptly by the PI or designee. Participants will be notified of any clinically significant abnormalities. If clinically significant abnormalities are identified at baseline, participants will be referred to their primary health provider or appropriate medical facility. Any test may be repeated if the investigator suspects test results are spurious.

The immunological assays to be performed include:

- Serum anti-SARS-CoV-2 IgG antibodies by ELISA.
- Serum neutralizing antibodies may be measured with SARS-CoV-2.

23.2 SPECIMEN PREPARATION, HANDLING, STORAGE, AND SHIPMENT

- Blood sample collection and specimen preparation should be per the site SOPs.
- The serum sample will be divided into aliquots. One aliquot for immunogenicity testing and the other will be a backup.

- Serum samples should be labeled with Subject number/initials, Date & time of sample collection, and study visit number.
- Hemolyzed specimens will not be accepted or tested.
- The serum specimen should be kept frozen (-20°C) until shipped for testing.
- Ship frozen samples on dry ice.
- Shipping of specimens shall be done in accordance with IATA Dangerous Goods Regulations. The sample should be placed in an insulated container with adequate dry ice to ensure specimens remain frozen until received (cold chain integrity) for testing.
- At the end of the study all the remaining serum samples if any should be sent to the sponsor (BBIL) or designee.

24. STUDY ASSESSMENTS

24.1 IMMUNOGENICITY ASSESSMENT

1. Neutralization antibody titer of the COVID-19 virus will be assessed by the micro-neutralization assay and evaluate the immunogenicity in terms of GMT of vaccine comparison with the control group, from baseline to Month 1 & 2 in immunogenicity subset subjects.

24.2 SAFETY ASSESSMENTS

1. Immediate Adverse Events (IAE) - All subjects will be kept under observation at the study clinic for 30 minutes after administration of each vaccine, for any immediate adverse events occurring between the administrations of the vaccine till 30 minutes after administration of the vaccine.
2. Adverse Events post-vaccination (AE) - The study team will make a daily telephonic enquiry for seven days after vaccination. During the enquiry, the subject will be asked for the occurrence of any adverse events (including local injection site reactions, fever, chills, ,headache, nausea, vomiting, fatigue, myalgia, and athralgia) and asked to write the information on the diary card provided. The data collected and from the diary card, the information will be recorded into the CRFs.

3. Serious Adverse Events - Safety data for the vaccine will be assessed through documentation of all serious adverse events (SAEs) obtained in all subjects from the day of vaccination to the end of the study. All SAEs identified during the study will be followed until resolution or stabilization. In the event of an SAE, a form containing details of all events that led to the event or hospitalization (SAE form) will be filled by a study physician.

4. Medically Attended Adverse Events (MAAEs) - MAAEs are defined as AEs leading to medically-attended visits that were not routine visits for physical examination or vaccination, such as an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason. AEs, including abnormal vital signs, identified on a routine study visit or during the scheduled illness visits will not be considered MAAEs.

5. Adverse Event of Special Interest (AESI) -The following AESIs (if any) will be evaluated during the study period:

   - Anaphylaxis
   - Vaccine-associated enhanced respiratory disease (VAERD)
   - Generalized convulsion

   An AESI can be either serious or non-serious. All AESIs will be recorded. Serious AESIs will be recorded and reported as per reporting guidelines for SAEs.

6. Any AEs that are present at the time of discontinuation/withdrawal should be followed up until resolution or until a time agreed to by the investigator and the sponsor designated medical monitor in accordance with the safety requirements specified in Good Clinical Practice guidelines.

Solicited AEs

The following local AEs will be considered as solicited AEs: pain at the injection site, swelling at the injection site, induration (hardness) at the injection site, erythema (redness) at the injection site.

The following systemic AEs will be considered as solicited: Fever, chills, headache, nausea, vomiting, fatigue, myalgia (muscle aches all over the body), arthralgia (aching in several joints).

List of Solicited Local and systemic adverse events:

Solicited Local AEs	Solicited Systemic AEs
• Pain at the injection site • Swelling at the injection site • Induration (hardness) at the injection site • Erythema (redness) at the injection site	• Fever • Chills • Headache • Nausea • Vomiting • Fatigue • Myalgia • Arthralgia

Unsolicited AEs

An unsolicited AE is any AE reported by the participant that is not specified as a solicited AR in the protocol, or is specified as solicited AEs in the protocol, but starts 7 days after administration Vaccine/Placebo.

Solicited Adverse events and Grades

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Injection site pain	None	Does not interfere with the activity	Repeated use of over-the-counter pain reliever > 24 hours or interferes with the activity	Any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization
Injection site erythema (redness) < 25 mm/ < 2.5 cm 25 in diameter	< 25 mm/ < 2.5 cm	25 - 50 mm/ 2.5 - 5 cm	51 - 100 mm/ 5.1 - 10 cm	> 100 mm/ > 10 cm	Necrosis or exfoliative dermatitis
Injection site swelling/induration (hardness)	< 25 mm/ < 2.5 cm in diameter	25 - 50 mm/ 2.5 - 5 cm in diameter	51 - 100 mm/ 5.1 - 10 cm in diameter	> 100 mm/ > 10 cm in diameter	Necrosis
Fever (oral)	< 38.0°C OR < 100.4°F	38.0 – 38.4°C OR 100.4 – 101.1°F	38.5 – 38.9°C OR 101.2 – 102.0°F	39.0 – 40.0°C OR 102.1 – 104.0°F	> 40.0°C OR > 104.0°F
Chills	None	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical	Requires emergency room visit or hospitalization
Headache	None	No interference with activity	Repeated use of over-the-counter pain reliever > 24 hours or some interference	Significant; any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization

			with activity		
Nausea	None	No interference with activity or 1-2 episodes/ 24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient intravenous hydration	Requires emergency room visit or hospitalization for hypotensive shock
Vomiting	None	No interference with activity or 1-2 episodes/ 24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient intravenous hydration	Requires emergency room visit or hospitalization for hypotensive shock
Fatigue	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Myalgia (muscle aches all over the body)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Arthralgia (joint aches in several joints)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization

