CLINICAL STUDY PROTOCOL

A Prospective, multicentre, Phase II Seamlessly Followed by Phase III Clinical Study to Evaluate the Immunogenicity and Safety of Biological E's CORBEVAX Vaccine for Protection Against COVID-19 Disease When Administered to COVID-19-Negative Adult Subjects.

Investigational product: Biological E's CORBEVAX Vaccine

Type of Study: Prospective, Interventional, Phase II seamlessly followed by a Phase-III

Protocol number: BECT/COVID-19-PHASE-III/069

Protocol Version: 2.1
Date of Protocol: 13 May 2021

Sponsor

Biological E. Limited,
18/1&3, Azamabad,
Hyderabad – 500020, Telangana, India.

Clinical Research Organization (CRO)
IQVIA RDS (India) Pvt. Ltd.
Omega Embassy Tech Square,
Marathahalli-Sarjapura Outer Ring Road, Kadubeesanahalli
Bangalore – 560103, Karnataka, India.

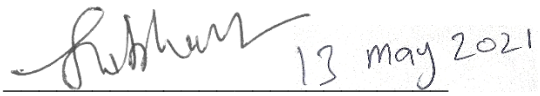
The study will be conducted according to the protocol and in compliance with the regulatory requirements in India [The New Drugs and Clinical Trials Rules 2019, Ministry of health and family welfare, Government of India; and National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, ICMR 2017], and applicable international guidelines [ICH GCP – E6 R2 and the Declaration of Helsinki October 2013].

SPONSOR SIGNATURE PAGE

Declaration by Sponsor or Responsible Medical Officer	
Protocol Number & Title:	BECT/COVID-19-PHASE-III/069 A Prospective, multicentre, Phase II Seamlessly Followed by Phase III Clinical Study to Evaluate the Immunogenicity and Safety of Biological E's CORBEVAX Vaccine for Protection Against COVID-19 Disease When Administered to COVID-19-Negative Adult Subjects.
Protocol Version & date:	Version 2.1 dated 13 May 2021

This study protocol was subjected to critical review. The information it contains is consistent with the current knowledge of risks and benefits of the study product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on GCP.

I have read this protocol and confirm that the procedure mentioned is in compliance with Good Clinical Practice (ICH E6 R2), Indian good clinical practice guidelines and The New Drugs and Clinical Trials Rules 2019 issued by the Central Drugs Standard Control Organization, Directorate General of Health Services, Government of India; and all other applicable rules and regulations in the country.



Signature & Date of Sponsor

Name: Dr. Subhash Thuluva
Designation: Vice President – Clinical Development
E-mail: Subhash.Thuluva@biologicale.com

INVESTIGATOR'S SIGNATURE PAGE

Protocol No: BECT/COVID-19-PHASE-III/069

Protocol Title: A Prospective, multicentre, Phase II Seamlessly Followed by Phase III Clinical Study to Evaluate the Immunogenicity and Safety of Biological E's CORBEVAX Vaccine for Protection Against COVID-19 Disease When Administered to COVID-19-Negative Adult Subjects.

Version & Date: Version 2.1 dated 13 May 2021

I, the undersigned, have read this protocol and agree with the content of this protocol and the confidential nature of the documentation made as part of this study.

I hereby agree to conduct the study in accordance with this protocol, within the time designated and in compliance with the principles of GCP guidelines issued by the Central Drugs Standard Control Organization, Directorate General of Health Services, Government of India; The New Drugs and Clinical Trials Rules 2019, and all other applicable rules and regulations in the country; as well as in compliance with ICH GCP (E6 R2) and the Declaration of Helsinki. I also agree to follow all the applicable standard operating procedures required for the conduct of this study.

The study will not be commenced without the prior written approval of a properly constituted IRB/IEC. No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB or IEC, except where necessary to eliminate an immediate hazard to the subjects.

I agree that the Sponsor or its representatives shall have access to any source documents from which case report form information may have been generated. I agree that regulatory authorities can audit and review source documents.

I agree to ensure that only coded study identifier(s) are associated with submitted study data, and that subject's personal identifying information (e.g. name, address, etc.) are not transmitted to the Data Coordinating Centre, Sponsor, or to other parties. When submitting data to the Data Coordinating Centre using the Internet-based Electronic Data Capture (EDC) system, the Principal Investigator and authorized study staff at this centre agree that their assigned username(s) and password(s) constitutes a digital signature that is required for authorized access to that system. Unauthorized access, including the use of this digital signature by another person, is prohibited. Each user is responsible for the transactions recorded by the system under their digital signature as if they had signed a document containing the same information using a traditional, handwritten signature. I understand that my digital signature (or that of a co-investigator) on eCRF indicates that the data therein has been reviewed and accepted by the signatory.

I further agree to ensure that all individuals assisting me in the conduct of this study are fully informed regarding their obligations.

I also acknowledge that the Sponsor of the study has the right to discontinue the study at any time.

Investigator's Name: _____

Investigator's Signature with Date: _____

Institute's Name: _____

STUDY ADMINISTRATIVE STRUCTURE

STUDY SPONSOR	**Biological E. Limited** 18/1 & 3, Azamabad, Hyderabad – 500020, Telangana. India. Phone: +91 40 30213999 Email: Subhash.Thuluva@biologicale.com
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CRO RESPONSIBLE FOR STUDY CONDUCT	**IQVIA RDS (India) Pvt. Ltd.** Omega Embassy Tech Square, Marathahalli-Sarjapura Outer Ring Road, Kadubeesanahalli Bangalore – 560103, Karnataka, India

STUDY MEDICAL MONITOR	**Dr. Arijit Sil** ***Associate Director, Medical*** IQVIA RDS (India) Pvt. Ltd. Omega Embassy Tech Square, Marathahalli-Sarjapura Outer Ring Road, Kadubeesanahalli Bangalore – 560103, Karnataka, India Phone: +91-7795658559 Email: Arijit.sil@quintiles.com
DATA MANAGEMENT AND BIOSTATISTICS	**Premier Research Group (India) Private Limited** Wework, 13th Floor, Salarpuria Magnificia No. 78, Doorvaninagar, Old Madras Road, Bengaluru, Karnataka – 560016, India
CENTRAL LABORATORY	Sponsor approved central laboratory.

Note:

Wherever “CORBEVAX” has appeared in the protocol, it should be read as Biological E’s SARS CoV-2 COVID-19 Vaccine (RBD subunit vaccine).

PROTOCOL SYNOPSIS

Title	A Prospective, multicentre, Phase II Seamlessly Followed by Phase III Clinical Study to Evaluate the Immunogenicity and Safety of Biological E's CORBEVAX Vaccine for Protection Against COVID-19 Disease When Administered to COVID-19-Negative Adult Subjects.
Protocol Number	BECT/COVID-19-PHASE-III/069
Study Phase	Phase II seamlessly followed by Phase-III
Study Objectives	**PHASE II** ***Primary Objective:*** • To assess the safety, tolerability and reactogenicity of two intramuscular doses of CORBEVAX vaccine in 18-55 years old (both inclusive) healthy adult males and non-pregnant female subjects. ***Secondary Objective:*** • To assess the immunogenicity of two intramuscular doses of SARS-CoV-2 COVID-19 vaccine, administered with a 28-day interval between doses, in 18-55 years old (both inclusive) healthy adult males and non-pregnant female subjects. **PHASE III** ***Primary Objective:*** • To assess the immunogenicity of two intramuscular doses of SARS-CoV-2 COVID-19 vaccine, administered with a 28-day interval between doses, in 18-80 years old (both inclusive) healthy adult males and non-pregnant female subjects. ***Secondary Objective:*** • To assess the safety, tolerability and reactogenicity of two intramuscular doses of CORBEVAX vaccine in 18-80 years old (both inclusive) healthy adult males and non-pregnant female subjects. ***Exploratory Objective:*** • Total IgG & neutralising antibodies at day 56 in a subset of subjects. • Persistence of both virus neutralising and IgG antibodies at 6 months and 12 months post 2nd dose. • Neutralising antibodies against UK, South Africa, Brazil, B.1.617 variants in a subset of population.

