CLINICAL TRIAL PROTOCOL

An Adaptive, Seamless Phase 1, Followed by Phase 2 Randomized, Double-blind, Multicenter Study to Evaluate the Safety, Reactogenicity, Tolerability and Immunogenicity of the Whole-Virion Inactivated SARS-CoV-2 Vaccine (BBV152) in Healthy Volunteers.

Protocol No: BBIL/BBV152-A/2020

Version No: 5.0; Date: 02-09-2020

Sponsored by:

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Genome Valley, Hyderabad, India.

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Declaration By Responsible Sponsor Representative(s)

An Adaptive, Seamless Phase 1, Followed by Phase 2 Randomized, Double-blind, Multicenter Study to Evaluate the Safety, Reactogenicity, Tolerability and Immunogenicity of the Whole-Virion Inactivated SARS-CoV-2 Vaccine (BBV152) in Healthy Volunteers.

This clinical study protocol version 5.0 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 64th WMA General Assembly, Fortaleza, Brazil, October 2013 and national and international guidelines on Good Clinical Practice and applicable regulatory requirements.

Signature and Date 02/Sep/2020

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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

Protocol Title: An Adaptive, Seamless Phase 1, Followed by Phase 2 Randomized, Double-blind, Multicenter Study to Evaluate the Safety, Reactogenicity, Tolerability and Immunogenicity of the Whole-Virion Inactivated SARS-CoV-2 Vaccine (BBV152) in Healthy Volunteers.

Protocol Number: BBIL/BBV152-A/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 decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate immediately such 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

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Protocol Title: An Adaptive, Seamless Phase 1, Followed by Phase 2 Randomized, Double-blind, Multicenter Study to Evaluate the Safety, Reactogenicity, Tolerability and Immunogenicity of the Whole-Virion Inactivated SARS-CoV-2 Vaccine (BBV152) in Healthy Volunteers.

Protocol Number: BBIL/BBV152-A/2020

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Table of Contents

1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS..... 10
2. PROTOCOL SYNOPSIS..... 17
3. INTRODUCTION..... 42
4. STUDY RATIONALE..... 43
5. RISK/BENEFIT ASSESSMENT..... 44
6. STUDY OBJECTIVES..... 45
7. STUDY ENDPOINTS..... 45
8. STUDY DESIGN..... 46
9. SUBJECT ELIGIBILITY..... 47
9.1 Phase 1:..... 47
9.2 Phase 2:..... 50
10. STUDY PROCEDURES..... 51
11. PREMATURE DISCONTINUATION OF THE TRIAL..... 55
12. EARLY DISCONTINUATION FROM OF THE STUDY..... 55
13. LOST TO FOLLOW-UP SUBJECTS..... 56
14. MONITORING SUBJECT COMPLIANCE..... 56
15. INVESTIGATIONAL VACCINE (INV)..... 56
15.1 Study Vaccines..... 56
15.2 Dosage form and route of administration..... 57
15.3 Dose regimen..... 57
15.4 Packaging..... 57
15.5 Labelling..... 57
15.6 Supplies and Handling of Materials..... 57
15.7 Accountability procedures for the Investigational Vaccines..... 58
15.8 Dispensing study vaccine..... 58
15. 9 Return or Destruction of Investigational Vaccine..... 59
16. MEDICATIONS DURING TRIAL PARTICIPATION..... 59
16.1 Drug Interactions..... 59

16.2 Prohibited Medication Prior and During Study....60
17. MANAGEMENT OF SPECIMENS....60
17.2 Specimen preparation, handling, storage and shipment....60
18. STUDY ASSESSMENTS....61
18.1 Immunogenicity Assessment....61
18.2 Safety Assessments....61
19. ADVERSE EVENT MANAGEMENT....62
19.1 Adverse Event (AE) or Adverse Experience....62
19.1 Definition of an Adverse Event....62
19.2 Possible AE's and Interactions....62
19.3 Adverse Drug Reaction (ADR)....63
19.4 Definition of a Serious Adverse Event....63
19.5 Clinical Laboratory Abnormalities and Other Abnormal Assessments....64
19.6 Recording of Adverse Events, Adverse Drug Reactions and Serious Adverse Events65
19.7 Relationship to INV:....65
19.8 Outcome of AE and SAE....66
19.9 Action Taken....66
19.10 Follow-up of Adverse Events, Adverse Drug Reactions and Serious Adverse Events66
19.11 Reporting of all Serious Adverse Events....66
20. DATA SAFETY MONITORING BOARD (DSMB)....68
21. STATISTICS....68
21.1 Statistical Analysis Plan and Methods....68
21.2 Sample Size and Power....69
22. QUALITY CONTROL AND QUALITY ASSURANCE....70
23. MONITORING....70
24. ETHICAL CONSIDERATIONS....71
24.1 IRB Review....72

25. RESPONSIBILITIES OF PRINCIPAL (SITE) INVESTIGATOR..... 72
26. APPLICABLE LAWS AND REGULATIONS.....72
27. DATA HANDLING AND RECORD KEEPING.....73
27.1 Data Management..... 73
27.2 Confidentiality..... 73
27.3 Source Documents..... 73
28. SUBJECT DIARY..... 74
29. CASE REPORT FORMS.....74
30. RECORDS RETENTIONS.....75
31. FINANCE AND INSURANCE.....75
32. PUBLICATION POLICY.....76
33. REFERENCES.....76

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 Immunisation
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 substance (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 infection	The presence of an infection without symptoms. Also known as unapparent or subclinical infection
BBIL	Bharat Biotech International Ltd.
B cells	Small white blood cells that help the body defend itself against infection. These cells are produced in bone marrow and develop into plasma cells which produce antibodies. Also known as B lymphocytes.
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.

Term/ Abbreviation	Definition/ Full Form
CDC	Centers for Disease Control and Prevention, Atlanta, USA
CDSCO	Central Drugs Standard Control Organisation
Clinical Trial	A systematic study of pharmaceutical products on human subjects – (whether patients or non-patient volunteers) – in order 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 personal 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 newborn 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 centres participating in a multicentre trial
COVID-19	Corona Virus Disease 2019
CRF	Case Report Form
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 in excess of what is normally expected.

Term/ Abbreviation	Definition/ Full Form
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
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 also referred as 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 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
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 defence against them. This defence is known as the immune response. It involves 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	An impartial independent witness who will not be influenced in any way by those who are

Term/ Abbreviation	Definition/ Full Form
Witness	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 in 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 has been provided to the potential subject.
Incidence	The number of new disease cases reported in a population over a certain period of time
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 may be called the principal investigator. CDSCO GCP: A person responsible for the conduct of the study at the trial site. 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 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 prior to 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 (IMP)	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 authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form
Investigational	Investigational vaccines are still in the testing and evaluation phase and are not licensed for use in the general public.

Term/ Abbreviation	Definition/ Full Form
vaccine *aka* IMP	
ITT	Intent-to-treat
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 are able to 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-Centric 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	Sudden appearance of a disease in a specific geographic area (e.g. neighbourhood or community) or population
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 prior to 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 time 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

Term/ Abbreviation	Definition/ Full Form
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
Standard Operating Procedures (SOP)	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)
UIP	Universal Immunisation Program
Vaccination	Injection of a killed or weakened infectious organism in order 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
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 a retaliatory 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. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes,

Term/ Abbreviation	Definition/ Full Form
	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 Adaptive, Seamless Phase 1, Followed by Phase 2 Randomized, Double-blind, Multicenter Study to Evaluate the Safety, Reactogenicity, Tolerability and Immunogenicity of the Whole-Virion Inactivated SARS-CoV-2 Vaccine (BBV152) in Healthy Volunteers.
Short Title	Phase 1/2 study to evaluate the Safety, Reactogenicity, Tolerability, and Immunogenicity of Whole-Virion Inactivated SARS-CoV-2 Virus Vaccine, BBV152 in Healthy Volunteers.
Clinical Trial Strategy	In view of the prevailing COVID-19 pandemic, the clinical trial has been designed in a seamless manner wherein compared to conventional approach. The sample size has been deliberately kept large to assess the immune responses from the vaccine ensuring a high degree of power. Appropriate sample sizes, dose schedule and clinical end points have been chosen. The phase 1 part of this clinical trial has completed, 375 subjects were recruitment,and the the safety data of 3 vaccine formulations was analyzed post 7 days of second dose and an interim report was prepared and submitted to CDSCO. Based on the Phase 1 study safety data and non-human primate challenge study results, the BBV152-A, BBV152-B formulations are selected to continue the Phase 2 study. The Clinical Trial Strategy is depicted in the Schematic, given in Annex 1.
Study Objectives	**Phase 1 (Completed):** ➢ To evaluate the safety, reactogenicity, tolerability, and immunogenicity of two doses of the two-sequentially escalating Groups [3 µg and 6 µg per single human dose (SHD) of 0.5 mL] of BBV152 (whole-virion inactivated SARS-CoV-2 virus) vaccine formulation BBV152A, BBV152B, and BBV152C, administered via the intramuscular route. ➢ In phase 1 study 375 subjects were recruited and vaccinated with two doses of BBV152 vaccine formulations and their safety data was analyzed and an interim report notified to CDSCO. Immunogenicity data analysis is under progress. **Phase 2:** ➢ To evaluate the safety and immunogenicity of selected formulations (BBV152-A and BBV152-B) (Whole-Virion Inactivated SARS-CoV-2 virus vaccine).