Any other adverse events will be graded as follows:

Adverse events	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Unsolicited or MAAEs	None	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Requires emergency room visit or hospitalization

25. COVID-19 CASEADJUDICATION COMMITTEE

Anonymized CRFs and other source data for each RT-PCR positive case will be submitted to the COVID-19 Case Adjudication Committee, an expert panel consisting of experts in internal medicine and pulmonology. It is possible that there will be suspected cases where the RT-PCR result is equivocal, or the symptomatology is suspect and not recorded correctly.In addition, the COVID-19Case Adjudication Committee will review any participant deaths that occur to assess whether they were COVID-19related. BBIL will develop a charter for the COVID-19Case Adjudication.

26. ADVERSE EVENT MANAGEMENT

26.1 ADVERSE EVENT (AE) OR ADVERSE EXPERIENCE

The investigator is responsible for the recording and documentation of events meeting the criteria and definition of an Adverse Event (AE), Adverse Drug Reaction (ADR), or Serious Adverse Event (SAE) as provided in this section. All AEs and SAEs that occur from the time of administration of the vaccineuntil completion of thefollow up as specified in the protocol will be recorded in the source document and the appropriate CRF pages. Information to be collected includes the nature, date and time of onset, severity, duration, causality, the action taken, and outcome of the event. Even if the AE is assessed by the investigator as not related to the investigational vaccine (INV), its occurrence must be recorded in the source documents and reported on the CRF. Details of any medications given to the subject for the AE should be recorded on the concomitant medication page.

Periodically during the study, after the subject has had an opportunity to spontaneously mention any problems, the investigator should inquire about the occurrence of AEs.

26.2 DEFINITION OF AN ADVERSE EVENT

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an INV and which does not necessarily have a causal relationship with this treatment. All conditions, which are pre-existing prior to study vaccine administration, must be recorded on the study participant's CRF.

An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

26.3 POSSIBLE AE'S AND INTERACTIONS

Following AEs were reported in various clinical trials with a cell-cultured inactivated virus vaccine.

An AE for evaluation of the safety of COVID-19 Vaccine does not include:

- Medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an AE.
- Day to day fluctuations of pre-existing disease or conditions present or detected at the start of the study (such as abdominal pain) that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g. hospitalizations for cosmetic elective surgery, social and/or convenience admissions).
- The disease or disorder being studied or sign or symptom associated with the disease or disorder unless more severe than expected for the subject's condition
- Overdose of the administered treatment or concurrent medication without any signs or symptoms.

26.4 ADVERSE DRUG REACTION (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to a medicinal product related to any dose should be considered ADRs. The phrase responses to a medicinal product mean that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

26.5 DEFINITION OF A SERIOUS ADVERSE EVENT

As provided in Title 21 Code of Federal Regulations (CFR) Part 312, SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization (Note: Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered to be an AE).
- Results in persistent or significant disability/incapacity (Note: The term disability means a

substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (e.g., sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption).

- Is a congenital anomaly/birth defect.
- Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above should also usually be considered serious. (Note: Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

26.6 RECORDING AND FOLLOW-UP OF PREGNANCY

- Female participants who have a positive pregnancy test at Screening will not be enrolled. The participants who have a positive pregnancy test at any time during the study should receive no further dosing with either Vaccine or Placebo but should be asked to remain in the study and be followed-up for safety.

- Details of all pregnancies in female participants will be collected after the start of study treatment till the end of the study.

- If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy.

- Abnormal pregnancy outcomes such as congenital anomalies and birth defect will be considered SAEs as per the New Drugs and Clinical Trials Rules, 2019. Pregnancies occurring in participants after enrollment must be reported to Sponsor or designee within 24 hours of the site learning of its occurrence. If the participant agrees to submit this information, the pregnancy must be followed to determine the outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects,congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if intended duration of the safety follow-up for the study has ended. Pregnancy report forms will be distributed to the study site to be used for this purpose. The investigator must immediately (within 24 hours of awareness) report to the Sponsor any pregnancy resulting in an abnormal outcome according to the procedures described for SAEs.

26.7 Clinical Laboratory Abnormalities and Other Abnormal Assessments

The criteria for determining whether an abnormal test(if any), should be reported as an adverse event are as follows:

- The test result is associated with accompanying symptoms, and/or;
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or;
- Test result leads to discontinuation of the subject from the study, additional concomitant drug treatment, or other therapy, and/or;
- The test result is considered to be an adverse event by the Investigator or sponsor
- If an abnormal laboratory value or assessment is related to a medically defined diagnosis or syndrome, the diagnosis or syndrome will be recorded on the AE page, not the individual laboratory values
- Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event. The investigator will exercise medical judgment in deciding whether abnormal laboratory values are clinically significant. In some cases, significant changes within the normal range will require similar judgment by the investigator.
- If any time during the study period, any subject develops the signs and symptoms of COVID-19, the subject will be tested with the RT-PCR method, and his/her management will be undertaken as per the decision of the principal investigator.