Study Endpoints	**PHASE II** ***Primary Endpoint:*** • Proportion of subjects with solicited adverse reactions/symptoms during first 60 minutes of post vaccination observation period and for subsequent 7 consecutive days (Day 0-6) captured through subject diary. • Proportion of subjects with unsolicited adverse events (AEs) during the subsequent 28-day follow-up period after each dose. • Serious adverse events (SAEs) and medically attended adverse events (MAAE) in all subjects at 6- and 12-months post 2nd dose. ***Secondary Endpoints:*** • Anti-RBD IgG concentrations (GMC, Fold Rise, GMFR) at baseline, day 28, 42 and 56 and at 6 and 12 months post second dose. • Anti-RBD IgG subclass assessment in terms of ratio of IgG1 to IgG4 titres at day 42 & day 56. • Neutralizing antibody titre (GMT, Fold Rise, GMFR) against SARS-CoV-2 (Pseudovirus or wild type) at baseline, day 28, 42, 56 and at 6 and 12 months post second dose. • Cell mediated immunity assessment in terms of cytokine expression from stimulated PBMCs (INF-γ, IL-4) at baseline and at day 42 (14 days' post-second dose) in a subset of subjects. **PHASE III** ***Primary Endpoint:*** • Anti-RBD IgG antibodies and subclass assessment in terms of ratio of IgG1 to IgG4 anti-RBD titres at day 42 and proportion of subjects with ≥4-fold rise in IgG1 anti-RBD antibody titres at day 42 vs baseline. • Neutralizing antibody titre against SARS-CoV-2 (Pseudovirus or wild type) at baseline and again at day 42. • Immunogenicity in terms of GMC/T of anti-RBD IgG antibodies and neutralizing antibodies at baseline and again at day 42.

	• Proportion of subjects seroconverted in terms of ≥2-fold & ≥4-fold rise in anti-RBD IgG antibodies and neutralizing antibodies by overall and by ≥4-fold rise in baseline seronegative subjects and ≥2-fold rise in baseline seropositive subjects along with their GMFR at day 42. • Cell mediated immunity assessment in terms of cytokine expression from stimulated PBMCs (INF-γ, IL-4) at baseline and at day 42 (14 days' post-second dose) in a subset of subjects. ***Secondary Endpoints:*** • Proportion of subjects with solicited adverse reactions/symptoms during first 60 minutes of post vaccination observation period and for subsequent 7 consecutive days (Day 0-6) captured through subject diary. • Proportion of subjects with unsolicited adverse events (AEs) during the 28-day follow up period after each dose. • Serious adverse events (SAEs), if any, during the entire study period. • Medically attended adverse events (MAAE), during the entire study period. • Safety follow-up visit for all subjects at 6- and 12-months post 2nd dose. ***Exploratory Endpoints:*** • Anti-RBD IgG concentrations & Neutralizing antibody titre (GMC, Fold Rise, GMFR) and Anti-RBD IgG subclass assessment in terms of ratio of IgG1 to IgG4 titres at day 56 in a subset of subjects. • Virus neutralising and IgG antibodies at 6 months and 12 months post 2nd dose in comparison with Day 42. • Neutralising antibodies against UK, South Africa, Brazil, B.1.617 variants in a subset of population at Day 42. <u>Definitions to be considered for this protocol:</u> • Seronegative (SN) is defined as subjects with no detectable VNT antibody (below the lower limit of detection [LLOD]) or no quantifiable antibody (below the lower limit of quantification [LLOQ]).

	• Seropositive (SP) is defined as subjects with detectable VNT antibody (above the lower limit of detection [LLOD]) or quantifiable antibody (above the lower limit of quantification [LLOQ]). • Seroconversion is defined as proportion of subjects achieving ≥4-fold rise in VNT antibodies in baseline seronegative subjects and ≥2-fold rise in baseline seropositive subjects. Note: In subjects with quantifiable VN antibody titre prior to vaccination, seroconversion is commonly predefined by a ≥2-fold-increase from pre- to post-vaccination as a measure of immunogenicity. Note: The neutralisation test is the standard method used to confirm the presence of neutralizing antibodies against SARS-CoV-2.
Study Design	This is a prospective, multicentre, phase II seamlessly followed by Phase III clinical study design to evaluate the immunogenicity and safety of CORBEVAX vaccine for protection against COVID-19 disease when administered to COVID-19 negative adult subjects ≥18 years of age. Adult males and females, from moderate to high-risk population, with and without comorbidities will be enrolled in both phases of the study. Subjects must be RT-PCR negative to SARS-CoV-2 from nasopharyngeal sample at the time of screening. A total of 100 subjects, aged 18 to 55 years, will be enrolled in Phase II for safety and immunogenicity assessment. The interim immunogenicity data will be submitted to CDSCO. After submission of the interim immunogenicity data to the CDSCO, the enrolment will commence into phase III part of the study. A total of 1168 subjects, aged 18 to 80 years, will be enrolled in Phase III part of the study.. Subjects will receive 0.5 mL dose of the test vaccine intramuscularly in a 2-dose schedule with 28 days' interval between doses. All subjects will be followed up 12-months post the second dose. **Independent DSMB Review:** An independent data safety monitoring board (DSMB) setup, will review cumulative day 56 Phase-III safety data (up to 28 days post 2nd dose) at visit-5, for all the enrolled

	subjects in this Phase-II seamlessly followed by Phase-III study.
Study Population	Male and female (non-pregnant) subjects aged 18-55 years at phase-II and 18-80 years at phase-III, who are RT-PCR negative to SARS-CoV-2 antigen from nasopharyngeal sample at the time of screening will be eligible for participation in this study. To be eligible for Phase II part, subject additionally should be seronegative to anti-SARS-CoV-2 antibody
Study Centres	The study will be conducted across approximately 15 centres in India.
Number of Subjects	The total sample size would be 1268 subjects of either gender • Phase II: 100 subjects, 18 to 55 years of age. • Phase-III: 1168 subjects, 18 to 80 years of age. o Subjects will be further age-stratified into 18 – 44 years, 45 – 64 years, and 65 – 80 years for data analysis purpose.
Study Duration	The duration of study participation for each subject is approximately 13 months in each of the phase (Phase II and Phase III) i.e. 3 days for Screening followed by 1 month for 2 dose administration, and follow-up till 12 months post second dose in each of the phases.
Subject Eligibility Criteria	*Subjects must meet ALL of the following inclusion criteria to be included in this study.* **Inclusion Criteria <u>ONLY</u> for Phase II:** 1. Male or female (non-pregnant) subject between ≥ 18 to 55 years of age. 2. Subject seronegative to anti-SARS-CoV-2 antibody prior to enrolment. **Inclusion Criteria <u>ONLY</u> for Phase III:** 1. Male or female subject between ≥ 18 to 80 years of age. **Inclusion Criteria for Phase II and Phase III:** 1. Subject or their legally acceptable representative (LAR) is willing to provide a written informed consent for voluntary participation in the study.

	2. Subject, in the opinion of the investigator, has ability to communicate and willingness to comply with the requirements of the protocol. 3. Subject is virologically seronegative to SARS-CoV-2 infection as confirmed by RT-PCR prior to enrolment. 4. Subject is seronegative to HIV 1 & 2, HBV and HCV infection prior to enrolment. 5. Subject is considered of stable health as judged by the investigator, determined by medical history and physical examination. 6. Female subject of child bearing potential must have a negative urine pregnancy test (UPT), and willingness to avoid becoming pregnant through use of an effective method of contraception or abstinence from the time of study enrolment until six weeks after the last dose of vaccination in the study. 7. Male subject, who is sexually active, must agree to use double-barrier contraception (e.g. condom with spermicide) with his female partner during the study period. Male subject should also agree to avoid semen donation or providing semen for in-vitro fertilization during the study duration. 8. Subject agrees not to participate in another clinical trial at any time during the total study period. 9. Subject agrees to refrain from blood donation during the course of the study. 10. Subject agrees to remain in the town where the study centre is located, for the entire duration of the study. **Exclusion criteria for Phase II and Phase III:** *Subjects who meet ANY of the following criteria will NOT BE ELIGIBLE for this study.* 1. History of vaccination with any investigational or approved vaccine against COVID-19 disease. 2. Subject living in the same household as that of any active COVID-19 positive individual at the time of enrolment. 3. History of receipt of any licensed vaccine within 1 month prior to screening, likely to impact on interpretation of the trial data (e.g., influenza vaccines); 4. Subjects with any clinically significant abnormal haematology and biochemical laboratory parameters tested at screening as judged by the investigator.