Study Sites	Multicenter study
Population	A total sample size of 755 healthy volunteers, with 375 ages ≥18-≤55 in the phase 1 study (4:1 test and placebo) and 380 ages ≥12 - ≤65 years in phase 2 study (1:1 test groups).
Study Duration	Approximately 12 months
Investigational Product	Whole-Virion Inactivated SARS-CoV-2 vaccine (BBV152) with three formulations, BBV152A, BBV152B and BBV152C were used in phase 1 and BBV152-A and BBV152-B is selected for phase 2 study
Comparator (Control)	Placebo will be used as the control (For Phase 1 only).
The rationale for conducting Parallel clinical and pre-clinical studies	Developing a vaccine quickly requires a new pandemic paradigm, with a fast start and many steps executed in parallel before confirming a successful outcome of another level. For example, for platforms with experience in humans, phase 1 clinical trials may be able to proceed in parallel with testing in animal models. Bharat Biotech has developed various inactivated vaccines based on well characterized vero cell platform, such as JENVAC®, INDIRAB®, Chikungunya vaccine, and Zika virus vaccine. Bharat Biotech has conducted clinical trials with these vaccine formulations and found that vaccines are safe and immunogenic[1,2] In such pandemic situations, it is anticipated that few or no pre-clinical and non-clinical data would be available. If the risk-benefit evaluation warrants such action, countries should be prepared to accept vaccines without these data[3,4]. However Bharat Biotech is trying to complete as many as toxicology studies as possible.
Study Purpose	The purpose of this study is to evaluate the safety, reactogenicity, tolerability, and immunogenicity of the whole-virion inactivated SARS-CoV-2 vaccine, BBV152. In this study, we will use three formulations of BBV152 vaccine for the intramuscular route of administration. This study will be conducted in a dose escalatory manner with a two-dose regimen fourteen days apart in Phase 1 and selected formulation (BBV152-A and BBV152-B) will be further evaluated in Phase 2.
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 hot-spots/outbreak areas where there is a high risk of transmission of SARS-CoV-2 infection and especially the elderly people (age >60 Years). Though SARS-CoV-2 infection may cause mild symptoms in many, nearly 14% develop severe disease that requires hospitalization and oxygen support, and 5% require admission to an intensive care unit (ICU). In severe cases, COVID-19 can be complicated by acute respiratory distress syndrome, sepsis, septic shock, and multiorgan failure with an estimated case fatality of 3.4% as of March 10, 2020[8,9]. The COVID-19 pandemic is rapidly worsening in all parts of the world, overwhelming health systems. There is a severe threat in 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 antiviral drug has been approved for COVID-19, although remdesivir has been given Emergency Use Authorization approval by USFDA. 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 mutations (eg: Adeno virus and traditional inactivated vaccines are under development[10,11,12,13]. 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[13]. The vaccine is under phase 1/2 clinical trial in China for evaluation of the safety and immunogenicity in adults ages 18 to 59 years. Two dosage formulations low and high concentrations or two doses of placebo were administered at either emergency schedule (Day 0,14) or routine schedule (Day 0, 28).

	The COVID-19 pandemic is rapidly worsening in all parts of the world, overwhelming health systems. It is important to generate clinically relevant information on the immune responses and safety. In conventional of clinical trials (in routine schedule), usually, 3 to 4 weeks intervals are maintained between two vaccine doses. However, based on the following 14 day interval dosing schedules; 1. Bharat Biotech pre-clinical data, 2. Another whole-virion inactivated Chinese (PicoVacc™) from the manufacturer Sinovac Biotech Ltd. (NCT04352608), Bharat Biotech is making an informed decision on selecting the 14 day interval dosing schedule. This dosing schedule will not compromise the immunogenicity profile and safety of the vaccine.
Rationale for BBV152-A & BBV152-B selection and dosage schedule change	The vaccine formulation BBV152-A and BBV152-B are selected for the phase 2 study based on the safety data of the 3 formulations in the phase 1 study and the non-human primate animal challenge study results. **Phase 1 safety data:** In this adaptive, seamless study of Whole-Virion Inactivated SARS-CoV-2 Vaccine (BBV152), subject recruitment for Phase 1 study was initiated on 15th July 2020. A total of 897 subjects have undergone screening. A total of 133 subjects have been found to be SAS-CoV-2 positive by RT-PCR testing and/or ELISA testing, and a total of 153 subjects had abnormal lab values. A total of 402 subjects have been enrolled for the 1st dose. A total of 394 subjects have been administered the 2nd dose, after 8 subject dropouts. No immediate adverse events were reported within 2 hours of vaccine administration. Among the 402 subjects who were administered the 1st dose, a total of 73 adverse events have been recorded, and among the 394 subjects who were administered the 2nd dose, a total of 18 adverse events have been recorded. Most of the adverse effects were mild in nature and resolved without any sequelae. One serious adverse event was reported where the subject was hospitalized with viral pneumonitis and has recovered. **Non-human Primate Animal Challenge Study:** Based on the immunogenicity data from the challenge studies of Hamster and Rhesus macaque monkeys conducted at NIV, Pune, we have identified the 2 desired

	formulation for the Phase 2 clinical trial. Data from this study is available to review by DCGI and which will ensure that appropriate formulation (BBV152-A & BBV152-B) is selected for Phase 2. **Dosage Schedule:** In the phase 1 study, vaccine was administered as two doses at 14 days interval (Accelerated dosage schedule), in phase 2 we would like to adopt the routine (0, 28 days) dosage schedule to compare the immunogenicity between two arms.
Study Endpoints	**Phase 1 (Completed):** **Primary** 1. The occurrence of immediate adverse events within two hours of vaccination [Time Frame: 2 hours]. 2. The occurrence of adverse events within seven days of vaccination [Time Frame: 7 days]. 3. The occurrence of any adverse events throughout the study duration [Time Frame: throughout the study duration]. 4. The occurrence of serious adverse events (SAEs) [Time Frame: throughout the study duration]. **Secondary** 1. To evaluate the immunogenicity in terms of GMT and four-fold seroconversion rate of neutralizing antibodies (NAb's) across the three formulations of BBV152 in comparison with placebo group, from baseline to days 14+2, 28±2,42±2, 104±7 and 194±7. **Phase 2:** **Primary** **1.** To evaluate the immunogenicity in terms of GMT and four-fold seroconversion rate of NAbs specific to SARS-CoV-2 virus in subjects administered with the selected BBV152-A and BBV152-B vaccine formulation from baseline to days 28+2,42±2, 56±2, 118±7 and 208±7, in two arms. **Secondary** 1. The occurrence of immediate adverse events within two hours of vaccination [Time Frame: 2 hours]. 2. The occurrence of adverse events within seven days of vaccination [Time Frame: 7

	days]. 3. The occurrence of any adverse events throughout the study duration [Time Frame: throughout the study duration]. 4. The occurrence of serious adverse events (SAEs) [Time Frame: throughout the study duration].
Exploratory endpoints	1. Immunogenicity indexes of IgG antibody for RBD and Spike proteins. 2. Immunogenicity indexes of specific cellular immune responses [Such as, Lymphocyte subset percent (CD3+, CD4+, and CD8+), Key cytokines (TNF-α, IFN-γ, IL-2, IL-4, IL-5, IL-6)]. 3. Evaluate the number of virologically confirmed symptomatic cases of COVID-19 (definition of a symptomatic case of COVID-19 would consist of fever + Positive confirmation of COVID-19) among different study arms. 4. Antibody-Dependent Enhancement (ADE), if any, will be evaluated.
Study Design	This is an adaptive, seamless phase 1 to be followed by phase 2 randomized, double-blind, multicenter study to evaluate the safety, reactogenicity, tolerability and immunogenicity of the Whole-Virion Inactivated SARS-CoV-2 vaccine (BBV152) in healthy volunteers. **Phase 1 Study (Completed):** The study is designed to evaluate the safety, reactogenicity, tolerability, and immunogenicity of Four arms of healthy volunteers who receive two intramuscular doses of BBV152 vaccine formulations or Placebo. A total no of 375 subjects will be enrolled in 4:1 ratio **Arm 1:** A total of 100 subjects will be enrolled in this arm and will receive two intramuscular doses of BBV152A . The two doses will be administered 14 days apart. Upon completion of 7 days of post-vaccination of the 50 participants in Arm 1 (either test or placebo), the Data Safety Monitoring Board (DSMB) will review all the available data, and recommend progression towards the next arms. Thereafter, participants will be further enrolled into the higher dose arms (Arm 2, 3), with the continuation of the remaining participants of Arm 1. **Arm 2:** A total of 100 subjects will be enrolled in this arm and will receive two intramuscular doses of BBV152B . The two doses will be administered 14 days apart.

	Arm 3: A total of 100 subjects will be enrolled in this arm and will receive two intramuscular doses of BBV152C. The two doses will be administered 14 days apart. **Arm 4:** A total of 75 subjects will be enrolled in this arm and will receive two intramuscular doses of Placebo. The two doses will be administered 14 days apart After completion of 14 days post 2nd dose vaccination (Day 28), immunogenicity & safety in arms 1, 2, 3 and 4 will be reviewed by Data Safety Monitoring Board (DSMB) and recommend the progression towards the next Phase of the trial. An interim report based on the safety and immunogenicity of the three formulation from Arm 1, Arm 2, Arm 3 and Arm 4 will be notified to the Central Drugs Standard Control Organisation (CDSCO), India, for further progressing the clinical development of the vaccine. This interim report will contain a detailed analysis of the data based on the primary and secondary objectives of all visits through Day 28 (Immunogenicity & Safety). The ultimate goal is the selection of a safe, well-tolerated, and immunogenic intramuscular vaccine, which will be further evaluated in the phase 2 study. **Phase 2 study** The study is designed to evaluate the safety, reactogenicity, tolerability, and immunogenicity of two arms of healthy volunteers who receive two intramuscular doses of BBV152 vaccine formulations (BBV152-A & BBV152-B) selected from phase 1 study will be administered in 1:1 ratio. This will be conducted in a double blinded manner with no control arm. **Arm 1:** A total of 190 subjects will be enrolled in this arm 1 and will receive two intramuscular doses of BBV152-A vaccine. The two doses will be administered 28 days apart. **Arm 2:** A total of 190 subjects will be enrolled in this arm and will receive two intramuscular doses of BBV152-B vaccine. The two doses will be administered 28 days apart. Data will be unblinded and an interim analysis will be performed at day 42 & 56 for

	Immunogenicity and safety
Eligibility Criteria	**Phase 1 (Completed):** **Inclusion** 1. Ability to provide written informed consent (Audio video consent for vulnerable subjects). 2. Participants of either gender of age between ≥18 to ≤55 years. 3. Good general health as determined by the discretion of investigator (vital signs (heart rate ≥60 to≤100 bpm; blood pressure systolic ≥90 mm Hg and <140 mm Hg; diastolic ≥ 60 mm Hg and <90 mm Hg; oral temperature <100.4ºF), medical history, and physical examination). 4. Expressed interest and availability to fulfill the study requirements. 5. 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 four weeks after the last vaccination 6. Male subjects of reproductive potential: Use of condoms to ensure effective contraception with the female partner from first vaccination until 3 months after last vaccination 7. Male subjects agree to refrain from sperm donation from the time of first vaccination until 3 months after last vaccination 8. Participants must refrain from blood or plasma donation from the time of first vaccination until 3 months after last vaccination 9. Agrees not to participate in another clinical trial at any time during the study period. 10. Agrees to remain in the study area for the entire duration of the study. 11. Willing to allow storage and future use of biological samples for future research. **Exclusion** 1. History of any other COVID-19 investigational vaccination. 2. Unacceptable laboratory abnormality from screening (prior to first vaccination) or safety testing, as listed below [Abnormal Complete Blood Count (CBC), Random blood sugar level, Renal function test (serum urea and Creatinine), liver function tests, urine analysis report, Positive serology for hepatitis C or HIV antibody or hepatitis B surface antigen].