All clinically significant abnormal laboratory results or assessments will be followed until they resolve (return to normal or baseline values) or stabilize, or until they are judged by the investigator to be no longer clinically significant.

26.8 Recording of Adverse Events, Adverse Drug Reactions, and Serious Adverse Events

All AEs occurring from administration of the first dose of vaccination (day 0) to the follow-up contact as specified in the protocolwill be recorded as AEs on the CRF. The investigator should review all documentation (e.g. hospital progress notes, laboratory, or diagnostic reports) relative to the event being reported. The investigator will then record all relevant information regarding an AE/ADR/SAE on the appropriate CRF page. The investigator will evaluate AEs using the following guidelines:

- Description of event (if the event consists of a cluster of signs and symptoms, a diagnosis should be

recorded [e.g., flu syndrome] rather than each sign and symptom

- Onset date and time
- Stop date and time
- Severity

Severity is defined as one of the following:

- Mild: Awareness of sign or symptom, but easily tolerated
- Moderate: Discomfort sufficient to cause interference with normal activities
- Severe: Incapacitating, with an inability to perform normal activities

Also,theBrighton collaboration guidelines on AEFI will be followed whenever applicable. It is important to distinguish between SAEs and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria. An AE of severe intensity need not necessarily be considered serious. For example, a migraine headache that incapacitates a subject for many hours may be considered a severe AE, whereas a stroke that results in a limited degree of disability may be considered mild, but should be reported as an SAE.

- Seriousness

The investigator must record whether or not the AE meets the definition of seriousness. If the event is serious, the investigator must complete an SAE report form.

26.9RELATIONSHIP TO INV:

The Investigator must make a causality assessment for all AEs and must decide whether there is any possibility that the AE may have been caused by the INV. The degree of certainty with which an adverse event can be attributed to treatment administration (or alternative causes, e.g. natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the event can be understood in terms of one or more of the following:

- The reaction of similar nature having previously been observed with this type of treatment
- The event having often been reported in the literature for similar types of treatments
- The event being temporally associated with study drug administration or reproduced on re-administration.
- Causality assessment by the investigator and the medical monitor of the Sponsor/designeeshould mention whether the AE's occurred is related or not related.

26.10 Outcome of AE and SAE

The outcome of AEs should be recorded as recovered, recovered with sequelae, event continuing, fatal, and unknown (not for SAE). If an AE is not resolved at the time of discontinuation, the AE should be followed until it is resolved (returns to normal or baseline values) or stabilized, or until it is judged by the investigator to be no longer clinically significant.

26.11 Action Taken

The action taken in response to the AE (e.g., none, medicinal or surgical treatment, or INV discontinued) should be recorded.

26.12 Follow-up of Adverse Events, Adverse Drug Reactions, and Serious Adverse Events

All AEs and SAEs must be followed until they are resolved (return to normal or baseline values), stabilized, or until they are judged by the investigator to be no longer clinically significant. Supplemental measurements and/or evaluations may be necessary to fully investigate the nature and/or causality of an AE and SAE. This may include additional laboratory tests, diagnostic procedures, or consultation with other healthcare professionals. In addition, the BBIL designated medical monitor may request additional blood tests, diagnostic imaging studies, or specialist physician consultations to further evaluate any AE or test abnormality considered to be clinically significant. If the subject dies, any post-mortem findings (if available, including histopathology) must be provided to the sponsor or designee.

26.13 Reporting of all Serious Adverse Events

All serious adverse events occurring during the study should be reported by the investigator immediately to the Central Licensing Authority (CLA), IEC/IRB(s), and Sponsor, but no later than 24 hours after the occurrence of the event, by email or telephone.

The investigator shall also leave a paper trail documenting that the adverse event has been properly reported. The notification must be sent to the address or email ID, which is provided in the investigator's files.

The following information must be communicated with the first notification of a serious adverse event:

1. Screeningnumber
2. Subject’s date of birth

3. Time and date of administration of the investigational vaccine
4. Time and date of occurrence of the event
5. A brief description of the event and resolution
6. Investigator's opinion of the relationship to investigational vaccine

The investigator will be requested to submit a report, which includes a description of the event, the therapy instituted, and the study procedures. Where applicable, information from relevant hospital records and autopsy reports will be obtained. The immediate and follow-up reports should only identify the subject by the unique subject number, and not by the subject's name or address.

BBIL is responsible for ensuring that serious adverse events are reported to local regulatoryauthorities in accordance with local regulatory requirements. Instances ofdeath, cancer,orcongenital abnormalities in the offspring, if brought to the notice of the Investigator at any timeafter cessation of INV, must be reported to BBIL.Investigators will also follow-up subjects with serious adverse events occurring at any time following study vaccineadministration until the event has disappeared or until the condition has stabilized.

All SAEs, whether related or not related to the study vaccine, should be informed to the Central Licensing Authority (CLA/CDSCO), IEC/IRB(s), and Sponsor within 24 hours by the Investigator. The sponsor or its representative (CRO) and the investigator shall forward the reports on serious adverse events after due analysis to the Central Licencing Authority (CDSCO), Ethics Committee, and the head of the institution within 14 calenderdays of the knowledge of occurrence of serious adverse events as per the New Drugs and Clinical Trial Rules, 2019.