	5. Subjects with Body temperature of ≥100.4°F (>38.0°C) or symptoms of an acute illness at the time of screening or prior to vaccination. 6. Pregnant women, nursing women or women of childbearing potential who are not actively avoiding pregnancy during the study. 7. Subjects with known current or chronic history of any of the following conditions, likely to affect participation in the study: • severe psychiatric conditions; • any bleeding disorder (e.g. factor deficiency, coagulopathy or platelet disorder); • allergic disease or reactions likely to be exacerbated by any component of the study vaccine (BE CORBEVAX vaccine); • neurological illness, and any other serious chronic illness requiring hospital specialist supervision. 8. Subjects requiring chronic administration (defined as more than 14 days in total) of immunosuppressant (e.g. corticosteroids, cytotoxic drugs or antimetabolites, etc.) or other immune-modifying drugs (e.g. interferons) during the period starting six months prior to the first vaccine dose including use of any blood products. • For corticosteroids, this will mean prednisone ≥0.5 mg/kg/day, or equivalent. • Inhaled and topical steroids are allowed. • Receipt of prohibited concomitant medication that may jeopardize the safety of the participant or interpretation of the data. 9. Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required). 10. Any medical condition that in the judgment of the investigator would make study participation unsafe. 11. Planned use of any investigational or non-registered product other than the study vaccine during the trial period or 3 months prior to enrolment. 12. Current or planned participation in prophylactic drug trials for the duration of the study.

	13. Individuals who are part of the study team or close family members of individuals conducting the study.
Study Vaccine	**Phase II & Phase III: Single-arm trial at both phases.** The study Vaccine is: ***Biological E's CORBEVAX Vaccine***; manufactured and supplied by Biological E Ltd., Hyderabad, India. The study vaccine will be administered at a dose of 0.5 mL intramuscularly in a 2-dose schedule with 28 days' interval between doses.
Concomitant Medications	The list of contraindicated and permitted medications is applicable to both Phase II and Phase III of this study. ***Contraindicated***: • Glucocorticoids at a dose ≥ 20 mg/day of prednisone or equivalent given daily or on alternate days for ≥ 14 consecutive days during the study period. ○ *Note:* Inhaled topical, or localized injections of corticosteroids (e.g., intra-articular or intrabursal administration) are permitted. • Any other systemically administered drugs with significant immunosuppressive activity, such as azathioprine, tacrolimus, cyclosporine, methotrexate, or cytotoxic chemotherapy during the study period. • Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after each study vaccination. ***Permitted:*** • Participants may take concomitant medications prescribed by their primary care provider for management of chronic medical conditions and/or for health maintenance. • Primary care providers, or where appropriate investigators, should prescribe appropriate concomitant medications or treatments deemed necessary to

	provide full supportive care and comfort during the study.
	• Participants who develop COVID-19 after receiving study intervention should be treated with approved medications and interventions according to standard of care.
	  • Unless the subject withdraws consent; the subject does not need to be withdrawn, and can continue with safety follow up till 12 months.
	  • If the subject develops COVID-19 infection between 1st and 2nd dose, the 2nd dose will be deferred till 1 to 3 months' post recovery at the discretion of the Investigator.
	• Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are permitted.

Study Visits Schedule and Assessments	**Phase II:** Each subject will undergo a total of 7 study visits during the study period, as below: • VISIT 1 : Screening Baseline (Day -3 to -1) • VISIT 2: Study Vaccine Dose #1 (Day 0) • VISIT 3: Study Vaccine Dose #2 (Day 28) • VISIT 4: Follow-up – 14 days post 2nd dose (Day 42) • VISIT 5: Follow-up – 28 days post 2nd dose (Day 56) • VISIT 6: Follow-up – 6 months post 2nd dose (Day 208) • VISIT 7: Follow-up – 12 months post 2nd dose (Day 393) **Phase III:** Each subject will undergo a total of 7 study visits during the study period, as below: • VISIT 1 : Screening Baseline (Day -3 to -1) • VISIT 2: Study Vaccine Dose #1 (Day 0) • VISIT 3: Study Vaccine Dose #2 (Day 28)

	• VISIT 4: Follow-up – 14 days post 2nd dose (Day 42) • VISIT 5: Follow-up – 28 days post 2nd dose (Day 56) • VISIT 6: Follow-up – 6 months post 2nd dose (Day 208) • VISIT 7: Follow-up – 12 months post 2nd dose (Day 393) The assessments to be performed during the stipulated study visits are listed in the Schedule of Assessments Tables for Phase II and Phase III below.
Statistical Considerations	The sample size estimate is based on results from human trials using a similar protein subunit-based vaccine (Yang, 2021). To evaluate immunogenicity, the following hypotheses will be tested: • Seroconversion co-primary endpoint $H_0: \theta_{sc} - \mu_{sc} \leq \delta_{sc}$ $H_1: \theta_{sc} - \mu_{sc} > \delta_{sc}$ where: θ_{sc} = Estimated seroconversion rate in the cohort (assumed to be 71%), μ_{sc} = Population background seroconversion rate (assumed to be 15%), δ_{sc} = Superiority margin of 60% (based on human trials with similar vaccines), α = 0.025 (one-sided test for superiority), β = 90% power. A total sample size of 1268 is required (n=100 at Phase-II and n=1168 at Phase-III) for this endpoint, assuming a 10% drop-out rate. Based on this, the study will need to demonstrate that the peak seroconversion rate induced by vaccination is greater than 60% to be considered a success. All data will be summarised descriptively, by visit/time point where possible. Safety data will be summarised by System Organ Class and Preferred term. Serious adverse events will be summarised separately.

	In addition to the analysis for the primary endpoints, immunogenicity data will be analysed using generalised linear regression models for longitudinal data. Data will also be presented graphically, where applicable. All data will be listed. Interim Clinical study report will be generated on day 56 completion for all subjects enrolled. Updated Final clinical study report will be generated on completion of 12 months follow-up period.
Safety & Data Monitoring	Independent Ethics Committee/Institutional Review Board's (IEC/IRB's) approval will be sought at each participating centre, prior to the initiation of the study. The study will be conducted in accordance to the regulatory requirements in India [The New Drugs and Clinical Trials Rules 2019 by the Ministry of health and family welfare, Government of India; The Ethical guidelines for biomedical and health research involving human participants by ICMR (Indian Council of Medical Research (2017)], and international guidelines [ICH (International Conference on Harmonization) E6 (R2) 'Guideline for Good Clinical Practice' and [Declaration of Helsinki (October, 2013)]. The Sponsor designated CRO shall be responsible for the clinical monitoring of the trial-related activities.

SCHEDULE OF ASSESSMENTS

SCHEDULE OF ASSESSMENTS [PHASE II]							
VISIT	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**
DAY	**Day -3 to -1**	**Day 0**	**Day 28 (+4)**	**Day 42 (+4)**	**Day 56 (+4)**	**Day 208 (+14)**	**Day 393 (+14)**
Assessments and Time Points	**Screen baseline**	**Dose-1**	**Dose-2**	**Follow-up**	**Follow-up**	**Follow-up**	**Follow-up**
Signed Informed consent	●						
Allocate subject identification number (Screening number) and registration in IWRS	●						
Inclusion/exclusion criteria evaluation	●	●					
Collect demographic data	●						
Record vaccination history	●						
Record personal medical history	●						
History directed physical examination	●	●	●	●	●	●	●
Check contraindications and warnings and precautions before vaccination		●	●				
Record body temperature	●	●	●	●	●	●	●
Record other vital signs (Pulse, BP, Respiratory rate)	●	●	●	●	●	●	●
Measure/record height and weight	●						
Record any concomitant medications/vaccinations	●	●	●	●	●	●	●

SCHEDULE OF ASSESSMENTS [PHASE II]							
VISIT	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**
DAY	**Day -3 to -1**	**Day 0**	**Day 28 (+4)**	**Day 42 (+4)**	**Day 56 (+4)**	**Day 208 (+14)**	**Day 393 (+14)**
Assessments and Time Points	**Screen baseline**	**Dose-1**	**Dose-2**	**Follow-up**	**Follow-up**	**Follow-up**	**Follow-up**
Only baseline screening against HIV 1&2, HBV and HCV	●						
Urine Pregnancy test in females only	●		●				
Real time RT-PCR nasopharyngeal swab)	●						
Immunogenicity assessments							
Blood sample collection	● (20 ml)	● (10 ml)	● (10 ml)	● (20 ml)	● (20 ml)	● (10 ml)	● (10 ml)
Haematology & Biochemistry parameters	●				●		
Anti-SARS-CoV-2 IgG antibody estimation	●		●	●	●	●	●
Anti-SARS-CoV-2 IgG subclasses IgG1 & IgG4 estimation	●			●	●		
SARS-CoV-2 virus neutralising Antibody (NAb) estimation	●		●	●	●	●	●
Cellular immunity assessment via ELISPOT or TrueCulture method		●		●			
Vaccine administration (0.5mL IM; deltoid muscle)		●	●				
60 minutes post-vaccination observation		●	●				
Safety Assessments							