	(*Subjects will be informed if their results are positive for hepatitis C, HIV 1 & 2 antibody or hepatitis B surface antigen (HBsAg) and will be referred to a primary care provider for follow up of these abnormal laboratory tests*.) 3. Confirmed SARS-CoV-2 at the time of screening using RT-PCR and/or ELISA method. 4. Health care workers. 5. For women, a positive serum pregnancy test (during screening within 45 days of enrolment) or positive urine pregnancy test (within 24 hours of administering each dose of vaccine). 6. 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. 7. Medical problems as a result of alcohol or illicit drug use during the past 12 months. 8. Receipt of an experimental agent (vaccine, drug, device, etc.) within 60 days before enrollment or expects to receive an investigational agent during the study period. 9. Receipt of any licensed vaccine within four weeks before enrolment in this study. 10. Known sensitivity to any ingredient of the study vaccines, or a more severe allergic reaction and history of allergies in the past. 11. Receipt of immunoglobulin or other blood products within the three months prior to vaccination in this study. 12. 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. 13. Long-term use (> 2 weeks) of oral or parenteral steroids (glucocorticoids) or high-dose inhaled steroids (>800 mcg/day of beclomethasone dipropionate or equivalent) within the preceding six months (nasal and topical steroids are allowed). 14. Any history of hereditary angioedema or idiopathic angioedema. 15. Any history of anaphylaxis in relation to vaccination. 16. Any history of albumin-intolerance.

	17. Pregnancy, lactation, or willingness/intention to become pregnant during the study. 18. History of any cancer. 19. History of psychiatric severe conditions likely to affect participation in the study. 20. A bleeding disorder (e.g. factor deficiency, coagulopathy or platelet disorder, or prior history of significant bleeding or bruising following IM injections or venepuncture. 21. Any other serious chronic illness requiring hospital specialist supervision. 22. Chronic respiratory diseases like severe acute respiratory syndrome (SARS), including mild asthma. 23. Chronic cardiovascular disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder, and neurological illness 24. Morbidly obese (BMI≥35 kg/m2) or underweight (BMI ≤18 kg/m2). 25. Living in the same household of any COVID-19 positive person. 26. Any other condition that in the opinion of the investigator would jeopardize the safety or rights of a volunteer participating in the trial or would render the subject unable to comply with the protocol. **Re-Vaccination Exclusion Criteria** 27. Pregnancy. 28. Anaphylactic reaction following administration of the investigational vaccine. 29. Virologically confirmed cases of COVID-19 **Phase 2:** **Inclusion** 1. Ability to provide written informed consent/assent (Audio video consent for vulnerable subjects). 2. Participants of either gender of age between ≥12 to ≤ 65 years. 3. Good general health as determined by the discretion of investigator (vital signs (heart rate ≥60 to≤100 bpm; blood pressure systolic ≥90 mm Hg and <140 mm Hg; diastolic ≥ 60 mm Hg and <90 mm Hg; oral temperature <100.4ºF), medical history, and physical examination). 4. Expressed interest and availability to fulfill the study requirements. 5. For a female participant of child-bearing potential, avoid becoming pregnant (use of an effective method of contraception or abstinence) from the time of study

	enrolment until at least four weeks after the last vaccination and agrees not to participate in another clinical trial at any time during the study period. 6. Male subjects of reproductive potential: Use of condoms to ensure effective contraception with the female partner from first vaccination until 3 months after last vaccination 7. Male subjects agree to refrain from sperm donation from the time of first vaccination until 3 months after last vaccination 8. Participants must refrain from blood or plasma donation from the time of first vaccination until 3 months after last vaccination. 9. Agrees to remain in the study area for the entire duration of the study. 10. Willing to allow storage and future use of biological samples for future research. **Exclusion** 1. History of any other COVID-19 investigational vaccination. 2. Confirmed SARS-CoV-2 at the time of screening using RT-PCR and ELISA method. 3. Health care workers. 4. Positive urine pregnancy test (within 24 hours of administering each dose of vaccine). 5. 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. 6. Medical problems as a result of alcohol or illicit drug use during the past 12 months. 7. Receipt of an experimental agent (vaccine, drug, device, etc.) within 60 days before enrolment or expects to receive an investigational agent during the study period. 8. Receipt of any licensed vaccine within four weeks before enrolment in this study. 9. Known sensitivity to any ingredient of the study vaccines, or a more severe allergic reaction and history of allergies in the past. 10. Receipt of immunoglobulin or other blood products within the three months prior to vaccination in this study. 11. 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.

	12. Long-term use (> 2 weeks) of oral or parenteral steroids (glucocorticoids) or high-dose inhaled steroids (>800 mcg/day of beclomethasone dipropionate or equivalent) within the preceding six months (nasal and topical steroids are allowed). 13. Any history of hereditary angioedema or idiopathic angioedema. 14. Any history of anaphylaxis in relation to vaccination. 15. Any history of albumin-intolerance. 16. Pregnancy, lactation, or willingness/intention to become pregnant during the study. 17. History of any cancer. 18. History of psychiatric severe conditions likely to affect participation in the study. 19. A bleeding disorder (e.g. factor deficiency, coagulopathy or platelet disorder, or prior history of significant bleeding or bruising following IM injections or venepuncture. 20. Any other serious chronic illness requiring hospital specialist supervision. 21. Chronic respiratory diseases like severe acute respiratory syndrome (SARS), including mild asthma. 22. Chronic cardiovascular disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder, and neurological illness 23. Morbidly obese (BMI≥35 kg/m2) or underweight (BMI ≤18 kg/m2). 24. Living in the same household of any COVID-19 positive person. 25. Any other condition that in the opinion of the investigator would jeopardize the safety or rights of a volunteer participating in the trial or would render the subject unable to comply with the protocol. **Re-Vaccination Exclusion Criteria** 26. Pregnancy. 27. Anaphylactic reaction following administration of the investigational vaccine. **28.** Virologically confirmed cases of COVID-19.
Sample Collection	**Phase 1 (Completed):** **Clinical laboratory testing:** A total of 15 ml of blood is collected at screening and day 28. **Immunogenicity analysis:** A total of 5 ml of blood is collected at days **0**, **14+2, 28±2,**

	42±2, 104±7 and 194±7. **Urine analysis:** the required amount of urine is collected on screening and day 28. **Pregnancy test:** Serum pregnancy test at screening and by using rapid test kit in remaining visits SARS-CoV-2 at the time of screening using RT-PCR and ELISA method. **Phase 2:** **Immunogenicity analysis:** A total of 5 ml of blood is collected at day **0**, **28+2, 42±2, 56±2, 118±7 and 208±7**. Blood (10 mL) will be collected on Day 0, 4, 14, 28, 42, 56, 118 and 208 from the subjects (30 in each group), who are willing to provide for the isolation of PBMCs to assess the cell mediate immunity. Blood sample for PBMCs will be collected from NIMS, Hyderabad and AIIMS, New Delhi. **Pregnancy test:** By using rapid test kit. SARS-CoV-2 at the time of Screening using RT-PCR and ELISA method.
Study Procedure	**Phase 1 (Completed):** **Screening (-7 Day to -1 Day)** All participants will been screened as per the eligibility criteria after consenting to participate in the study. All participants will be screened for clinical laboratory safety (haematology, biochemistry, serology, COVID-19 by using RT-PCR and ELISA method) and eligible subjects will be enrolled. **Visit 1: Baseline (Day 0)** If eligible, study participants will attend the OPD for physical, general examination, and specific symptoms for COVID-19. When no clinically significant abnormalities are detected, blood samples will be withdrawn prior to vaccination. A study vaccine/placebo will be administered. Following vaccination, participants will remain at the study site for at least 2 hours of observation to record any adverse event.

	Day 1-7: The study participants will be telephonically followed up by the site for the first seven days post-vaccination to know their current health status. **Visit 2: (Day 14+2)** Study participants will return to the OPD for physical, general examination, and specific symptoms for COVID-19. Blood samples will be withdrawn prior to vaccination for immunogenicity test. A study vaccine/placebo will be administered. Following vaccination, participants will remain at the study site for at least 2 hours of observation to record any adverse event. **Phase 1:** Day 15-21; The study participants will be telephonically followed up by the site or first seven days post-vaccination to know their current health status. **Visit 3: (Day 28±2)** Study participants will return to the OPD for physical, general examination, and specific symptoms for COVID-19 and laboratory investigation. Blood samples will be withdrawn to assess clinical laboratory safety and immunogenicity for inactivated (COVID-19) vaccine. **Visit 4: (Day 42±2)** Study participants will return to the OPD for physical, general examination, and specific symptoms for COVID-19 and laboratory investigation. Blood samples will be withdrawn to assess immunogenicity for inactivated (COVID-19) vaccine. **Visit 5: (Day 104±7)** Study participants will return to the OPD for physical, general examination, and specific symptoms for COVID-19. Blood samples will be withdrawn on to assess immunogenicity for inactivated (COVID-19) vaccine. **Visit 6: (Day 194±7)** Study participants will return to the OPD for physical, general examination and specific symptoms for COVID-19. Blood samples will be withdrawn on to assess immunogenicity for inactivated (COVID-19) vaccine. Detailed information can be found in Table 1. **Safety Monitoring:**