27. STATISTICS

27.1 Statistical Analysis Plan and Methods

This study is a randomized, double-blind, multicenter, placebo-controlled Phase 3 study of vaccine safety and efficacy, with immunogenicity and lot comparability study imbedded. The study is designed to accrue PCR-confirmed symptomatic COVID-19 in 130 study participants for the primary efficacy analysis, during follow-up beginning 14 days after the second dose of vaccine or placebo and ending approximately a year after the last remaining participant in follow-up received his or her second dose. In order to reach this number of cases with high statistical power, the planned number of randomized study participants is approximately 25,800. Follow-up of all randomized participants is planned to continue until the required number of confirmed COVID-19 cases has been reached or the study is stopped early for demonstrated

efficacy, futility, or concerns for participant safety. Multiple COVID-19 cases in the same study individual are not expected, but data will be collected and presented for all cases occurring during the study.

Descriptive statistics will be presented for baseline participant characteristics as well as data generated after randomization. In general, for continuous variables these statistics will include the mean, median, minimum, maximum, standard deviation (SD), and two-sided 95% CI around the mean; for categorical variables, the number of observations and proportion will be presented for each category, with an exact 95% CI for the proportion of events if the variable is dichotomous. Summaries will be presented by treatment received (vaccine or placebo) and, where relevant, by age, presence of co-morbidity, and/or time point. Inference regarding vaccine efficacy (VE) will be based on the lower bound of a CI for VE; equivalently, the hypothesis test of VE will be one-sided. In other analyses, unless otherwise specified here or in the more detailed Statistical Analysis Plan (SAP), statistical tests and confidence intervals (CIs) will be computed using a two-sided 5% significance level.

For the randomized study population, medical history will be listed and summarized by category. Using the WHO Drug Dictionary, concomitant medications will be tabulated by anatomical therapeutic chemical classification, preferred drug name, and treatment received. A medical history will be tabulated by MedDRA System Organ Class, preferred term, and treatment received.

Summaries of subject disposition will be prepared for all participants, including the number and percent enrolled, screened, randomized, and administered the vaccine, as well as a Consolidated Standards of Reporting Trials (CONSORT) diagram describing study participation and discontinuation. The reasons for screening failures and discontinuations will be summarized and listed.

A more detailed Statistical Analysis Plan (SAP) will be developed before data unblinding occurs, except possibly for unblinding of the study treatment received by an individual participant that is considered necessary for determining the medical care of the participant. Any deviations in the SAP from the statistical analyses specified in the protocol will be described in the SAP and the clinical study report. Changes from the analyses in the original SAP will be described in a revised SAP.

The serum will be collected on Day 0, before vaccination, for assessment of seroprevalence (presence of binding antibody titers to COVID-19) at baseline. At a later time point, once these samples are analyzed, participants who are positive at baseline will be excluded from immunogenicity and efficacy analyses, but they will continue to be followed up for safety outcomes.

Randomization

Participants will be allocated at random in a 1:1 ratio to receive two doses of either BBV152 vaccine or placebo, via an interactive web response system. Randomization will be stratified by whether or not any of a group of underlying co-morbidities [assessed based on medical history or physical examination at baseline (Month 0)] is present. Co-morbidities as mentioned in the stratification section below will be stratified between the vaccinated and the placebo group in 1:1 ratio. At study sites designated for the immunogenicity study, vaccine from each of three lots of BBV152 will be distributed to each site in approximately equal numbers and in a sequence such that the number of randomizations to each lot will be approximately balanced over time.

Stratification:

At least 30% of enrolled participants, but not to exceed 40%, will be either ≥ 60 years of age or < 60 years of age with co-morbid conditions, and not more than 5% of HCPs, who has high risk for severe COVID-19 illness at Screening. The Sponsor will frequently review the number of enrolled participants, by age and co-morbidities, to ensure that this quota is maintained.

Participants who are < 60 years old will be categorized as at risk for severe COVID-19 illness ifthey have at least 1 of the following risk factors at Screening:

• Stable chronic lung disease (eg, emphysema and chronic bronchitis), idiopathic pulmonaryfibrosis and cystic fibrosis) or mild to moderate asthma

• Stable cardiac disease (eg, heart failure, coronary artery disease, congenital heartdisease, cardiomyopathies, hypertension,and pulmonary hypertension)

• Severe obesity (body mass index ≥ 35 kg/m2)

• Controlled Diabetes (Type 1, Type 2)

• Stable Liver disease

Analysis populations:

Population	Description
Randomization Set	All randomized participants, classified according to the study product (vaccine or placebo) to which they were randomized.
Full Analysis Set (FAS)	All randomized participants who had no immunologicevidence of prior COVID-19 (i.e, negative against SARS-CoV-2 antibodies) at Visit 1 before the first dose of IP.Participants will be analyzed according to

	the study product (vaccine or placebo) received.
Per-protocol (PP) Set	All participants in the FAS who received planned doses of IP per schedule, seronegative for SARS-CoV-2 Antibody by ELISA at baseline,and have no major protocol deviations, as determined and documented by the Sponsor.Participants will be analyzed according to the study product (vaccine or placebo) received.
Immunogenicity Subset	Designated participants at study sites included in the immunogenicity study who had a valid immunogenicity test result before the first dose of IP and at least 1 valid result after thefirst dose of IP, classified according to the study product received.
Safety Set	The Safety Set consists of all randomized participants who received at least one dose of IP and contributed any solicited AE information, classified according to the study product received.