SCHEDULE OF ASSESSMENTS [PHASE II]							
VISIT	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**
DAY	**Day -3 to -1**	**Day 0**	**Day 28 (+4)**	**Day 42 (+4)**	**Day 56 (+4)**	**Day 208 (+14)**	**Day 393 (+14)**
Assessments and Time Points	**Screen baseline**	**Dose-1**	**Dose-2**	**Follow-up**	**Follow-up**	**Follow-up**	**Follow-up**
Distribution of diary		●	●				
Recording of solicited local and systemic AEs within 7 days post-vaccination after each dose		●	●	●			
Recording of unsolicited AEs		●	●	●	●		
Return of diary *Diary to be reviewed and re-distributed at Day 42 for recording of AE*s			●	●	●		
Recording of SAEs and medically attended AEs		●	●	●	●		
Safety follow up after Day 56 for any SAEs and medically attended AEs for 12 months post 2nd dose						●	●

SCHEDULE OF ASSESSMENTS [PHASE III]									
VISIT	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	*Interim Clinical Study Report*	**Visit 6**	**Visit 7**	*Clinical Study Report*
DAY	**Day -3 to -1**	**Day 0**	**Day 28 (+4)**	**Day 42 (+4)**	**Day 56 (+4)**		**Day 208 (+14)**	**Day 393 (+14)**	
Assessments and Time Points	**Screen baseline**	**Dose-1**	**Dose-2**	**Follow-up**	**Follow-up**	*v1.0*	**Follow-up**	**Follow-up**	*v2.0*
Signed Informed consent	●								
Allocate subject identification number (Screening number) and registration in IWRS	●								
Inclusion/exclusion criteria evaluation	●	●							
Collect demographic data	●								
Record vaccination history	●								
Record personal medical history	●								
History directed physical examination	●	●	●	●	●		●	●	
Check contraindications and warnings and precautions before vaccination		●	●						
Record body temperature	●	●	●	●	●		●	●	
Record other vital signs (Pulse, BP, Respiratory rate)	●	●	●	●	●		●	●	

SCHEDULE OF ASSESSMENTS [PHASE III]									
VISIT	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	*Interim Clinical Study Report*	**Visit 6**	**Visit 7**	*Clinical Study Report*
DAY	**Day -3 to -1**	**Day 0**	**Day 28 (+4)**	**Day 42 (+4)**	**Day 56 (+4)**		**Day 208 (+14)**	**Day 393 (+14)**	
Assessments and Time Points	**Screen baseline**	**Dose-1**	**Dose-2**	**Follow-up**	**Follow-up**	*v1.0*	**Follow-up**	**Follow-up**	*v2.0*
Measure/record height and weight	●								
Record any concomitant medications/vaccinations	●	●	●	●	●		●	●	
Only baseline screening against HIV 1&2, HBV and HCV	●								
Urine Pregnancy test in females only	●		●						
Real time RT-PCR nasopharyngeal swab)	●								
Immunogenicity assessments									
Blood sample collection	● (20 mL)	● (10 mL)		● (20 mL)	● (20 mL)		● (10 mL)	● (10 mL)	
Haematology & Biochemistry parameters	●				●				
Anti-SARS-CoV-2 IgG antibody estimation	●			●	●		●	●	

SCHEDULE OF ASSESSMENTS [PHASE III]									
VISIT	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	*Interim Clinical Study Report*	**Visit 6**	**Visit 7**	*Clinical Study Report*
DAY	**Day -3 to -1**	**Day 0**	**Day 28 (+4)**	**Day 42 (+4)**	**Day 56 (+4)**		**Day 208 (+14)**	**Day 393 (+14)**	
Assessments and Time Points	**Screen baseline**	**Dose-1**	**Dose-2**	**Follow-up**	**Follow-up**	*v1.0*	**Follow-up**	**Follow-up**	*v2.0*
Anti-SARS-CoV-2 IgG subclasses IgG1 & IgG4 estimation	●			●	●				
SARS-CoV-2 virus neutralising Antibody (NAb) estimation	●			●	●		●	●	
Cellular immunity assessment via ELISPOT or TrueCulture method		●		●					
Vaccine administration (0.5mL IM; deltoid muscle)		●	●						
60 minutes post-vaccination observation		●	●						
Safety Assessments									
Distribution of diary		●	●						
Recording of solicited local and systemic AEs within 7 days post-vaccination after each dose		●	●	●					
Recording of unsolicited AEs		●	●	●	●				

SCHEDULE OF ASSESSMENTS [PHASE III]									
VISIT	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	*Interim Clinical Study Report*	**Visit 6**	**Visit 7**	*Clinical Study Report*
DAY	**Day -3 to -1**	**Day 0**	**Day 28 (+4)**	**Day 42 (+4)**	**Day 56 (+4)**		**Day 208 (+14)**	**Day 393 (+14)**	
Assessments and Time Points	**Screen baseline**	**Dose-1**	**Dose-2**	**Follow-up**	**Follow-up**	*v1.0*	**Follow-up**	**Follow-up**	*v2.0*
Return of diary *- Diary to be reviewed and re-distributed at Day 42 for recording of AEs*			•	•	•				
Recording of SAEs and medically attended AEs		•	•	•	•				
Safety follow up after Day 56 for any SAEs and medically attended AEs for 12 months post 2nd dose							•	•	

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ABBREVIATIONS

-	Minus
+	Plus
®	Registered
%	Percentage
<	Less than
>	More than
≤	Equal to (or) less than
≥	Equal to (or) more than
±	Plus or minus
^{0}C	Degrees Celsius
^{0}F	Degrees Fahrenheit
µg	Microgram
ACE2	Angiotensin Converting Enzyme 2
ADE	Adverse Drug Event
ADL	Activities of Daily living
ADR	Adverse Drug Reaction
AE	Adverse Event
AEFI	Adverse Event Following Immunisation
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine aminotransferase
AP	Alkaline Phosphatase
AST	Aspartate aminotransferase
ATP	According to Protocol
BE	Biological E
BECT	Biological E Clinical Trials
BE LTD	Biological E. Limited
BP	Blood Pressure
bpm	Beats per minute
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CDC	Centre for Disease Control and Prevention
CDM	Clinical Data Management
cm	Centimetre
CND	Critical Neutralizing Domain
COVID	Coronavirus Disease
CSR	Clinical Study Report
CRF/eCRF	Case Report Form/Electronic Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DB	Direct Bilirubin
DAIDS	Division of AIDS
DCGI	Drug Controller General of India
'E'	Enrolment
GMFR	Geometric Mean Fold Rise
MERS	Middle East Respiratory Syndrome
ELISA	Enzyme-Linked Immunosorbent Assay
ENT	Ear, Nose & Throat
GCP	Good Clinical Practice
gm	Gram
GMT	Geometric Mean Titre
GMC	Geometric Mean Concentration
Hb	Haemoglobin
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HR1	Heptad repeats1
HR2	Heptad repeats2
ICF	Informed Consent Form
ICH	International Council on Harmonization
ICMR	Indian Council of Medical Research
i.e.	That is
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
INF- γ	Interferon-Gamma
IP	Investigational product
IRB	Institutional Review Boards
ITT	Intent-to-treat
IM	Intramuscular

IV	Intravenous
IWRS	Interactive Web Response System
KFT	Kidney Function Test
kg	Kilogram
LAR	Legally Acceptable Representative
LFT	Liver Function Test
LLOD	Lower Limit of Detection
LLOQ	Lower Limit of Quantitation
LTD	Limited
MAAE	Medically Attended Adverse Event
MedDRA	Medical Dictionary for Regulatory Activities
mL	Millilitre
MoH & FW	Ministry of Health and Family Welfare
n	Sub sample
N	Total sample
NAb	Neutralizing Antibody
NaCl	Sodium Chloride
PC	Platelet Count
PCV	Packed Cell Volume
PHEIC	Public health emergency of international concern
PI	Principal Investigator
PP	Per-Protocol
RBC	Red Blood Cell
RBD	Receptor Binding Domain
rpm	Revolutions per minute
RNA	Ribonucleic Acid
RT-PCR	Reverse Transcription polymerase Chain Reaction
'S'	Screening
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SARS-COV-2	Severe Acute Respiratory Syndrome Coronavirus2
SC	Serum Creatinine
SHD	Single Human Dose
SN	Sero Negative
SNT	Serum Neutralization Test
SOP	Standard Operating Procedure
SP	Sero Positive
TB	Total Bilirubin
TMF	Trial Master File
TRF	Test Requisition Form
UPT	Urine Pregnancy Test
VN	Virus Neutralisation
VNT	Virus Neutralisation (VN) Antibody Titer
VPI	Valid Professional Indemnity
WBC	White Blood Cell
WFI	Water for Injection
WHO	World Health Organization
WMA	World Medical Association

1. INTRODUCTION

The severe acute respiratory syndrome (SARS)–associated coronavirus (SARS-CoV2) first originated in Dec 2019 in China, causing symptoms in the respiratory system at different levels of severity; and causing the coronavirus disease (COVID-19). It was declared as a global pandemic by the World Health Organization (WHO) on 12th March 2020.