	• Subjects will be observed for two hours after vaccination for immediate adverse events • Active surveillance will be conducted for all participants for seven days after each dose of vaccine to ascertain information on solicited adverse events ("Reactogenicity") **Unscheduled visits:** If any subject develops fever or is concerned about his/her health, they 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. **Phase 2:** **Screening (-7 Day to -1 Day)** All participants will been screened as per the eligibility criteria after consenting to participate in the study. All subjects will be diagnose on Day -7 to Day 0 from base line for COVID-19 by using RT-PCR and ELISA method, and eligible subjects will be enrolled. **Visit 1: Baseline (Day 0)** If eligible, study participants will attend the OPD for physical, general examination, and specific symptoms for COVID-19. When no clinically significant abnormalities are detected, blood samples will be withdrawn prior to vaccination. A study vaccine/placebo will be administered. Following vaccination, participants will remain at the study site for at least 2 hours of observation to record any adverse event. Day 1-7: The study participants will be telephonically followed up by the site for the first seven days post-vaccination to know their current health status. **Visit 2: (Day 28+2)** Study participants will return to the OPD for physical, general examination, and specific symptoms for COVID-19. Blood samples will be withdrawn prior to vaccination for immunogenicity test. A study vaccine/placebo will be administered. Following vaccination, participants will remain at the study site for at least 2 hours of

	observation to record any adverse event. **Phase 1:** Day 29-36; The study participants will be telephonically followed up by the site or first seven days post-vaccination to know their current health status. **Visit 3: (Day 42+2)** Study participants will return to the OPD for physical, general examination, and specific symptoms for COVID-19 and laboratory investigation. Blood samples will be withdrawn to assess clinical laboratory safety and immunogenicity for inactivated (COVID-19) vaccine. **Visit 4: (Day 56±2)** Study participants will return to the OPD for physical, general examination, and specific symptoms for COVID-19 and laboratory investigation. Blood samples will be withdrawn to assess immunogenicity for inactivated (COVID-19) vaccine. **Visit 5: (Day 118±7)** Study participants will return to the OPD for physical, general examination, and specific symptoms for COVID-19. Blood samples will be withdrawn on to assess immunogenicity for inactivated (COVID-19) vaccine. **Visit 6: (Day 208±7)** Study participants will return to the OPD for physical, general examination and specific symptoms for COVID-19. Blood samples will be withdrawn on to assess immunogenicity for inactivated (COVID-19) vaccine. Detailed information can be found in Table 2. **Safety Monitoring:** • Subjects will be observed for two hours after vaccination for immediate adverse events • Active surveillance will be conducted for all participants for seven days after each dose of vaccine to ascertain information on solicited adverse events ("Reactogenicity") **Unscheduled visits:** If any subject develops fever or is concerned about his/her health, they 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.
DSMB & Interim report	**Phase 1 (Completed):** After completion of 14 days post 2nd dose vaccination (Day 28), immunogenicity & safety in Arm 1, 2 and 3 will be reviewed by Data Safety Monitoring Board (DSMB) and recommend progression towards the next Phase of the trial. An interim report based on the safety and immunogenicity of the three formulation from Arm 1, Arm 2, Arm 3 and Arm 4 will be notified to the Central Drugs Standard Control Organisation (CDSCO), India, for further progressing the clinical development of the vaccine. This interim report will contain a detailed analysis of the data based on the primary and secondary objectives of all visits through Day 28 (Immunogenicity & Safety). ***Arm 1 (subset, n=50) → 1st DSMB Review → Arm 1, 2 & 3 → 2nd DSMB Review → Interim report on safety and immunogenicity → Phase 2 Study.*** **Phase 2:** Arm 1: Data will be unblinded at day 42 and an interim report on day 42 and 56 based on the safety and immunogenicity of the BBV152-A and BBV152-B will be prepared and notified to CDSCO. This interim report will contain a detailed analysis of the data based on the primary and secondary objectives on Day 42 and 56 (Immunogenicity & Safety)
Randomization	Block randomization works by randomizing participants within blocks such that equal number is assigned to each treatment. Allocation proceeds by randomly selecting one of the orderings and assigning the next block of participants to study groups according to the specified sequence. Block randomization ensures that the number of participants in the study groups is nearly equal. Block randomization is done by creating blocks of sequences, which will ensure that the same number of participants will be allocated to the study groups within each block.

	The block size is determined by the treatment arms and block size will be fixed. **Phase 1 (Completed):** The Randomization will be done by the independent third party for the both Phase 1 & 2. The Block Randomization will be generated for 375 subjects in the age group of ≥18 - ≤55 using the SAS PROC PLAN procedure. Out of 375 subjects, a subset of 1-50 subjects will be randomized for vaccine formulation in the ratio of 4:1 for treatments BBV152A & placebo arm i.e; (3µg and placebo arm). The remaining subset of 325 subjects will be randomized for the vaccine formulation of BBV152A, BBV152B, BBV152C and placebo arms in the respective of (A-3µg, B-6 µg, C-6 µg & placebo) treatments in the 4:1 ratio. The Master Randomization List (MRL) will be uploaded in the IWRS system and the treatment will be allotted by a unique number for the participant for each dose based on the IWRS system (Interactive web response system). **Phase 2:** The Block Randomization will be generated for 380 subjects in the age group of ≥12-≤65 using the SAS PROC PLAN procedure in the ratio of 1:1 of Test groups. The Master Randomization List (MRL) will be uploaded for the both Phase I & II in the IWRS system and the treatment will be allotted by a unique number for the participant for each dose based on the IWRS system (Interactive web response system).
Safety Assessment	Specification of Safety Parameters Safety parameters include local reactions at the site of injection (pain/tenderness, redness/erythema, swelling and induration) and systemic adverse events fever, fatigue/malaise, myalgia, body aches, headache, nausea, vomiting, loss of appetite/anorexia, chills, rigor, rash, and diarrhea for 7 days after vaccination. **Safety Labs:**

	Phase 1 (Completed): 1. 10 mL of whole blood will be collected in EDTA anticoagulation tubes for Hematology [Hb%, total and differential WBC, RBC count, Platelet count, Hematocrit, MCV, MCH, MCHC, Total Cholesterol. 2. 5 mL of whole blood will be collected in serum collection tubes for LFT [alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), serum bilirubin (total, direct and indirect), serum lipase, prothrombin time (PT), partial thromboplastin time (PTT), gamma-glutamyl transferase (GGT)], and renal function test (RFT) [serum urea and serum creatinine]. 3. Random blood glucose. 4. Serum pregnancy test while screening and rapid test kit in other visits 5. Urine analysis. Safety will be assessed by frequency and incidence of AEs and SAEs in each dose group. 6. 5 mL of the sample will be collected for immunogenicity at baseline, Days 14+2, 28±2, 42±2, 104±7 and 194±7 **Phase 2:** **1. Arm 1**: 5 mL of the sample will be collected for immunogenicity at baseline, Days 28+2, 42±2, 56±2 118±7 and 208±7 **2. Arm 2:** 5 mL of the sample will be collected for immunogenicity at baseline, 28+2, 42±2, 104±7 and 194±7 **3.** Pregnancy test with rapid test kit. **4.** Blood (10 mL) will be collected on **Day 0, 4, 14, 28, 42, 56, 118 and 208** from the subjects (30 in each group), who are willing to provide for the isolation of PBMCs to assess the cell mediate immunity. Blood sample for PBMCs will be collected from NIMS, Hyderabad and AIIMS, New Delhi.
Study Hypothesis	We hypothesize that all formulations of BBV152 will be well-tolerated and two dosage levels tested will elicit robust serum anti-neutralizing antibody responses.
Sample Size	Assuming seroconversion rates are 85% for one BBV152-A and 95% for BBV152-B with a standard deviation of 0.5 for log10 titer. The required sample size for 90%

	power to find a significant difference (between vaccine formulations differing in GMT by a ratio of 2) in a trial with 1:1 allocation, using a two-sample z-test at the two-sided 5% significance level, is 171 per group. Assuming 10% loss during the study, the number becomes 190 per group. A total sample size of 755 healthy volunteers, with 375 ages ≥18-≤55 in the phase 1 study (4:1 test vs placebo) and 380 ages ≥12-≤65 in phase 2 study (1:1 test groups). We assume immunogenicity data will be available for 90% of randomized study participants, resulting in sample sizes for analysis of 90 BBV152 recipients per formulation in Phase 1, and 171 per Arm 1 and Arm 2 in Phase 2.
Statistical Analysis Plan	**Interim Data Analysis:** **Phase 1:** Data will be unblinded upon completion of visit 4 by all participants in Arm 1, 2 and 3. Safety analysis of all vaccine-related events would be conducted up to Day 28 to examine the acceptability of the vaccine. Immunology data of BBV152 vaccine titers will be compared to placebo titers i.e., baseline (Day 0) vs. day 14, and Day 28. A clinical study report will be generated at day 28 for the interim analysis. **Phase 2:** Data will be unblinded at day 42 and an interim report will be prepared on day 42 and 56 based on the safety and immunogenicity of the BBV152-A will be prepared and notified to CDSCO.. **Final Data Analysis:** Final data will be analyzed after the completion of all the subjects final visit follow-up. **Statistical Methods** Exact binomial calculation will be used for confidence interval estimation of proportions. Chi-square test or Fisher's exact test will be used to test differences in proportions. Confidence interval estimation for geometric mean titer (GMT) will be based on log10 (titer) and the assumption that log10 (titer) is normally distributed. A comparison of GMTs will be by t-test on means of log10 (titer). Significance will be set at $p < 0.025$ (1-sided) or $p < 0.05$ (2-sided). No formal adjustment for multiple

	comparisons is planned.
Data Documentation	Electronic/Paper Case Report Form and Subject Diary Card.

List of sites used in Phase 2 study

	Site Name	PI name
1	NIMS Hospital, Hyderabad, Telangana	Dr Prabhakar Reddy
2	PGIMS, Rohtak, Haryana	Dr Savita Verma
3	AIIMS, Patna	Dr C M Singh
4	Redkar Hospital, GOA	Dr Sagar Vivek Redkar
5	Gillukar Multispeciality Hospital, Nagpur	Dr Chandrasekhar Gillurkar
6	Prakhar Hospital, Kanpur	Dr Jitendra Kushwaha
7	SRM Hospital & Research center, Tamil Nadu	Dr Satyajit Mohapatra
8	AIIMS, New Delhi	Dr. Sanjay Rai

Table 1: Study Design chart

Phase 1 (Completed)	Test	placebo	Screening -7 to -1 days	Day 0	Day 8	Day 14	Day 28	Day 42	Day 104	Day 194
BBV152A	100	25	BS/Swab	BS/Vac	50 subset DSMB	BS/Vac	BS	BS	BS	BS
BBV152B	100	25	BS/Swab	BS/Vac		BS/Vac	BS	BS	BS	BS
BBV152C	100	25	BS/Swab	BS/Vac		BS/Vac	BS	BS	BS	BS
							DSMB			
DSMB review at Day 28 (Safety) and interim report to notify CDSCO – continue to Phase 2										
Phase 2			Screening -7 to -1 days	Day 0		Day 28	Day 42	Day 56	Day 118	Day 208
Arm 1	175		Sample	BS/Vac		BS/Vac	BS	BS	BS	BS
Arm 2	175		Sample	BS/Vac		BS/Vac	BS	BS	BS	BS
Day 42, 56 (Immunogenicity & Safety) interim report to notify CDSCO – continue to follow-up subjects										

Table 2: Study Flow Chart of Phase 1 study (Completed)

Parameters	Screening	Visit 1 (Baseline)	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	-7 to -1 days	Day 0	Day 14+2	Day 28±2	Day 42±2	Day 104±7	Day 194±7
Informed consent	✓						
Inclusion/ exclusion criteria	✓	✓					
Screening number	✓						
Demography	✓						
Current Health Status	✓	✓	✓	✓	✓	✓	✓
General & Systemic Examination	✓	✓	✓	✓	✓	✓	✓
COVID-19 Symptoms examination	✓	✓	✓	✓	✓	✓	✓
Vital signs	✓	✓	✓	✓	✓	✓	✓
Pregnancy test - Serum	✓						
Urine pregnancy test		✓	✓	✓	✓	✓	✓
Lab Investigations#	✓			✓			
HIV 1 & 2, HBs(Ag), HCV	✓						
COVID-19 screening	✓						
Randomization		✓					
Blood sample for Immunogenicity		✓	✓	✓	✓	✓	✓
Investigational vaccine administration		✓	✓				
Subject Diary distribution		✓	✓				
Concomitant medication		✓	✓	✓	✓	✓	
Adverse event recording		✓	✓	✓	✓	✓	✓
Telephonic follow-up		✓	✓				

#Laboratory Investigations include Hematology [Hb%, total and differential WBC, RBC count, Platelet count, Hematocrit, MCV, MCH, MCHC, RBS, Total Cholesterol, Renal Function Test (BUN, Creatinine), Liver Function Test (albumin, bilirubin, ALT, AST, alkaline phosphatase) and Urine analysis.