Primary efficacy analysis

Estimation of vaccine efficacy (VE) in this study is based on person-time incidence rates: VE = 1 – (nv/Fv) / (np/Fp) = 1 – R, where R = (nv/Fv) / (np/Fp); nv and np are the numbers of participants who develop PCR-confirmed symptomatic COVID-19 among BBV152 vaccine and placebo recipients, respectively, and Fv and Fp are the corresponding total lengths of follow-up in years in the two groups, with follow-up in years defined as a follow-up in days divided by 365.25. VE will typically be expressed as a percentage. We assume that nv and np follow Poisson distributions with respective parameters λvFv and λpFp; the true (unknown) VE is 1 – λv / λp. Then, conditional on n = nv + np, the total number of participants who develop symptomatic COVID-19, the number nv in the vaccine group follows a binomial distribution with n trials and probability parameter λvFv / (λvFv + λpFp), estimated by P = nv / (nv+np). Hypotheses about VE can also be stated in terms of P and the ratio h = Fp/Fv, which is expected to be very close to 1, since by the above definitions R = hP / (1-P) and thus VE = 1 – hP / (1-P). A two-sided confidence interval (CI) around the estimated VE will be obtained by converting an exact CI for the probability parameter P, using the observed Fp/Fv, to a CI for VE.

The primary analysis of VE will be based on the per-protocol population, excluding participants who were positive for binding antibody titers to SARS-CoV-2 on Day 0, with follow-up for each participant beginning 14 days after the second dose of vaccine or placebo and continuing until the onset of a confirmed COVID-19 case, a protocol deviation that could affect the risk of COVID-19 (for example, receipt of another vaccine against a viral disease), or the end of follow-up. VE will be estimated with a 95% CI or, if

an interim efficacy analysis has been done previously (see next section), with a CI adjusted as needed for the interim analysis.

Interim analyses

Formal interim analyses are planned when approximately 1/3 and 2/3 of the target number of participants with confirmed symptomatic COVID-19 have been accrued, to determine whether the sample size and/or length of follow-up should be increased. The analysis will be done on unblinded data using the method of Chen, DeMets, and Lan **(23)**in accord with their method, it is planned to increase sample size only for conditional power ≥ 50%, assuming the true VE is as observed in the interim data, or for an unexpectedly low COVID-19 event rate. In addition, at approximately 2/3 of the target number of participants with confirmed symptomatic COVID-19 (87 of 130), an interim analysis is anticipated for 1) possible early stopping for demonstrated efficacy, testing the null hypothesis that VE ≤ 30% using the Lan-DeMets α-spending function framework **(24)** with α = 0.005, one-sided, to define the boundary to be used as a guideline; or 2) possible early stopping for futility (low efficacy or negative efficacy), using conditional power calculations **(25)**.The stopping guideline for demonstrated efficacy at the interim analysis is equivalent to requiring a two-sided exact 99% CI for VE with a lower limit of ≥ 30%. The use of this relatively stringent criterionfor early stopping for efficacy means that only a slight correction, from a 95% CI to a slightly wider 95.3% CI, will be necessary at the final analysis if the study is not stopped early. The probability of meeting the early stopping guideline is 38% for a true underlying VE of 60% but increases to 81% if VE = 70%. The DSMB will be asked to consider a recommendation to stop the study for futility conditional power ≤ 20% to show any significant VE (i.e., a two-sided 95% CI for VE with lower bound > 0), assuming true VE = 60%. The SAP will include more details on the proposed interim analyses.

Review of interim efficacy and safety data and recommendations based on the data will be within the purview of the external DSMB. The DSMB may recommend stopping the study because of concerns for participant safety at the time of formal interim analysis or at any other time it reviews safety data.

Secondary efficacy analyses

VE will be estimated for confirmed symptomatic SARS-CoV-2 infection in the vaccinated population, excluding participants who were seropositive for SARS-CoV-2 on Day 0 and any participants who inadvertently received one dose of vaccine and one dose of placebo. In addition, VE will be estimated for the period between the first dose and 14 days after the second dose.

Other secondary efficacy analyses will compare the treatment groups with regard to 1) severe PCR-confirmed COVID-19 disease and 2) PCR-confirmed SARS-CoV-2 infection, regardless of

symptomatology. In addition, VE estimation will be done in linear models with the study site as a random effect and with adjustment for covariates (e.g., age, presence of co-morbidities at baseline). These analyses will be done for endpoint events with onset 14 days or more after the second dose and also for all participants with events after the first dose. VE and its 95% CI will be estimated as in the primary analysis.

Safety analyses

Safety analyses will be including all participants in the vaccinated population who provided any safety data. Data will be collected on immediate adverse events (AEs) within 2 hours of vaccination, solicited local and systemic AEs within 7 days after each dose of vaccine or placebo, and all AEs during the study. These categories of events, as well as serious adverse events (SAEs), including deaths, will be tabulated by treatment group. Rates of events and the corresponding two-sided exact CIs will be presented. Rates will be compared between treatment groups using two-sided z-tests.

Solicited events will be summarized by the proportion of participants reporting any event, as well as proportions reporting specific types of events. Summaries will be prepared corresponding to maximum severity and duration per participant, where relevant.

Unsolicited and medically attended AEs will be coded, listed, and summarized. Except for summaries of SAEs, summaries of unsolicited AEs will be made using only those events recorded with onset within 28 days of vaccination, and with severity grade ≥ 2. Additional summaries will present unsolicited AEs, regardless of grade and onset, which may be recorded due to a suspected or known case of COVID-19. Unsolicited AEs will primarily be summarized on the participant level, where a participant contributes once to a given event type under the maximum severity and/or causality, as appropriate; they will also be summarized by severity and relationship to vaccination. The total number of events of a given type observed within a group will also be presented. SAEs will be summarized by type, relationship to vaccination, and reason for designation as SAE. All AEs, including SAEs, will be coded with MedDRA and summarized by System Organ Class and Preferred Term. Tables will be prepared for all unsolicited AEs and also for SAEs. Rates of participants experiencing an AE and withdrawing from the study will be presented. Listings will be prepared for AEs and SAEs.