To date, there is no specific antiviral medicine to treat COVID-19, and hence, developing an effective and safe vaccine is urgently needed to prevent infection by SARS-CoV2-19. Research is undertaken by various pharma and academic institutes, globally as well as in India, to develop vaccines that can educate the immune system to defending itself from the virus. As a part of the global effort, Biological E. Ltd. has initiated research towards development of a novel protein RBD (receptor-binding domain) subunit vaccine targeting the spike antigen of the novel corona virus-2.

The objective of this clinical study is to evaluate the immunogenicity and safety of CORBEVAX vaccine when administered to COVID-19 negative subjects with 18 – 80 years of age. Detailed information of the study vaccine (CORBEVAX vaccine) is provided in the Investigator's Brochure.

1.1. Coronavirus Disease 2019 (COVID-19)

Coronavirus disease 2019 (COVID-19) is defined as illness caused by a novel coronavirus now called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; formerly called 2019-nCoV). Viruses of the Coronaviridae family have a positive-sense, single strand, RNA structure with 26 to 32 kilobases length. Coronaviruses have been recognized in numerous avian hosts and in several mammals, such as bats, camels, mice, cats, dogs and more recently in scaly anteaters.

Most of Coronaviruses are pathogenic to humans but they produce mild symptoms or asymptomatic infections. In December 2019, a new member of the Coronaviridae family associated with severe pneumonia was detected in Wuhan, City, Hubei Province, China [1].

It was initially reported to the WHO on December 31, 2019. On January 30, 2020, the WHO declared the COVID-19 outbreak a global health emergency [2, 3]. On March 11, 2020, the WHO declared COVID-19 a global pandemic, its first such designation since declaring H1N1 influenza a pandemic in 2009[4]. On February 11, 2020, the Coronavirus Study Group of the International Committee on Taxonomy of Viruses issued a statement announcing an official designation for the novel virus: severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [5, 6]. Illness caused by SARS-CoV-2 was termed COVID-19 by the WHO, the acronym derived from "coronavirus disease 2019" [7]. COVID-19 has been labelled as a public health emergency of international concern (PHEIC) [8] and the epidemic curves are still on the rise.

As of 12 Apr 2021, worldwide there were 136,660,675 infected worldwide, and the death toll at 2,950,158 across 221 countries and territories[9]. The first case of COVID-19 in India, which originated from China, was reported on 30 January 2020. As of 12 Apr 2021, the Ministry of Health and Family Welfare (MoH&FW) has confirmed a total

of 13,527,717 cases, of which 12,01,009 are active, 121,56,529 recoveries and 1,70,176 deaths in the country [9,10]. India currently has the largest number of confirmed cases in Asia, [9] and has the second highest number of confirmed cases in the world [9].

The cause of the COVID-19 pandemic is a novel and highly pathogenic coronavirus, termed SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2). SARS-CoV-2 is a member of the Coronaviridae family of viruses [11]. The genome of SARS-CoV-2 is similar to other coronaviruses, and is comprised of four key structural proteins: S, the spike protein, E, the envelope protein, M, the membrane protein, and N, the nucleocapsid protein[12]. Coronavirus spike proteins are class I fusion proteins and harbor an ectodomain, a transmembrane domain, and an intracellular tail [13,14]. The highly glycosylated ectodomain projects from the viral envelope surface and facilitates attachment and fusion with the host cell plasma membrane. The ectodomain can be further subdivided into host receptor-binding domain (RBD) (S1) and membrane-fusion (S2) subunits, which are produced upon proteolysis by host proteases at S1/S2 and S2' sites. S1 and S2 subunits remain associated after cleavage and assemble into crown-like homotrimers [12,14]. In humans, both SARS-CoV and SARS-CoV-2 spike proteins utilize the angiotensin-converting enzyme 2 (ACE2) protein as a receptor for cellular entry [15-17]. Spike protein subunits represent a key antigenic feature of coronavirus virions, and therefore represent an important target of vaccines, novel therapeutic antibodies, and small-molecule inhibitors [18,19].

1.2. Study Product [Test Vaccine]: About CORBEVAX Vaccine

Bio E's COVID-19 vaccine candidate is based on classical vaccine technology of a protein antigen, SARS-CoV-2 Spike RBD, adsorbed to the adjuvant Alhydrogel (Alum), in combination with another approved adjuvant, CpG 1018. The RBD of S1 subunit binds to the Angiotensin Converting Enzyme-2 (ACE2) receptor on host cell membrane and facilitates virus entry.

RBD protein is expressed in yeast Pichia pastoris, and is similar to technology Bio E is employing for large-scale commercial production of Hep B vaccines. The Baylor College of Medicine construct "RBD N1C1" was selected as the final vaccine antigen candidate on the basis of its manufacturability, due to the yields of protein antigen achieved, ease of process steps and favourable formulation aspects.

The combination of Alum with CpG with N1C1 antigen elicited a highly synergistic, balanced immune response in preclinical models. Potential advantages of this vaccine candidate include scalability and thermostability, which could make it suitable for deployment at scale in low-resource settings.

1.2.1. Preclinical Experience

<u>Single Dose Acute Toxicity Study of SARS-CoV-2 (COVID-19) Vaccine with AH+Co-Adjuvant in Sprague Dawley Rats by Intramuscular Route.</u>

The objective of this study was to determine the acute toxicity of the test item SARS-CoV-2 (COVID-19) Vaccine with AH+Co-adjuvant after single dose intramuscular administration to Sprague Dawley Rats. The study was conducted as per as per

sponsor driven protocol based on the requirement of New Drugs & Clinical Trial Rules, 2019 and WHO guidelines.

Animals were acclimatized for 5 days before the initiation of the treatment. A total of 30 male and 30 female Sprague Dawley rats were randomly divided into three (G1 to G3) groups. Each group comprised of 10 male and 10 female rats.

A 0.5 mL/animal (0.25 mL / site x 2 sites / animal) of Vehicle Placebo for SARS-CoV-2 (COVID-19) Vaccine with AH + Co-Adjuvant, AH+Co-Adjuvant Placebo and SARS-CoV-2 (COVID-19) Vaccine with AH + Co-Adjuvant was administered to group G1, G2 and G3 respectively (0.25 mL/site) in the left and right thigh muscles.

Post treatment, all animals were observed for cage side clinical signs once daily up to 15 days. Detailed clinical examination was performed outside the home cage for all animals on the last day of acclimatization and on day 7 and 14. Body weight was recorded on the day of receipt, prior to randomization, prior to initiation of dosing on day 1 and on day 3, 5, 8, 11 and 15.

All animals were sacrificed terminally on day 15. The sacrificed rats were subjected to detailed gross pathological examination. Injection sites from all the treatment groups were examined macroscopically and collected and preserved in 10 % neutral buffered formalin.

No morbidity or mortality was observed in any of the groups. No clinical signs or changes at injection sites in placebo (G1, G2) and test item (G3) treatment group were observed. No abnormality detected in Ophthalmological examination in all group animals.

No treatment related significant differences in the body weight, body weight gain and feed consumption were observed in test item treated group (G3) male and female when compared with placebo group (G1 and G2) male and female respectively. No treatment related significant differences in the body weight, body weight gain and feed consumption were observed in AH+Co-Adjuvant Placebo (G1) treated group male and female when compared with Vehicle Placebo for SARS-CoV-2 (COVID-19) Vaccine with AH + Co-Adjuvant (G2) male and female respectively.

From day 1 to 15, percentage increase in body weight was observed 36.07 % in test item treated group (G3), as compared to 34.45 % and 36.27 % in the placebo group G1 and G2 respectively in male rats. In female rats, from day 1 to 15 percentage increase in body weight was observed 19.04 % in test item treated group (G3) as compared to 20.97 % and 18.28 % in the placebo group G1 respectively.