Table 3: Study Flow Chart of Phase 2 Study

Parameters	Screening	Visit 1 (Baseline)	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	-7 to -1 days	Day 0	Day 28+2	Day 42±2	Day 56±2	Day 118±7	Day 208±7
Informed consent	✓						
Inclusion/ exclusion criteria	✓	✓					
Screening number	✓						
Demography	✓						
Current Health Status	✓	✓	✓	✓	✓	✓	✓
General & Systemic Examination	✓	✓	✓	✓	✓	✓	✓
COVID-19 Symptoms examination		✓	✓	✓	✓	✓	✓
Vital signs	✓	✓	✓	✓	✓	✓	✓
Urine pregnancy test	✓	✓	✓	✓	✓	✓	✓
COVID-19 screening	✓						
Randomization		✓					
Blood sample for Immunogenicity		✓	✓	✓	✓	✓	✓
Investigational vaccine administration		✓	✓	✓			
Subject Diary distribution		✓	✓	✓			
Concomitant medication		✓	✓	✓	✓		
Adverse event recording		✓	✓	✓		✓	✓
Telephonic follow-up		✓	✓	✓			

Annexure 1:

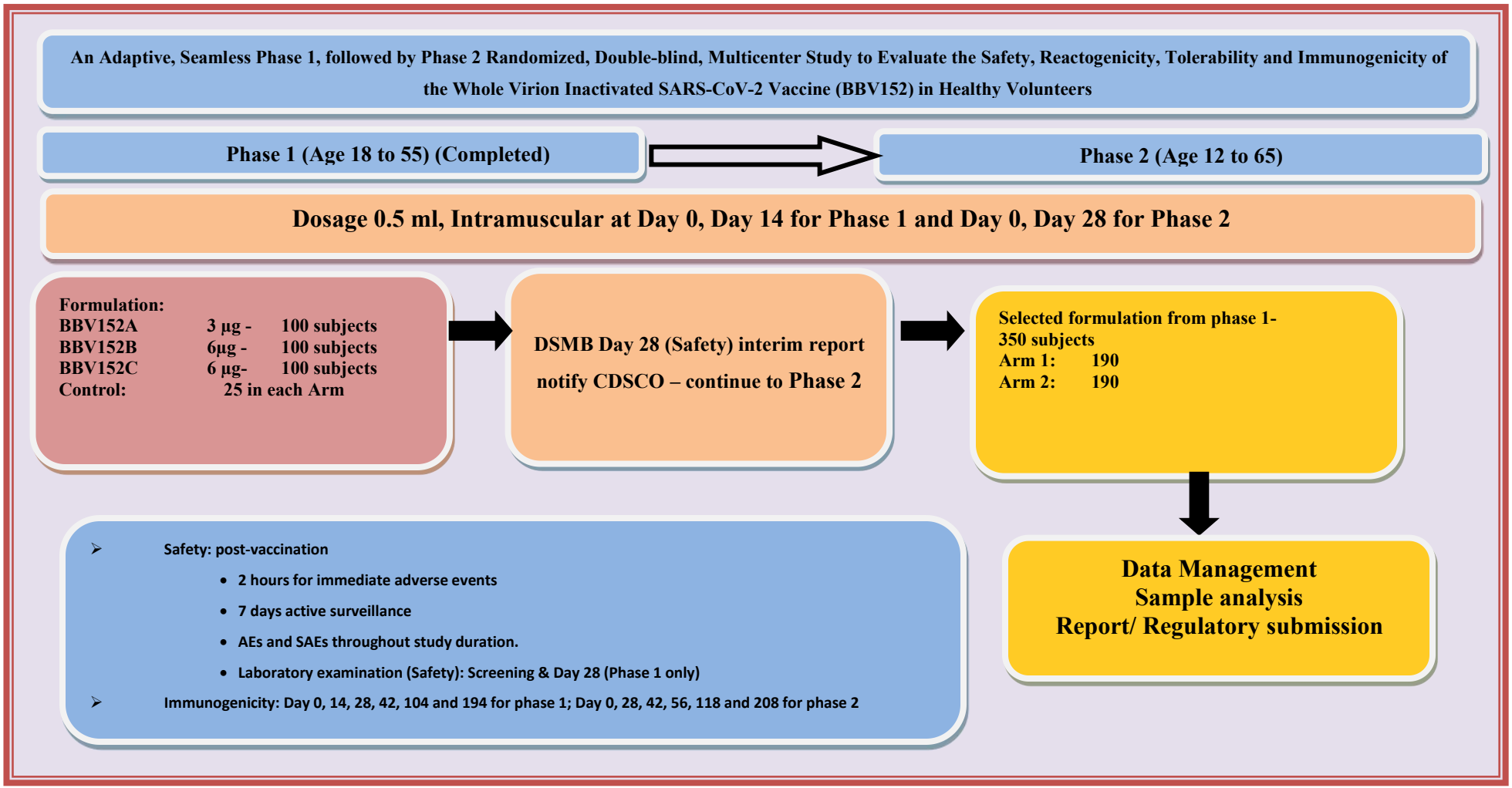

Figure 1: Schematic explanation of the study design

3. INTRODUCTION

The outburst of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2/COVID-19) has, as on May 3,2020, spread to over 210 countries across the Globe,with a total of ~3.5 Million confirmed cases and ~250,000 deaths. The number of reported SARS-CoV-2 cases in India is also on an increase with ~40,000 confirmed cases and 1300 deaths[14]. Corona viruses are severe threat to the humans and other animals, earlier other members of the same family coronaviridae, SARS-CoV infected ~8000 people with death rate of 10% and other member Middle East Respiratory Syndrome (MERS) virus was out-broken in Middle East region and infected ~2000 people with 35% fatality rate[15]. 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[15].

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[15]. SARS-CoV-2 virus transmits from person to person mainly through respiratory droplets[8].

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[16,17]. 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[18]. The symptoms of SARS-CoV-2 infection appear after an incubation period of ~5 days[19]. 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 status of the patient's immune system. It was shorter among patients >70 years old compared with those under the age of 70[20]. The most common symptoms at onset of SARS-CoV-2 illness are fever, cough, and fatigue, while other symptoms include sputum production, headache, haemoptysis, diarrhoea, dyspnoea, and lymphopenia[21,22]. Till date, no specific treatment was recommended for SARS-CoV-2 infection hence, there is a necessity to develop 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: Adeno virus) and traditional inactivated vaccines are under development[10,11,12,13].

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 severe disease that requires hospitalization and oxygen support, and 5% require admission to an intensive care unit (ICU). In severe cases, COVID-19 can be complicated by the acute respiratory distress syndrome, sepsis, septic shock and multiorgan failure with an estimated case fatality of 3.4% as of March 10, 2020[8,9].

The COVID-19 pandemic is rapidly worsening in all parts of the world, overwhelming health systems. There is a serious threat to densely populated country like India. Also, reports from all over the world demonstrate that the disease takes a severe course in the 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 population.

Till 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 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: Adeno virus) and traditional inactivated vaccines are under development [10,11,12,13]. A Chinese based vaccine manufacturing company (Sinovac Biotech Ltd.) has developed an inactivated vaccine formulation against SARS-CoV-2 virus and proved its safety and immunogenicity in animals such as mice, rats and non-primate mammal, *Rhesus macacque* monkeys[13].

The COVID-19 pandemic is rapidly worsening in all parts of the world, overwhelming health systems. It is important to generate clinically relevant information on the immune responses and safety. In conventional of clinical trials (in routine schedule), usually, 3 to 4 weeks intervals are maintained between two vaccine

doses. However, based on the following 14 day interval dosing schedules; 1. Bharat Biotech pre-clinical data, 2. Another whole-virion inactivated Chinese (PicoVacc™) from the manufacturer Sinovac Biotech Ltd. (NCT04352608), Bharat Biotech is making an informed decision on selecting the 14 day interval dosing schedule. This dosing schedule will not compromise the immunogenicity profile and safety of the vaccine.

Rationale for Parallel Toxicology studies:

Developing a vaccine quickly requires a new pandemic paradigm, with a fast start and many steps executed in parallel before confirming a successful outcome of another step. For example, for platforms with experience in humans, phase 1 clinical trials may be able to proceed in parallel with testing in animal models. Bharat Biotech has developed various inactivated vaccines such as JENVAC®, INDIRAB®, Chikungunya vaccine and Zikavirus vaccine. Bharat Biotech has conducted clinical trials with these vaccine formulations and found that vaccines are safe and immunogenic[1,2]

In such pandemic situations, it is anticipated that few or no preclinical and nonclinical data would be available. If the risk-benefit evaluation warrants such action, countries should be prepared to accept vaccines without these data[3,4].
However Bharat biotech is trying to complete as many as toxicology studies as possible.

Study Purpose:

The purpose of this study is to evaluate the safety, reactogenicity, tolerability, and immunogenicity of the whole virion inactivated SARS-CoV-2 vaccine, BBV152.

In this study, we will use three formulations of BBV152 vaccine for the intramuscular route of administration.

This study will be conducted in a dose escalatory manner with a two-dose regimen fourteen days apart in Phase 1 and selected formulations will be further evaluated in Phase 2 study with routine dosage schedule on day 0 and day 28.

5. RISK/BENEFIT ASSESSMENT

This study involves administration of two doses of BBV152 vaccine with adjuvant in 12 to 65 years age group healthy volunteers. Safety of these vaccine formulations will be evaluated in healthy subjects. The strain was obtained from the National Institute of Virology (NIV), Pune, India to develop the vaccine. The seed virus was grown in VERO cell culture by means of standard processes. Vaccination against BBV152

virus is an important public health measure to help protect against the morbidity and mortality associated with the virus.