The primary safety analysis for the Phase 3 study will be based on the number of participants in each treatment group with at least one SAE through Month 12.

The potential for the vaccine-associated enhanced respiratory disease will be evaluated by comparing the rates of severe respiratory events, in addition to rates of confirmed symptomatic COVID-19, between

treatment groups. The frequency of severe respiratory events among all COVID-19 cases will also calculate. Severity scores will be compared using a Wilcoxon rank-sum test.

Immunogenicity analysis

Lot consistency will be assessed using 3 consecutively manufactured lots of BBV152. The analysis will be based on the GMTs of neutralizing antibodies at Day 56. GMTs and GMT ratios for each pair of lots, with the corresponding two-sided 95% CIs, will be presented. The CIs will be calculated from CIs for log_{10}-transformed neutralizing antibody titer, assuming log_{10} (titer) is normally distributed. The criterion for lot consistency is that 95% CIs for GMT ratios for all pairs of lots must be contained within the interval [0.5, 2.0].

27.2 SAMPLE SIZE AND POWER

It is planned to continue the Phase 3 trial until 130 study participants in the per-protocol population develop PCR-confirmed symptomatic COVID-19 disease during follow-up beginning 14 days after the second dose of vaccine or placebo. We estimate that approximately 25,800 participants should be randomized to accrue these 130 events. These numbers are obtained as follows.

The study is designed to obtain a 95% confidence interval for vaccine efficacy with a lower bound ≥ 30%. (Any adjustment of the confidence level necessary because of interim analysis will be slight.) For assumed true efficacy of 60%, the required number of cases for 85% power is 130, based on exact binomial calculations. The total number of participants required depends on the assumed incidence during the follow-up period. If we assume an average incidence among placebo recipients of 1% during follow-up beginning 14 days after the second dose, the expected number of participants required to accrue 130 cases is approximately 18,572. Allowing for baseline seropositivity and RT-PCR confirmed COVID-19 casesasexclusions for efficacy (20%) and other losses (loss to follow-up, etc.) of 10%, the number becomes 25,794. It is planned to randomize approximately 25,800 study participants.

With 130 study participants with symptomatic COVID-19, the study would have approx. 89% power to get a point estimate > 50% for vaccine efficacy, if the true efficacy is 60%.

The lot consistency analysis is expected to include data on 150 study participants in each of 3 consecutively manufactured lots of BBV152 vaccines. To estimate power to show lot consistency, we assume SD = 0.40 for log_{10}-transformed neutralization antibody titer. This may be a conservative estimate, as SD for log_{10}

(titer) was 0.352 in a sample of 20 individuals. For SD = 0.40 and 150 study participants in each of two groups, the power to obtain a two-sided 95% CI that falls within the interval [0.5, 2.0], assuming $\log_{10}$ (titer) is normally distributed, is approximately 98.1% for a true GMT ratio of 1.3 and > 0.999 for a true ratio of 1.0. Then, for a GMT ratio ≤ 1.3 for each of the three pairwise comparisons, the power to show lot consistency (i.e., that the two-sided 95% CI falls within the interval [0.5, 2.0] for each pairwise comparison) is > 95%; a good approximation**(26)** to the power is (0.981)(0.981)(0.999) = 0.961.

The assumption of Vaccine Efficacy of 60% is for sample size estimations only. The allocation of treatments in the ratio of 1:1 of vaccine or placebo. The intended success criteria for vaccine efficacy is 50%, in agreement with the minimum requirement given in the WHO Target Product Profile. Since the study is designed to obtain a two-sided 95% confidence interval for VE with a lower bound ≥ 30%, if the true VE is 60%. The power calculation includes the possibility that the point estimate of VE might be < 60%. The probability is high, however, that the observed VE will be > 50%. To have that high probability, we must assume the true VE is some quantity > 50%. Hence, there is no discordance between assuming VE is 60% and obtaining a point estimate of 50-59%.

The null hypothesis Vaccine Efficacy value may be adaptively modified to below 30% during the trial, based on a lower-than-projected COVID-19 attack rate or case accrual rate, with collaborative decision-making by DSMB. Starting with a 30% null hypothesis VE value rather than a lower value helps assure that vaccine efficacy is estimated with sufficient precision to support decision-making about a vaccine, which may include regulatory approval and acceptance of the vaccine for manufacturing and widespread use.

28. QUALITY CONTROL AND QUALITY ASSURANCE

Quality control procedures will be implemented and maintained to ensure the accuracy and reliability of the data. For any missing data, clarification will be communicated to the sites for resolution. The study site will provide direct access to all study-related source data/documents, and reports for the purposes of monitoring and auditing that may be conducted by the sponsor, and inspection by local and regulatory authorities.The documentation of the study will be adequate for the reconstruction of the course of events (audit trail). Following written SOPs, the Monitor will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the study protocol, GCP, and the applicable regulatory requirements. Monitoring will occur periodically via contact with the site and on-site visits. The extent, nature, and frequency of onsite visits will be based on study complexity, enrolment rate, and data quality at the site. Through frequent communications (e.g., letter, email, and telephone), the

study monitor will ensure that the investigation is conducted according to the protocol and regulatory requirements.