From day 1 to 15 percentage changes in the feed consumption was noticed in test item treatment group (G3) – 3.23 to 9.46 % in male rats and – 9.01 to 0.87 % in female rats when compared with placebo group (G1). From day 1 to 15 percentage changes in the feed consumption was noticed in test item treatment group (G3) – 1.64 to 2.66 % in male rats and – 3.76 to 2.68 % in female rats when compared with placebo group (G2).

Gross pathological examination in the placebo, test item treated groups did not reveal any macroscopic changes at injection site. No gross lesions were observed in any

internal and external organs of the animals belong to placebo (G1, G2) and test item treated groups (G3).

Based on the above findings it is concluded that the test item, SARS-CoV-2 (COVID-19) Vaccine with AH+Co-Adjuvant treated groups did not produce any adverse effect in Sprague Dawley rats up to 0.5 mL/rat following single dose of intramuscular administration under conditions tested.

Repeated Dose Toxicity Study of SARS-CoV-2 (COVID-19) Vaccine with AH+Co-adjuvant in Sprague Dawley Rats by Intramuscular Route

The objective of this study is to determine the toxicity of the test item SARS-CoV-2 (COVID-19) Vaccine with AH+Co-adjuvant after repeated dose intramuscular administration to Sprague Dawley rats on days 1, 15 and 29 for a total of 3 injections. This study is also intended to provide information on progression, persistence, or reversibility of observed changes, if any after discontinuation for 4-weeks (recovery period) of treatment with the test item. In addition, the immune response of rats to the vaccine will be analysed. This study will provide a rational basis for toxicological risk assessment in humans.

No morbidity, mortality and adverse clinical signs were observed throughout the experiment in any of the animals of all groups except swelling at injection site in one male animal of group G2, two male animals of group G3, and two animals each of each sex of group G3R. No abnormal local reactions were observed at site of injection on the day of each dose administration prior to dosing and approximately at 4-, 24- and 48- hours following dose administration.

No treatment related significant difference in the mean body weight, body weight gain and feed consumption were observed in test item treated group when compared with respective AH+Co-Adjuvant placebo group and in AH+Co-Adjuvant placebo group when compared with respective Vehicle Placebo for SARS-Co V -2 (Covid-19) Vaccine with AH+ CoAdjuvant group.

In male rats from day 1 to 31, percentage increase in body weight was observed 52% in test item treated group (G3), as compared to 48% and 52 % in the vehicle Placebo for SARS-CoV-2 (COVID-19) Vaccine with AH + Co-Adjuvant group Gl and AH+Co-Adjuvant placebo group G2 respectively. In female rats, from day 1 to 31 percentage increase in body weight was observed 25 % in test item treated group (G3) as compared to 27 % and 24 % in the vehicle Placebo for SARS-CoV-2 (Covid-19) Vaccine with AH + Co-Adjuvant group Gl and G2 AH+Co-Adjuvant placebo respectively.

From day 1 to 56, 72% increase in body weight was observed in test item treated group (G3R), as compared to 74% and 71 % in the vehicle Placebo for SARS-CoV-2 (Covid-19) Vaccine with AH + Co-Adjuvant recovery group GIR and AH+Co-Adjuvant placebo recovery G2R respectively in male rats. In female rats, from day 1 to 56 34 % increase in body weight was observed in test item treated group (G3R) as compared to 43 % and 43 % in the vehicle Placebo for SARS-CoV -2 (Covid-19) Vaccine with AH + Co-Adjuvant recovery group GlR and AH+Co-Adjuvant placebo recovery group G2R respectively.

No treatment related changes in FOB observations were noticed in test item group when compared with respective AH+Co-Adjuvant placebo group and in AH+Co-Adjuvant group when compared with respective Vehicle Placebo for SARS-CoV -2 (Covid-19) Vaccine with AH + Co-Adjuvant group.

No adverse treatment related changes were observed in rectal temperature in the test item group when compared with respective AH+Co-Adjuvant placebo group and in AH+CoAdjuvant group when compared with respective Vehicle Placebo for SARS-CoV-2 (Covid- 19) Vaccine with AH + Co-Adjuvant group except for few sporadically significant changes (within physiological range). Ophthalmological examination does not reveal any abnormality in all group animals.

No treatment related significant changes in the clinical pathology parameters (haematology, clinical chemistry and urine analysis) and organ weight (absolute and relative weight) was observed in test item treated group when compared with respective AH+Co-Adjuvant placebo group and in AH+Co-Adjuvant group when compared with respective Vehicle Placebo for SARS-CoV-2 (Covid-19) Vaccine with AH + Co-Adjuvant group.

No gross findings were observed in any of the male and female animals in all groups except white nodules was observed at left and/or right injection site in male and female animals of AH+Co-Adjuvant Placebo (G2 and G2R) and SARS-CoV-2 (Covid-19) Vaccine with AH+ Co-Adjuvant (G3 and G3R) groups Microscopically, no test item related systemic changes were observed in male and female animals in Vehicle Placebo, AH+Co-Adjuvant Placebo and SARS-CoV-2 (Covid-19) Vaccine with AH + Co-Adjuvant groups.

Granulomatous inflammation was observed in skeletal muscle at injection sites (left and right sides) in all male and female animals of G2 and G3 groups. The changes observed at injection site (left and right side) persisted in both sexes of recovery (G2R and G3R) groups. The occurrence and severity of these reactions observed at the injection sites of test item treated group was comparable to the AH+Co-Adjuvant Placebo group.

The changes observed at the site of injection were considered to be the consequence of aluminium and not adverse reactions to treatment. Aluminium salts are being used as an adjuvant in many vaccines. The observed changes at the site of injection compared well with those reported by various workers earlier. The literature reports that histopathological changes induced by aluminium based adjuvant vaccines are self-limiting without any systemic consequences.

All statistically significant changes observed in different parameters were considered as incidental and not related to test item and does not have any toxicological significance.

Conclusion: Based on the above findings it is concluded that the test item, SARS-CoV-2 (Covid-19) Vaccine with AH + Co-Adjuvant treated groups did not produce any adverse effect in Sprague Dawley rats at dose levels of 0.5 mL/rat when repeatedly administered by intramuscular route following N+ 1 = 3 schedule on day 1, 15 and 29 under the conditions tested.

Repeated Dose Toxicity Study of SARS-CoV-2 (COVID-19) Vaccine with AH+Co-adjuvant in New Zealand White Rabbits By Intramuscular Route

The objective of this study is to determine the toxicity of the test item of SARS-CoV-2 (COVID-19) Vaccine with AH+Co-adjuvant after repeated dose intramuscular administration to New Zealand White Rabbits on days 1, 15 and 29 for a total of 3 injections. This study is also intended to provide information on progression, persistence, or reversibility of observed changes, if any after discontinuation for 4-weeks (recovery period) of treatment with the test item. In addition, the immune response of rabbits to the vaccine will be analysed. This study will provide a rational basis for toxicological risk assessment in humans**.**

No morbidity, mortality and adverse clinical signs were observed throughout the experiment in any of the animals of all groups. No abnormal local reactions were observed at site of injection on the day of each dose administration prior to dosing and approximately at 4-, 24- and 48- hours following dose administration.

No treatment related significant difference in the mean body weight, body weight gain and feed consumption were observed in test item treated group when compared with respective AH+Co-Adjuvant placebo group and in AH+Co-Adjuvant placebo group when compared with respective Vehicle Placebo for SARS-CoV-2 (Covid-19) Vaccine with AH + Co-Adjuvant group.

In male rabbits from day 1 to 31, percentage increase in body weight was observed 22% in test item treated group (G3), as compared to 17% and 23 % in the vehicle Placebo for SARS-CoV-2 (Covid-19) Vaccine with AH + Co-Adjuvant group G1 and AH+Co-Adjuvant placebo group G2 respectively. In female rabbits, from day 1 to 31 percentage increase in body weight was observed 19 % in test item treated group (G3) as compared to 28 % and 29 % in the vehicle Placebo for SARS-CoV-2 (Covid-19) Vaccine with AH + Co-Adjuvant group G1 and AH+Co-Adjuvant placebo group G2 respectively.

From day 1 to 56, 34% increase in body weight was observed in test item treated group (G3R), as compared to 32% and 41 % in the vehicle Placebo for SARS-CoV-2 (Covid-19) Vaccine with AH + Co-Adjuvant recovery group G1R and AH+Co-Adjuvant placebo recovery group G2R respectively in male rabbits. In female rabbits from day 1 to 56, 36 % increase in body weight was observed in test item treated group (G3R) as compared to 39 % and 38 % in the vehicle Placebo for SARS-CoV-2 (Covid-19) Vaccine with AH + Co-Adjuvant recovery group G1R and AH+Co-Adjuvant placebo recovery group G2R respectively.