6. STUDY OBJECTIVES

Phase 1 (Completed):

- To evaluate the safety, reactogenicity, tolerability, and immunogenicity of two doses of the two-sequentially escalating Groups [3 µg and 6 µg per single human dose (SHD) of 0.5 mL] of BBV152 (whole-virion inactivated SARS-CoV-2 virus) vaccine formulation BBV152A, BBV152B, and BBV152C, administered via the intramuscular route.

Phase 2:

- To evaluate the safety and immunogenicity of selected formulations (BBV152-A and BBV152-B).

7. STUDY ENDPOINTS

Phase 1 (Completed):

Primary

1. The occurrence of immediate adverse events within two hours of vaccination [Time Frame: 2 hours].
2. The occurrence of adverse events within seven days of vaccination [Time Frame: 7 days].
3. The occurrence of any adverse events throughout the study duration [Time Frame: throughout the study duration].
4. The occurrence of serious adverse events (SAEs) [Time Frame: throughout the study duration].

Secondary

1. To evaluate the immunogenicity in terms of GMT and four-fold seroconversion rate of neutralizing antibodies (NAb's) across the three formulations of BBV152 in comparison with placebo arm, from baseline to days 14, 28, 42, 104 and 194.

Phase 2:

Primary

1. To evaluate the immunogenicity in terms of GMT and four-fold seroconversion rate of NAbs specific to SARS-CoV-2 virus in subjects administered with the selected BBV152-A and BBV152-B vaccine formulation from baseline to days 28+2,42±2,56±2 118±7 and 208±7, in two arms.

Secondary

1. The occurrence of immediate adverse events within two hours of vaccination [Time Frame: 2 hours].
2. The occurrence of adverse events within seven days of vaccination [Time Frame: 7 days].

3. The occurrence of any adverse events throughout the study duration [Time Frame: throughout the study duration].
4. The occurrence of serious adverse events (SAEs) [Time Frame: throughout the study duration].

Exploratory end points

1. Immunogenicity indexes of IgG antibody for RBD and Spike proteins.
2. Immunogenicity indexes of specific cellular immune responses [Such as, Lymphocyte subset percent (CD3+, CD4+, and CD8+), Key cytokines (TNF-α, IFN-γ, IL-2, IL-4, IL-5, IL-6)].
3. Evaluate the Number of virologically confirmed symptomatic cases of COVID-19 (definition of a symptomatic case of COVID-19 would consist of fever + Positive confirmation of COVID-19) among all the groups.
4. Antibody-Dependent Enhancement (ADE), if any, will be evaluated.

8. STUDY DESIGN

This is an adaptive, seamless phase 1 to be followed by phase 2 randomized, double-blind, multicenter study to evaluate the safety, reactogenicity, tolerability and immunogenicity of the Whole-Virion Inactivated SARS-CoV-2 vaccine (BBV152) in healthy volunteers.

Phase 1 Study (Completed):

The study is designed to evaluate the safety, reactogenicity, tolerability, and immunogenicity of Four arms of healthy volunteers who receive two intramuscular doses of BBV152 vaccine formulations or Placebo. A total no of 375 subjects will be enrolled in 4:1 ratio

Arm 1: A total of 100 subjects will be enrolled in this arm and will receive two intramuscular doses of BBV152A . The two doses will be administered 14 days apart.

Upon completion of 7 days of post-vaccination of the 50 participants in Arm 1 (either test or placebo), the Data Safety Monitoring Board (DSMB) will review all the available data, and recommend progression towards the next arms. Thereafter, participants will be further enrolled into the higher dose arms (Arm 2, 3), with the continuation of the remaining participants of Arm 1.

Arm 2: A total of 100 subjects will be enrolled in this arm and will receive two intramuscular doses of BBV152B . The two doses will be administered 14 days apart.

Arm 3: A total of 100 subjects will be enrolled in this arm and will receive two intramuscular doses of BBV152C. The two doses will be administered 14 days apart.

Arm 4: A total of 75 subjects will be enrolled in this arm and will receive two intramuscular doses of Placebo. The two doses will be administered 14 days apart

After completion of 14 days post 2nd dose vaccination (Day 28), immunogenicity & safety in arms 1, 2, 3 and 4 will be reviewed by Data Safety Monitoring Board (DSMB) and recommend the progression towards the next Phase of the trial.

An interim report based on the safety and immunogenicity of the three formulation from Arm 1, Arm 2, Arm 3 and Arm 4 will be notified to the Central Drugs Standard Control Organisation (CDSCO), India, for further progressing the clinical development of the vaccine. This interim report will contain a detailed analysis of the data based on the primary and secondary objectives of all visits through Day 28 (Immunogenicity & Safety).

The ultimate goal is the selection of a safe, well-tolerated, and immunogenic intramuscular vaccine, which will be further evaluated in the phase 2 study.

Phase 2 study

The study is designed to evaluate the safety, reactogenicity, tolerability, and immunogenicity of three arms of healthy volunteers who receive two intramuscular doses of BBV152 vaccine formulations (BBV152-A & BBV152-B) selected from phase 1 study will be administered in 1:1 ratio.

Arm 1: A total of 171 subjects will be enrolled in this arm 1 and will receive two intramuscular doses of BBV152-A vaccine. The two doses will be administered 28 days apart.

Arm 2: A total of 171 subjects will be enrolled in this arm and will receive two intramuscular doses of BBV152-B vaccine. The two doses will be administered 28 days apart.
Data will be unblinded and an interim analysis will be performed at day 42 & 56 for Immunogenicity and safety

9. SUBJECT ELIGIBILITY

9.1 PHASE 1 (COMPLETED):

Inclusion

1. Ability to provide written informed consent (Audio video consent for vulnerable subjects).
2. Participants of either gender of age between ≥18 to ≤55 years.

3. Good general health as determined by the discretion of investigator (vital signs (heart rate ≥60 to≤100 bpm; blood pressure systolic ≥90 mm Hg and <140 mm Hg; diastolic ≥ 60 mm Hg and <90 mm Hg; oral temperature <100.4ºF), medical history, and physical examination).
4. Expressed interest and availability to fulfill the study requirements.
5. 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 four weeks after the last vaccination
6. Male subjects of reproductive potential: Use of condoms to ensure effective contraception with the female partner from first vaccination until 3 months after last vaccination
7. Male subjects agree to refrain from sperm donation from the time of first vaccination until 3 months after last vaccination
8. Participants must refrain from blood or plasma donation from the time of first vaccination until 3 months after last vaccination
9. Agrees not to participate in another clinical trial at any time during the study period.
10. Agrees to remain in the study area for the entire duration of the study.
11. Willing to allow storage and future use of biological samples for future research.

Exclusion

1. History of any other COVID-19 investigational vaccination.
2. Unacceptable laboratory abnormality from screening (prior to first vaccination) or safety testing, as listed below.

[Abnormal Complete Blood Count (CBC), Random blood sugar level, Renal function test (serum urea and Creatinine), liver function tests, urine analysis report, Positive serology for hepatitis C or HIV antibody or hepatitis B surface antigen].

(*Subjects will be informed if their results are positive for hepatitis C, HIV 1 & 2 antibody or hepatitis B surface antigen (HBsAg) and will be referred to a primary care provider for follow up of these abnormal laboratory tests*.)

3. Confirmed SARS-CoV-2 at the time of screening using RT-PCR and/or ELISA method.

4. Health care workers

5. For women, a positive serum pregnancy test (during screening within 45 days of enrolment) or positive urine pregnancy test (within 24 hours of administering each dose of vaccine).
6. 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.

7. Medical problems as a result of alcohol or illicit drug use during the past 12 months.
8. Receipt of an experimental agent (vaccine, drug, device, etc.) within 60 days before enrollment or expects to receive an investigational agent during the study period.
9. Receipt of any licensed vaccine within four weeks before enrolment in this study.
10. Known sensitivity to any ingredient of the study vaccines, or a more severe allergic reaction and history of allergies in the past.
11. Receipt of immunoglobulin or other blood products within the three months prior to vaccination in this study.
12. 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.
13. Long-term use (> 2 weeks) of oral or parenteral steroids (glucocorticoids) or high-dose inhaled steroids (>800 mcg/day of beclomethasone dipropionate or equivalent) within the preceding 6sixmonths (nasal and topical steroids are allowed).
14. Any history of hereditary angioedema or idiopathic angioedema.
15. Any history of anaphylaxis in relation to vaccination.
16. Any history of albumin-intolerance.
17. Pregnancy, lactation, or willingness/intention to become pregnant during the study.
18. History of any cancer.
19. History of psychiatric severe conditions likely to affect participation in the study.
20. A bleeding disorder (e.g. factor deficiency, coagulopathy or platelet disorder, or prior history of significant bleeding or bruising following IM injections or venepuncture.
21. Any other serious chronic illness requiring hospital specialist supervision.
22. Chronic respiratory diseases like severe acute respiratory syndrome (SARS), including mild asthma.
23. Chronic cardiovascular disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder, and neurological illness
24. Morbidly obese (BMI≥35 kg/m2) or underweight (BMI ≤18 kg/m2).
25. Living in the same household of any COVID-19 positive person.
26. Any other condition that in the opinion of the investigator would jeopardize the safety or rights of a volunteer participating in the trial or would render the subject unable to comply with the protocol.

Re-Vaccination Exclusion Criteria

27. Pregnancy.
28. Anaphylactic reaction following administration of the investigational vaccine.
29. Virologically confirmed cases of COVID-19

9.2 PHASE 2:

Inclusion

1. Ability to provide written informed consent (Audio video consent for vulnerable subjects).
2. Participants of either gender of age between ≥12 to ≤ 65 years.
3. Good general health as determined by the discretion of investigator (vital signs (heart rate ≥60 to≤100 bpm; blood pressure systolic ≥90 mm Hg and <140 mm Hg; diastolic ≥ 60 mm Hg and <90 mm Hg; oral temperature <100.4ºF), medical history, and physical examination).
4. Expressed interest and availability to fulfill the study requirements.
5. For a female participant of child-bearing potential, avoid becoming pregnant (use of an effective method of contraception or abstinence) from the time of study enrolment until at least four weeks after the last vaccination and agrees not to participate in another clinical trial at any time during the study period.
6. Male subjects of reproductive potential: Use of condoms to ensure effective contraception with the female partner from first vaccination until 3 months after last vaccination
7. Male subjects agree to refrain from sperm donation from the time of first vaccination until 3 months after last vaccination
8. Participants must refrain from blood or plasma donation from the time of first vaccination until 3 months after last vaccination.
9. Agrees to remain in the study area for the entire duration of the study.
10. Willing to allow storage and future use of biological samples for future research.