29. MONITORING

In accordance with applicable regulations, GCP, and the procedures of the sponsor or designee, the study monitor/designee will periodically contact the site, and conduct on-site visits. The extent, nature, andfrequency of on-site visits will be based on study complexity, enrolment rate, and data quality at thesite. Through frequent communications (e.g., letter, e-mail, and telephone), the studymonitorwillensure that the investigation is conducted according to the protocol and regulatory requirements.

The Investigator will permit the study monitor/designee at agreed appointments to check and verify the study documentation (source data verification) including the CRF and other information. Corrections, amendments, or clarifying statements will be made to/by the Investigator whenever necessary usingthe data clarification form.

When BBIL Monitor visits the site, the investigator is responsible for producing the documentsrequired. He/she can delegate this work to one of the team members. The documents generallyrequired are the Source Documents, informed consent form signed by both the Principal Investigator and the subject, communication if any, drugdispensing log, Drug Accountability log, lab reports and filled CRFs, etc.

Monitoring activities will be done to verify that the:

- Data are authentic, accurate, and complete
- The safety and rights of the subjects are being protected
- The study is conducted in accordance with the currently approved protocol (and any amendments), GCP, and all applicable regulatory requirements

The investigator will allow the study monitor direct access to all relevant documents, and allocatehis/her time and the time of his/her staff to the study monitor to discuss findings and any relevantissues.

Protocol Deviation and Violation

A protocol violation is any failure to comply with the final study protocol as approved by the EthicsCommittee. A violation is a serious non-compliance with the protocol resulting from error, fraud,or misconduct and might result in the exclusion of a subject from the study. A protocol deviation is a less serious non-compliance, usually to deal with unforeseen circumstances. All violations and/or deviations must bereported to BBIL and Ethics Committee as soon as possible.

30. ETHICAL CONSIDERATIONS

This study is to be conducted according to Schedule Y of the Drugs and Cosmetics Act, and GCP, in which the ethical principles have their origin in the revised Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013). The medical care is given to, and a medical decision made on behalf of study participants will always be the responsibility of a Principal (Site) Investigator. Each individual involved in conducting the study shall be qualified by education, training, and experience to perform his or her respective task(s).

The study can only start at the Investigator's site when the relevant IECs have given, signed, and dated approval of the study protocol, written informed consent/assent forms and other written information to be provided to the study participants. The IEC should maintain written records of its activities and minutes of its meetings. All relevant records pertaining to the study should be kept for a period of at least 5 years after the completion or formal discontinuation of the study and should be available to regulatory authorities on request. The PI should report promptly to its IEC when any of the following occurs:

1. Deviations from, or change of, the protocol to eliminate immediate hazards to the study participants
2. Changes increasing the risk to study participants and/or affecting significantly the conduct of the study
3. All adverse drug reactions that are serious whether expected or unexpected
4. New information that may affect adversely the safety of the study participant or the conduct of the study
5. When the study has been terminated/discontinued/completed.

30.1 IRB REVIEW

Before the start of the study, the study protocol, ICF, and any other appropriate documents will be submitted to the IRB/IEC with a cover letter or form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. As per institutional requirements, the study protocol and any other appropriate documents will be submitted to the scientific committee for approval.

The investigator will forward to BBIL, or designee, a copy of the IRB's/IEC's approval of this protocol, amendments, ICF, and any changes to the ICF. The investigator will also keep documentation of the study approved by the internal scientific committee per institutional requirements.

The IEC should maintain written records of its activities and minutes of its meetings. All relevant records pertaining to the study should be kept for a period of at least 5years after the completion or formal discontinuation of the study and should be available to regulatory authorities on request.

31. RESPONSIBILITIES OF PRINCIPAL (SITE) INVESTIGATOR

The Principal (Site) Investigator is responsible for ensuring that the clinical study is performed in accordance with the written SOPs, the currently approved study protocol, ICH guidelines on Good Clinical Practice (GCP), and applicable local and regulatory requirements. The Investigator should ensure that he/she has sufficient time to conduct and complete the study and has adequate qualified staff and appropriate facilities which are available for the duration of the study and also ensure that other studies do not divert study staff or facilities away from the study at hand.

32. APPLICABLE LAWS AND REGULATIONS

This study will be conducted in accordance with the principles of the 18th World Medical Assembly (Helsinki, June 1964), and amendments of the 29th (Tokyo, 1975), 35th (Venice, 1983), 41st (Hong Kong, 1989), 48th (Somerset West, 1996), 52nd (Edinburgh, 2000), 53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added), 55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added) and 59th WMA General Assembly, Seoul, October 2008.

33. DATA HANDLING AND RECORD KEEPING

33.1 DATA MANAGEMENT

All activities of data management will be done by a designated independent third party/designee selected by the sponsor. Data will be reviewed, validated, and quality checked by the site monitor.

33.2 CONFIDENTIALITY

Subject names will remain confidential and will not be included in the database supplied to BBIL or its designee. Only screening number, subject initials, and birth date will be recorded on the eCRF. If the subject's name appears on any other document collected (e.g. hospital discharge summary), the name must be obliterated before the document is transmitted to BBIL or its designee. All study findings will be stored in electronic databases. The subjects will give explicit permission for representatives of the sponsor, regulatory authorities, and the IRB/IEC to inspect their medical records to verify the

information collected. Subjects will be informed that all personal information made available for inspection will be handled in the strictest confidence and in accordance with all state, local, and federal data protection/privacy laws. The investigator will maintain a subject identification log (enrolment numbers and corresponding subject names) to enable records to be identified.