No adverse treatment related changes were observed in rectal temperature in the test item group when compared with respective AH+Co-Adjuvant placebo group and in AH+Co-Adjuvant group when compared with respective Vehicle Placebo for SARS-CoV-2 (Covid-19) Vaccine with AH + Co-Adjuvant group except for few sporadically significant changes (within physiological range). Ophthalmological examination does not reveal any abnormality in all group animals.

No treatment related significant changes in the clinical pathology parameters (haematology, clinical chemistry and urine analysis) and organ weight (absolute and

relative weight) was observed in test item treated group when compared with respective AH+Co-Adjuvant placebo group and in AH+Co-Adjuvant group when compared with respective Vehicle Placebo for SARS-CoV-2 (Covid-19) Vaccine with AH + Co-Adjuvant group.

No gross findings were observed in any of the male and female animals in all groups except white nodules was observed at right injection site in male animals of SARS-CoV-2 (Covid-19) Vaccine with AH + Co-Adjuvant (G3) treated group. Microscopically, no test item related systemic changes were observed in male and female animals in Vehicle Placebo, AH+Co-Adjuvant Placebo and SARS-CoV-2 (Covid-19) Vaccine with AH + Co-Adjuvant groups.

Granulomatous inflammation was observed in skeletal muscle at injection sites (left and right sides) in all male and female animals of G2 and G3 groups. The changes observed at injection site (left and right side) persisted in both sexes of recovery (G2R and G3R) groups. The occurrence and severity of these reactions observed at the injection sites of test item treated group was comparable to the AH+Co-Adjuvant Placebo group.

The changes observed at the site of injection were considered to be the consequence of aluminium and not adverse reactions to treatment. Aluminium salts are being used as an adjuvant in many vaccines. The observed changes at the site of injection compared well with those reported by various workers earlier. The literature reports that histopathological changes induced by aluminium based adjuvant vaccines are self-limiting without any systemic consequences.

All statistically significant changes observed in different parameters were considered as incidental and not related to test item and does not have any toxicological significance.

Conclusion: Based on the above findings it is concluded that the test item, SARS-CoV-2 (Covid-19) Vaccine with AH+Co-adjuvant treated groups did not produce any adverse effects in New Zealand White Rabbits at dose level of 0.5 mL/rabbit when repeatedly administered by intramuscular route following N+1 = 3 schedule on day 1, 15 and 29 under the conditions tested.

Please refer to the Investigator's Brochure for complete details on the pre-clinical studies conducted for the study vaccine.

1.2.2. Clinical Experience

A phase-I seamlessly followed by phase-II clinical trial was conducted in India to assess the safety, tolerability, reactogenicity and immunogenicity of this novel protein RBD subunit vaccine to induce anti-SARS-CoV-2 IgG and neutralising antibodies for blocking virus binding and fusion thereby offering preventive protection.

Phase I/II study & results summary

Immunogenicity results:

Immunoglobulin G (IgG) antibody immune response - Geometric Mean Concentrations (GMCs)

Overall:

At screening, the geometric mean concentration of IgG antibodies of the ATP population was 633.56 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 665.97 : 521.87 : 687.79 : 673.40].

At Day 28, the geometric mean concentration of IgG antibodies of the ATP population was 2773.99 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 2392.82 : 2390.67 : 3257.91 : 3171.51] and the post/pre-vaccination geometric mean titres (GMT) was 4.38 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 3.59 : 4.58 : 4.74 : 4.71].

At Day 42, the geometric mean concentration of IgG antibodies of the ATP population was 13640.60 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 12290.55 : 11497.35 : 17300.64 : 14123.50] and the post/pre-vaccination geometric mean titres (GMT) was 21.53 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 18.46 : 22.03 : 25.15 : 20.97].

At Day 56, the geometric mean concentration of IgG antibodies of the ATP population was 14731.24 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 12974.20 : 11067.51 : 19495.69 : 16769.50] and the post/pre-vaccination geometric mean titres (GMT) was 23.25 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 19.48 : 21.21 : 28.35 : 24.90].

Phase I:

At screening, the geometric mean concentration (GMC) of IgG antibodies of the ATP population was 588.91 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 404.62 : 298.62 : 1353.17 : 769.60].

At Day 28, the geometric mean concentration of IgG antibodies of the ATP population was 2191.78 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 1456.56 : 1305.75 : 2804.65 : 3650.93] and the post/pre-vaccination geometric mean titres (GMT) was 3.72 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 3.60 : 4.37 : 2.07 : 4.74].

At Day 42, the geometric mean concentration of IgG antibodies of the ATP population was 14956.43 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 7310.67 : 14169.47 : 37796.36 : 18630.26] and the post/pre-vaccination geometric mean titres (GMT) was 25.40 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 18.07 : 47.45 : 27.93 : 24.21].

At Day 56, the geometric mean concentration of IgG antibodies of the ATP population was 20192.37 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 11304.70 : 15852.31 : 31521.21 : 31042.83] and the post/pre-vaccination geometric mean titres (GMT) was 34.29 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 27.94 : 53.08 : 23.29 : 40.34].

Phase II:

At screening, the geometric mean concentration (GMC) of the ATP population was 638.61 [BECOV2D: BECOV2C: BECOV2B : BECOV2A :: 714.45 : 543.36 : 655.34 : 659.53].

At Day 28, the geometric mean concentration of IgG antibodies of the ATP population was 2845.94 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 2566.33 : 2497.51 : 3292.96 : 3102.68] and the post/pre-vaccination geometric mean titres (GMT) was 4.46 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 3.59 : 4.60 : 5.02 : 4.70].

At Day 42, the geometric mean concentration of IgG antibodies of the ATP population was 13504.74 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 13224.78 : 11324.97 : 16361.39 : 13526.89] and the post/pre-vaccination geometric mean titres (GMT) was 21.15 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 18.51 : 20.84 : 24.97 : 20.51].

At Day 56, the geometric mean concentration of IgG antibodies of the ATP population was 14234.87 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 13228.70 : 10783.75 : 18837.97 : 15234.95] and the post/pre-vaccination geometric mean titres (GMT) was 22.29 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 18.52 : 19.85 : 28.75 : 23.10].

Immunoglobulin G (IgG) antibody immune response - Fold Rise & GMFR from Day 28

Overall:

A total of 265 (74.2%) subjects reported ≥2 fold rise in the IgG antibodies against SARS-CoV-2 RBD antigen from Day 28 to Day 42 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 71 (79.8%) : 67 (75.3%) : 65 (72.2%) : 62 (69.7%)], while 188 (52.7%) subjects reported ≥4 fold rise in the IgG antibodies against SARS-CoV-2 RBD antigen from Day 28 to Day 42 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 47 (52.8%) : 49 (55.1%) : 47 (52.2%) : 45 (50.6%)] and the Geometric Mean Fold Rise (GMFR) was 4.92 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 5.14 : 4.81 : 5.31 : 4.45].

A total of 272 (76.2%) subjects reported ≥2 fold rise in the IgG antibodies against SARS-CoV-2 RBD antigen from Day 28 to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 65 (73.0%) : 72 (80.9%) : 70 (77.8%) : 65 (73.0%)], while 202 (56.6%) subjects reported ≥4 fold rise in the IgG antibodies against SARS-CoV-2 RBD antigen from Day 28 to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 54 (60.7%) : 51 (57.3%) : 49 (54.4%) : 48 (53.9%)] and the Geometric Mean Fold Rise (GMFR) was 5.31 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 5.42 : 4.63 : 5.98 : 5.29].

Phase I:

A total of 25 (71.4%) subjects reported ≥2 fold rise in the IgG antibodies against SARS-CoV-2 RBD antigen from Day 28 to Day 42 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 7 (63.6%) : 5 (83.3%) : 5 (83.3%) : 8 (66.7%)], while 21 (60.0%) subjects reported ≥4 fold rise in the IgG antibodies against SARS-CoV-2 RBD antigen from Day 28 to Day 42 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 5 (45.5%) : 5 (83.3%) : 5 (83.3%) : 6 (50.0%)] and the Geometric Mean Fold Rise (GMFR) was 6.82 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 5.02 : 10.85 : 13.48 : 5.10].

A total of 30 (85.7%) subjects reported ≥2 fold rise in the IgG antibodies against SARS-CoV-2 RBD antigen from Day 28 to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 8 (72.7%) : 6 (100.0%) : 5 (83.3%) : 11 (91.7%)], while 27 (77.1%) subjects reported ≥4 fold rise in the IgG antibodies against SARS-CoV-2 RBD antigen from Day 28 to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 8 (72.7%) : 6 (100.0%) : 5 (83.3%) : 8 (66.7%)] and the Geometric Mean Fold Rise (GMFR) was 9.21 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 7.76 : 12.14 : 11.24 : 8.50].