Exclusion

1. History of any other COVID-19 investigational vaccination.
2. Confirmed SARS-CoV-2 at the time of screening using RT-PCR and /or ELISA method.
3. Health care workers
4. Positive urine pregnancy test (within 24 hours of administering each dose of vaccine).
5. 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.
6. Medical problems as a result of alcohol or illicit drug use during the past 12 months.
7. Receipt of an experimental agent (vaccine, drug, device, etc.) within 60 days before enrolment or expects to receive an investigational agent during the study period.
8. Receipt of any licensed vaccine within four weeks before enrolment in this study.
9. Known sensitivity to any ingredient of the study vaccines, or a more severe allergic reaction and history of allergies in the past.

10. Receipt of immunoglobulin or other blood products within the three months prior to vaccination in this study.
11. 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.
12. Long-term use (> 2 weeks) of oral or parenteral steroids (glucocorticoids) or high-dose inhaled steroids (>800 mcg/day of beclomethasone dipropionate or equivalent) within the preceding 6sixmonths (nasal and topical steroids are allowed).
13. Any history of hereditary angioedema or idiopathic angioedema.
14. Any history of anaphylaxis in relation to vaccination.
15. Any history of albumin-intolerance.
16. Pregnancy, lactation, or willingness/intention to become pregnant during the study.
17. History of any cancer.
18. History of psychiatric severe conditions likely to affect participation in the study.
19. A bleeding disorder (e.g. factor deficiency, coagulopathy or platelet disorder, or prior history of significant bleeding or bruising following IM injections or venepuncture.
20. Any other serious chronic illness requiring hospital specialist supervision.
21. Chronic respiratory diseases like severe acute respiratory syndrome (SARS), including mild asthma.
22. Chronic cardiovascular disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder, and neurological illness
23. Morbidly obese (BMI≥35 kg/m2) or underweight (BMI ≤18 kg/m2).
24. Living in the same household of any COVID-19 positive person.
25. Any other condition that in the opinion of the investigator would jeopardize the safety or rights of a volunteer participating in the trial or would render the subject unable to comply with the protocol.

Re-Vaccination Exclusion Criteria

26. Pregnancy.
27. Anaphylactic reaction following administration of the investigational vaccine.
28. Virologically confirmed COVID-19.

10. STUDY PROCEDURES

Phase 1 (Completed):

Screening (-7 Day to -1 Day)

All participants will been screened as per the eligibility criteria after consenting to participate in the study.

All participants will be screened for clinical laboratory safety (haematology, biochemistry, serology, COVID-19 by using RT-PCR and ELISA method) and eligible subjects will be enrolled.

Visit 1: Baseline (Day 0)

If eligible, study participants will attend the OPD for physical, general examination, and specific symptoms for COVID-19. When no clinically significant abnormalities are detected, blood samples will be withdrawn prior to vaccination. A study vaccine/placebo will be administered. Following vaccination, participants will remain at the study site for at least 2 hours of observation to record any adverse event.

Day 1-7: The study participants will be telephonically followed up by the site for the first seven days post-vaccination to know their current health status.

Visit 2: (Day 14+2)

Study participants will return to the OPD for physical, general examination, and specific symptoms for COVID-19. Blood samples will be withdrawn prior to vaccination for immunogenicity test. A study vaccine/placebo will be administered. Following vaccination, participants will remain at the study site for at least 2 hours of observation to record any adverse event.

Phase 1: Day 15-21; The study participants will be telephonically followed up by the site or first seven days post-vaccination to know their current health status.

Visit 3: (Day 28±2)

Study participants will return to the OPD for physical, general examination, and specific symptoms for COVID-19 and laboratory investigation. Blood samples will be withdrawn to assess clinical laboratory safety and immunogenicity for inactivated (COVID-19) vaccine.

Visit 4: (Day 42±2)

Study participants will return to the OPD for physical, general examination, and specific symptoms for COVID-19 and laboratory investigation. Blood samples will be withdrawn to assess immunogenicity for inactivated (COVID-19) vaccine.

Visit 5: (Day 104±7)

Study participants will return to the OPD for physical, general examination, and specific symptoms for COVID-19. Blood samples will be withdrawn on to assess immunogenicity for inactivated (COVID-19) vaccine.

Visit 6: (Day 194±7)

Study participants will return to the OPD for physical, general examination and specific symptoms for COVID-19. Blood samples will be withdrawn on to assess immunogenicity for inactivated (COVID-19) vaccine.

Detailed information can be found in Table 1.

Safety Monitoring:

- Subjects will be observed for two hours after vaccination for immediate adverse events
- Active surveillance will be conducted for all participants for seven days after each dose of vaccine to ascertain information on solicited adverse events ("Reactogenicity")

Unscheduled visits:

If any subject develops fever or is concerned about his/her health, they 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.

Phase 2:

Screening (-7 Day to -1 Day)

All participants will been screened as per the eligibility criteria after consenting to participate in the study.

All subjects will be diagnose on Day -7 to Day 0 from base line for COVID-19 by using RT-PCR and ELISA method, and eligible subjects will be enrolled.

Visit 1: Baseline (Day 0)

If eligible, study participants will attend the OPD for physical, general examination, and specific symptoms for COVID-19. When no clinically significant abnormalities are detected, blood samples will be withdrawn prior to vaccination. A study vaccine/placebo will be administered. Following vaccination, participants will remain at the study site for at least 2 hours of observation to record any adverse event.

Day 1-7: The study participants will be telephonically followed up by the site for the first seven days post-vaccination to know their current health status.

Visit 2: (Day 28+2)

Study participants will return to the OPD for physical, general examination, and specific symptoms for COVID-19. Blood samples will be withdrawn prior to vaccination for immunogenicity test. A study vaccine/placebo will be administered. Following vaccination, participants will remain at the study site for at least 2 hours of observation to record any adverse event.

Phase 1: Day 29-36; The study participants will be telephonically followed up by the site or first seven days post-vaccination to know their current health status.

Visit 3: (Day 42+2)

Study participants will return to the OPD for physical, general examination, and specific symptoms for COVID-19 and laboratory investigation. Blood samples will be withdrawn to assess clinical laboratory safety and immunogenicity for inactivated (COVID-19) vaccine.

Visit 4: (Day 56±2)

Study participants will return to the OPD for physical, general examination, and specific symptoms for COVID-19 and laboratory investigation. Blood samples will be withdrawn to assess immunogenicity for inactivated (COVID-19) vaccine.

Visit 5: (Day 118±7)

Study participants will return to the OPD for physical, general examination, and specific symptoms for COVID-19. Blood samples will be withdrawn on to assess immunogenicity for inactivated (COVID-19) vaccine.

Visit 6: (Day 208±7)

Study participants will return to the OPD for physical, general examination and specific symptoms for COVID-19. Blood samples will be withdrawn on to assess immunogenicity for inactivated (COVID-19) vaccine.

Detailed information can be found in Table 2.

Safety Monitoring:

- Subjects will be observed for two hours after vaccination for immediate adverse events
- Active surveillance will be conducted for all participants for seven days after each dose of vaccine to ascertain information on solicited adverse events (“Reactogenicity”)

Unscheduled visits:

If any subject develops fever or is concerned about his/her health, they 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.

11. 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 Institutional Ethics Committee (IEC) 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 Sponsor, IEC and/or regulatory authority.

12. EARLY DISCONTINUATION FROM OF THE STUDY

Failure of subject to comply with 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 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 is encouraged to complete 3rd month visit assessments.

13. 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 till the end of study period. 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. Subject is considered lost to follow up only after 3 documented attempts to contact have been made.

14. MONITORING SUBJECT COMPLIANCE

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

15. INVESTIGATIONAL VACCINE (INV)

15.1 STUDY VACCINES

- Whole Virion Inactivated SARS-CoV-2 vaccine (BBV152) with three formulations, BBV152A, BBV152B and BBV152C. Either of these three formulations will be administered as intramuscular injection.

Active Ingredient	**Quantity**		
Whole Virion, Inactivated Corona Virus Antigen (Strain: NIV-2020-770)	**BBV152A**	**BBV152B**	**BBV152C**
	3 mcg	6 mcg	6mcg
Inactive Ingredients			
Aluminium Hydroxide Gel equivalent to Al^{+++}	250 mcg	250 mcg	250 mcg

TLR7/8 Agonist	15 mcg	15 mcg	----
2-Phenoxyethanol (2PE) I.P.	2.5 mg	2.5 mg	2.5 mg
Phosphate Buffered Saline	q.s. to 0.5 mL	q.s. to 0.5 mL	q.s. to 0.5 mL

15.2 Dosage form and route of administration

- COVID-19 Vaccine: Is a liquid 0.5 mL vero cell derived inactivated vaccine containing NLT 3µg/6µg and administered as a single dose intramuscularly (IM).

15.3 Dose regimen

- COVID-19 Vaccine: It is administered as two dose on Day 0 and Day 14 for phase 1 and Day 0 and Day 28 for phase 2.

15.4 Packaging

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

15.5 Labelling

The label of the INV will also state the following:

- Protocol Number
- Name of the institution or study centre
- Manufacturer's name, address and telephone number
- Screening number
- Batch/Lot number
- Date of manufacture
- Content
- Dosage
- Date of expiry
- 'To be stored at +2°C and +8°C'
- 'Vaccine for Clinical Trial Use Only'

15.6 Supplies and Handling of Materials

All the study vaccines will be supplied by Bharat Biotech. 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 35°F and 46°F (2°C and 8°C). All discrepancies in shipment conditions, shipment receipt times, and condition of the vaccines must be reported to the sponsor.

15.7 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 a 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 sponsor of any damage or unusable study vaccines that were supplied to the Investigator's Site. The investigational vaccine will not be delivered to 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 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 sponsor. Appropriate cold chain will be maintained for all vaccines that would be used in the study.

15.8 DISPENSING STUDY VACCINE

Either the investigator or the designated staff should reconcile the investigational vaccines at 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/designee 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 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 Sponsor or its designee will perform INV accountability and reconciliation before INV are returned to Sponsor or its designee for destruction. The investigator will retain the original documentation regarding INV accountability log, and return, and copies will be sent to the sponsor.

15. 9 Return or Destruction of Investigational Vaccine

After the completion of the study or at the last patient last visit, there will be a final reconciliation of 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. List of INV (used and unused) returned to the sponsor will be documented in the study files.