33.3 SOURCE DOCUMENTS

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include Hospital records, clinical and office charts, laboratory reports, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial. At minimum source documentation must be available to *confirm data collected in the* CRF, subject identification, eligibility, discussion and date of informed consent/assent and study visit dates, telephonic follow up, record and follow up of adverse events, concomitant medication, Investigational vaccine administration and receipt/return records, date of study completion, the reason for early discontinuation of study vaccine or early withdrawal from the study, if applicable.

Corrections, if any, in the source documents should be made in such a way (i.e. crossing out the incorrect entry by using a simple line) that the original always remains legible. The original entry must not be obliterated, overwritten, or erased when a correction is made.

E.g.23 ~~28~~

Any corrections must be dated, signed (initialed), and justified where appropriate.In all cases, the use of correction fluid is strictly prohibited.

34. SUBJECT DIARY

The study staff should explain to the study subjects regarding the entries in the subject dairy. The study subjects should complete and bring the subject diary to the site during every visit as instructed by the site. The PI or designee should review the diary for completeness of the information and if required should give instructions for any incompleteness or missing entries.

35. CASE REPORT FORMS

The CRF will be used to record all of the information required by the protocol to be reported on each study Subject.

All the data in the CRF must be transcribed from the source documents (e.g. physical exam report, associated medical records, date and version of informed consent/assent form, etc.) by delegatedsite personnel.

Corrections will be made in such a way (i.e. crossing out the incorrect entry by using a simple line) that the original always remains legible (i.e. an audit trail will be maintained). The original entry must not be obliterated, overwritten, or erased when a correction is made. Any corrections must be dated, signed, and justified where appropriate.

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Corrections due to spelling mistakes, errors in transcription, or difficulties incorrectly completing the CRF do not routinely need to be justified. They will be explained if the reliability of the data could be questioned, especially if documentation of inclusion/exclusion criteria, adverse events, and/or the primary endpoint is concerned. In all cases, the use of correction fluid is strictly prohibited.

The CRF contains 2 copies, one original and one duplicate. After completion, the top original CRF page is detached and collected/returned to the sponsor (BBIL). The second copy of the CRF page remains at the Investigator's site.

When subsequent corrections or additions to the entries in the CRF are deemed necessary, queries will be raised. All the queries raised will be sent/brought to the attention of the investigator requesting him/her to confirm or make the correction, or enter additional or missing data as required. The investigator must keep records of the changes and corrections.

All clinical documentation and data arising from the study are to be kept by the investigator. Signatures must be hand-written by the investigator or delegated person, stamping is not allowed.

Whenever a study visit as per the protocol is completed, it is anticipated that the relevant sections of the eCRF will be completed by the Investigator (or designated staff). As soon as the study participant has completed/withdrawn from the study and the eCRF is completed, the Principal (Site) Investigator or designated physician(s) under his/her supervision should sign the Study Completion Information pages of the eCRF to confirm that they have reviewed the data and that the data is complete and accurate. Signatures will be electronic by the Investigator or delegated person.

The study monitor will review completed CRFs during monitoring and if errors are detected may seek clarification and/or correction of such errors by the investigator/designee. The investigator will resolve the queries or make necessary corrections on being brought to his/her attention. Any questions or comments related to the eCRF/study conduct will be directed to the assigned site monitor.

36. RECORDS RETENTIONS

At the end of the study, investigators are required to retain all study documents including administrative documentation relating to each subject screened or enrolled. The principal (Site) Investigator will return any unused study material supplied for the performance of the study to the sponsor. The study documents include informed consent/assent, locator information, and all source documents. The PI shall retain all the records pertaining to the receipt and return of study supplies (particularly INV) and electronic copies of final case report forms, worksheets, and other pertinent source documents for a minimum of 5 years from the date of marketing authorization or formal discontinuation of the study. The sponsor will inform the date ofthedestruction of the study related documents appropriately.

37. FINANCE AND INSURANCE

The details of the funding provided will be documented in the clinical trial agreement between the sponsor (BBIL) and the investigator involved. All applicable laws regarding the insurance of trial subjects will be followed and spelled out in a separate agreement. The liability and insurance provisions for this study are specified in the investigator's contract.

38. PUBLICATION POLICY

If this clinical research leads to patentable results, the investigator (or entity acting on his/her behalf according to local requirements) shall refrain from filing a patent application(s). Patent applications will be filed by BBIL or another entity delegated by BBIL.

All information concerning the product as well as any information such as clinical uses of Vaccine, its formula, methods of manufacture, and other scientific data relating to it, that have been provided by BBIL or designee, and are unpublished, are confidential and must remain the sole property of BBIL. The investigator will agree to use the information only to carry out this study and for no other purpose unless prior written permission from the sponsor is obtained. BBIL has full ownership of the CRFs completed as part of the study.

By signing the study protocol, the investigator agrees that the results of the study may be used for the purposes of the national and international registration, publication, and information for medical and pharmaceutical professionals by BBIL. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement. The BBIL or designee will prepare a final report on the study. In addition, the results of the study will be published in an international or national journal and may be presented at scientific meetings. The investigator may not publish or present any information on this study without the written approval of BBIL. The investigator has the right to review a manuscript for a defined period (60 days) before publication but has no right to deny the publication of the study's full results.

39. MEDIA ATTENTION

The Principal Investigator and all the site staff involved in the trial must keep the study-related information utmost confidential. The study-related information should not be disclosed in any media (Print media, broadcast media, Internet, or social media) without prior approval from the sponsor.

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