16. MEDICATIONS DURING TRIAL PARTICIPATION

16.1 Drug Interactions

Chloroquines and Corticosteroids are known to depress antibody response.

Contraindications to subsequent doses of the study vaccines

- Anaphylaxis or other indications of 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

During the trial period all EPI and IAP vaccines can be administered as per the schedule and any other concomitant medication received by the subject will be recorded in the CRF.

Details of dose, dosage, date, and route of administration, 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.

16.2 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 products 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.

17. MANAGEMENT OF SPECIMENS

- 5 ml of blood sample will be collected on day 0 before vaccination and day 14, day 28, day 42, day 104 and day 194 to measure baseline and post-vaccination neutralizing antibodies.

17.2 SPECIMEN PREPARATION, HANDLING, STORAGE AND SHIPMENT

- Blood sample collection and specimen preparation should be per the site SOPs
- Serum sample will be divided into aliquots. One aliquots for immunogenicity testing and the other will be a backup.
- Serum samples should be labelled with Subject number/initials, Date & time of sample collection and study visit number.
- Hemolyzed specimens will not be accepted or tested
- Serum specimen should be kept frozen (-80°C) until shipped for testing.
- Ship frozen samples on dry ice.
- Shipping of specimens shall be done in accordance to 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 sponsor (BBIL) or designee.

18. STUDY ASSESSMENTS

18.1 IMMUNOGENICITY ASSESSMENT

1. Neutralization antibody titer of COVID-19 virus will be assessed by the micro-neutralization assay and evaluate the immunogenicity in terms of four fold seroconversion rateand GMT across the two dose strengths of BBV152 (3µg and 6µg) with BBV152A, BBV152B formulation and BBV152C in comparison with placebo group, from baseline to days 14, 28, 42, 104 and 194.

18.2 SAFETY ASSESSMENTS

1. Immediate Adverse Events (IAE) - All subjects will be kept under observation at the study clinic for a period of 2 hours after administration of each vaccine, for any immediate adverse events occurring between the administrations of the vaccine till 2 hours after administration of the last vaccine.
2. Adverse Events post-vaccination (AE) - The study team will make daily telephonic enquiry for seven days after vaccination. During the enquiry, the subject will be asked for occurrence of any adverse events (including fever, local reaction, vomiting, diarrhea, cough, runny nose, irritability, and rash) 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 end of the study. All SAEs identified during the study will be followed till 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.

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.

19. ADVERSE EVENT MANAGEMENT

19.1 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 vaccine until completion of the followup are recorded in source document and inthe appropriate CRF pages. Information to be collected includes the nature, date and time of onset, intensity, duration, causality, action taken, and outcome of the event. Even if the AE is assessed by the investigator as not related to 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.

19.1 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.

19.2 POSSIBLE AE'S AND INTERACTIONS

Following AEs were reported in various clinical trials with cell cultured inactivated virus vaccine.
The most commonly reported events were injection-site pain and tenderness. Solicited local adverse events were graded as mild with no severe local adverse events reported. Of solicited systemic Adverse Events, the most commonly reported events were fever, headache, malaise, and myalgia. Of solicited systemic adverse events, the majority reported events that were mild to moderate in intensity and that resolved within 48 hrs with standard treatment.

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 lead 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.

19.3 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 means 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.

19.4 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 fulfils 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, diarrhoea, 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).

19.5 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:

- 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 subject from the study, additional concomitant drug treatment, or other therapy, and/or;
- Test result is considered to be an adverse event by the Investigator or sponsor
- If an abnormal laboratory value or assessment is clearly 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, subject will be tested with 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.

19.6 RECORDING OF ADVERSE EVENTS, ADVERSE DRUG REACTIONS AND SERIOUS ADVERSE EVENTS

All AEs occurring from administration of first dose of vaccination (day 0)to the follow-up contact must 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 inability to perform normal activities

Also Brighton 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.

19.7 RELATIONSHIP 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:

- Reaction of similar nature having previously been observed with this type of treatment
- The event having often been reported in literature for similar types of treatments
- The event being temporally associated with study drug administration or reproduced on re-administration.
- The relationship of an adverse event to INV should be classified as per the New clinical Trial Rules,2019. Causality assessment by investigator and the medical monitor of Sponsor/designee should clearly mention whether the AE's occurred is related or not related.

19.8 Outcome of AE and SAE

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.

19.9 Action Taken

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

19.10 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 in order 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.

19.11 Reporting of all Serious Adverse Events

All serious adverse event 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 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: Appendix -XI

1. Screening number
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 regulatory authorities in accordance with local regulatory requirements. Instances of death,cancer or congenital abnormalities in the offspring, if brought to the notice of the Investigator at any time after cessation of INV, must be reported to BBIL.Investigators will also follow-up subjects with serious adverse events occurring at any time following study vaccine administration until the event has disappeared or until the condition has stabilized.

All SAEs, whether related or not related to study vaccine, should be informed to the Central Licensing authority (CLA), IEC/IRB(s) and Sponsor within 24 hours by the Investigator. Sponsor should also submit the SAE report to regulatory authority with local regulatory requirements within the 14 calendar days (New Drugs & Clinical Trial Rules, 2019).

20. DATA SAFETY MONITORING BOARD (DSMB)

A DSMB will be constituted to include experts from the therapeutic area, statisticians, epidemiology amongst others. The DSMB will be responsible for safeguarding the interests of trial participants and assessing the safety of the interventions during the trial. This responsibility will be exercised by providing recommendations about stopping, continuing or modifying the clinical trial. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. Based on evaluation of safety data submitted, the Data Safety Monitoring Board will make a recommendation about stopping, continuing or changes in the study conduct. The DSMB will be advisory to Bharat Biotech International Ltd, Hyderabad through their Management. BBIL will be responsible for promptly reviewing the DSMB recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in study conduct are required. The DSMB will function in accordance with the principles of the following documents:

- Ethical Guidelines for Biomedical Research on Human Participants. Indian Council of Medical Research, New Delhi, 2017.
- Operational Guidelines for the Establishment and Functioning of Data and Safety Monitoring Boards. WHO / TDR, Geneva, 2005 (TDR / GEN / Guidelines / 05.1).
- Guideline on Data Monitoring Committees. European Medicines Agency, July 2005 (EMEA / CHMP / EWP / 5872 / 03 Corr).
- Guidance for Clinical Trial Sponsors: On the Establishment and Operation of Clinical Trial Data Monitoring Committees. US Department of Health and Human Services, 2006 (0910-0581).

Total of 750 subjects will be recruited in this study and all the DSMB meetings recommendation will be followed as showed in the Table 1.

21.STATISTICS

21.1 STATISTICAL ANALYSIS PLAN AND METHODS

Exact binomial calculation will be used for confidence interval estimation of seroconversion (SC) rates. Chi-square test or Fisher's exact test will be used to test differences in SC rates for different formulations of BBV152. Confidence interval estimation for geometric mean titer (GMT) will be based on log10 (titer) and the assumption that log10 (titer) is normally distributed. Comparison of GMTs will

be by t-test on means of log10 (titer). Significance will be set at $p < 0.025$ (1-sided) or $p < 0.05$ (2-sided). No formal adjustment for multiple comparisons is planned.

Power for Comparison for seroconversion (SC) rates			
α=0.05, two sided			
Sample size per formulation	SC rate formulation 1	SC rate formulation 2	Power
90	0.40	0.60	0.779
90	0.50	0.70	0.804
90	0.60	0.80	0.848
90	0.70	0.90	0.938
270	0.40	0.55	0.941
270	0.50	0.65	0.943
270	0.60	0.75	0.963
270	0.70	0.85	0.989
270	0.80	0.95	>99.9
270	0.40	0.50	0.653
270	0.50	0.60	0.653
270	0.60	0.70	0.689
270	0.70	0.80	0.771
270	0.75	0.85	0.834
270	0.80	0.90	0.911

Thus, in Phase 1 the power to find a significant difference between seroconversion rates will be at least 80% for an absolute difference of 20% if the lower underlying SC rate is at least 50%.In Phase 2 the power will be > 90% for an absolute difference of 15% if the lower SC rate is at least 40%, and > 80% for an absolute difference of 10% if the lower SC rate is at least 75%.

21.2 SAMPLE SIZE AND POWER

Assuming seroconversion rates are 85% for one BBV152-A and 95% for BBV152-B with a standard deviation of 0.5 for log10 titer. The required sample size for 90% power to find a significant difference (between vaccine formulations differing in GMT by a ratio of 2) in a trial with 1:1 allocation, using a two-sample z-test at the two-sided 5% significance level, is 171 per group. Assuming 10% loss during the study, the number becomes 190 per group.

A total sample size of 755 healthy volunteers, with 375 ages ≥18-≤55 in the phase 1 study (4:1 test vs placebo) and 380 ages ≥12-≤65 in phase 2 study (1:1 test groups). We assume immunogenicity data will be available for 90% of randomized study participants, resulting in sample sizes for analysis of 90 BBV152 recipients per formulation in Phase 1, and 171 per Arm 1 and Arm 2 in Phase 2.

22. 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 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 on site 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.

23.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, and frequency 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 study monitor will ensure 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 using the data clarification form.

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

Monitoring activities will be done in order to verify that the:

- Data are authentic, accurate, and complete
- Safety and rights of the subjects are being protected

- 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 allocate his/her time and the time of his/her staff to the study monitor to discuss findings and any relevant issues.

Protocol Deviation and Violation

A protocol violation is any failure to comply with the final study protocol as approved by the Ethics Committee. 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 violation and/or deviations must be reported to BBIL and Ethics Committee as soon as possible.

24. 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 given to, and 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.

24.1 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 scientific committee for approval.

The investigator will forward toBBIL, 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 alsokeepdocumentation of study approval by 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 5 years after the completion or formal discontinuation of the study and should be available to regulatory authorities on request.

25. 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 current 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.

26. 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.

27. DATA HANDLING AND RECORD KEEPING

27.1 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.

27.2 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.

27.3 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 at medico-technical departments involved in the clinical trial. At a 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, 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.

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

28. 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 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.

29. 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.

e.g. 6 **__xyz____**

20.07.13

Corrections due to spelling mistakes, errors in transcription, or difficulties in correctly completing the CRF do not routinely need to be justified. They will be explained if 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, 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 sponsor(BBIL). The second copy of 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 investigatorrequesting 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 is 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.

30. 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 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. Sponsor will inform the date for destruction of the study related documents appropriately.

31. FINANCE AND INSURANCE

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

32. PUBLICATION POLICY

In the event that this clinical research leads to patentable results, the investigator (or entity acting on his/her behalf according to local requirements) shall refrain from filing 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 for the purposes of carrying 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 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.

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