Phase II:

A total of 240 (74.5%) subjects reported ≥2 fold rise in the IgG antibodies against SARS-CoV-2 RBD antigen from Day 28 to Day 42 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 64 (82.1%) : 62 (74.7%) : 60 (71.4%) : 54 (70.1%)], while 167 (51.9%) subjects reported ≥4 fold rise in the IgG antibodies against SARS-CoV-2 RBD antigen from Day 28 to Day 42 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 42 (53.8%) : 44 (53.0%) : 42 (50.0%) : 39 (50.6%)] and the Geometric Mean Fold Rise (GMFR) was 4.75 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 5.15 : 4.53 : 4.97 : 4.36].

A total of 242 (75.2%) subjects reported ≥2 fold rise in the IgG antibodies against SARS-CoV-2 RBD antigen from Day 28 to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 57 (73.1%) : 66 (79.5%) : 65 (77.4%) : 54 (70.1%)], while 175 (54.3%) subjects reported ≥4 fold rise in the IgG antibodies against SARS-CoV-2 RBD antigen from Day 28 to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 46 (59.0%) : 45 (54.2%) : 44 (52.4%) : 40 (51.9%)] and the Geometric Mean Fold Rise (GMFR) was 5.00 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 5.15 : 4.32 : 5.72 : 4.91].

Immunoglobulin G (IgG) antibody immune response - Fold Rise & GMFR from Screening

Overall:

A total of 197(55.2%) subjects reported ≥2 fold rise in the IgG antibodies against SARS-CoV-2 RBD antigen from Screening to Day 28 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 47(52.8%) : 46(51.7%) : 53(58.9%) : 51(57.3%)], while 156(43.7%) subjects reported ≥4 fold rise in the IgG antibodies against SARS-CoV-2 RBD antigen from Screening to Day 28 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 33(37.1%) : 41(46.1%) : 42(46.7%) : 40(44.9%)] and the Geometric Mean Fold Rise (GMFR) was 4.38 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 3.59 : 4.58 : 4.74 : 4.71].

A total of 318(89.1%) subjects reported ≥2 fold rise in the IgG antibodies against SARS-CoV-2 RBD antigen from Screening to Day 42 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 77(86.5%) : 82(92.1%) : 81(90.0%) : 78(87.6%)], while 292(81.8%) subjects reported ≥4 fold rise in the IgG antibodies against SARS-CoV-2 RBD antigen from Screening to Day 42 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 70(78.7%) : 73(82.0%) : 79(87.8%) : 70(78.7%)] and the Geometric Mean Fold Rise (GMFR) was 21.53 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 18.46 : 22.03 : 25.15 : 20.97].

A total of 325(91.0%) subjects reported ≥2 fold rise in the IgG antibodies against SARS-CoV-2 RBD antigen from Screening to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 77(86.5%) : 78(87.6%) : 88(97.8%) : 82(92.1%)], while 295(82.6%) subjects reported ≥4 fold rise in the IgG antibodies against SARS-CoV-2 RBD antigen from Screening to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 70(78.7%) : 70(78.7%) : 81(90.0%) : 74(83.1%)] and the Geometric Mean Fold Rise (GMFR) was 23.25 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 19.48 : 21.21 : 28.35 : 24.90].

Phase I:

A total of 19(54.3%) subjects reported ≥2 fold rise in the IgG antibodies against SARS-CoV-2 RBD antigen from Screening to Day 28 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 6(54.5%) : 3(50.0%) : 3(50.0%) : 7(58.3%)], while 13(37.1%) subjects reported ≥4 fold rise in the IgG antibodies against SARS-CoV-2 RBD antigen from Screening to Day 28 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 3(27.3%) : 3(50.0%) : 2(33.3%) : 5(41.7%)] and the Geometric Mean Fold Rise (GMFR) was 3.72 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 3.60 : 4.37 : 2.07 : 4.74].

A total of 33(94.3%) subjects reported ≥2 fold rise in the IgG antibodies against SARS-CoV-2 RBD antigen from Screening to Day 42 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 11(100.0%) : 6(100.0%) : 6(100.0%) : 10(83.3%)], while 30(85.7%) subjects reported ≥4 fold rise in the IgG antibodies against SARS-CoV-2 RBD antigen from Screening to Day 42 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 9(81.8%) : 6(100.0%) : 6(100.0%) : 9(75.0%)] and the Geometric Mean Fold Rise (GMFR) was 25.40 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 18.07 : 47.45 : 27.93 : 24.21].

A total of 33(94.3%) subjects reported ≥2 fold rise in the IgG antibodies against SARS-CoV-2 RBD antigen from Screening to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 10(90.9%) : 6(100.0%) : 6(100.0%) : 11(91.7%)], while 32(91.4%) subjects reported ≥4 fold rise in the IgG antibodies against SARS-CoV-2 RBD antigen from Screening to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 10(90.9%) : 6(100.0%) : 5(83.3%) : 11(91.7%)] and the Geometric Mean Fold Rise (GMFR) was 34.29 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 27.94 : 53.08 : 23.29 : 40.34].

Phase II:

A total of 178(55.3%) subjects reported ≥2 fold rise in the IgG antibodies against SARS-CoV-2 RBD antigen from Screening to Day 28 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 41(52.6%) : 43(51.8%) : 50(59.5%) : 44(57.1%)], while 143(44.4%) subjects reported ≥4 fold rise in the IgG antibodies against SARS-CoV-2 RBD antigen from Screening to Day 28 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 30(38.5%) : 38(45.8%) : 40(47.6%) : 35(45.5%)] and the Geometric Mean Fold Rise (GMFR) was 4.46 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 3.59 : 4.60 : 5.02 : 4.70].

A total of 285(88.5%) subjects reported ≥2 fold rise in the IgG antibodies against SARS-CoV-2 RBD antigen from Screening to Day 42 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 66(84.6%) : 76(91.6%) : 75(89.3%) : 68(88.3%)], while

262(81.4%) subjects reported ≥4 fold rise in the IgG antibodies against SARS-CoV-2 RBD antigen from Screening to Day 42 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 61(78.2%) : 67(80.7%) : 73(86.9%) : 61(79.2%)] and the Geometric Mean Fold Rise (GMFR) was 21.15 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 18.51 : 20.84 : 24.97 : 20.51].

A total of 292(90.7%) subjects reported ≥2 fold rise in the IgG antibodies against SARS-CoV-2 RBD antigen from Screening to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 67(85.9%) : 72(86.7%) : 82(97.6%) : 71(92.2%)], while 263(81.7%) subjects reported ≥4 fold rise in the IgG antibodies against SARS-CoV-2 RBD antigen from Screening to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 60(76.9%) : 64(77.1%) : 76(90.5%) : 63(81.8%)] and the Geometric Mean Fold Rise (GMFR) was 22.29 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 18.52 : 19.85 : 28.75 : 23.10].

Immunoglobulin G (IgG1 & IgG2) antibody immune response - Geometric Mean Concentrations (GMCs)

Overall:

The GMC of IgG1 antibodies of the ATP population at screening was 75.17 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 88.97 : 65.16 : 74.05 : 74.38], and GMC of IgG1 antibodies at Day 56 was 2400.78 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 2219.11 : 1884.30 : 2940.07 : 2696.11]; the post/pre-vaccination geometric mean titres (GMT) was 31.94 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 24.94 : 28.92 : 39.70 : 36.25].

The GMC of IgG2 antibodies of the ATP population at screening was 90.40 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 86.25 : 92.51 : 89.78 : 93.23], and GMC of IgG2 antibodies at Day 56 was 517.86 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 478.47 : 446.08 : 459.48 : 734.32]; the post/pre-vaccination geometric mean titres (GMT) was 5.73 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 5.55 : 4.82 : 5.12 : 7.88].

Phase I:

The GMC of IgG1 antibodies of the ATP population at screening was 75.79 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 46.95 : 44.54 : 158.74 : 105.95], and GMC of IgG1 antibodies at Day 56 was 2841.48 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 1324.41 : 2015.87 : 7183.76 : 4271.49]; the post/pre-vaccination geometric mean titres (GMT) was 37.49 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 28.21 : 45.25 : 45.25 : 40.32].

The GMC of IgG2 antibodies of the ATP population at screening was 126.83 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 137.04 : 56.12 : 224.49 : 133.48], and GMC of IgG2 antibodies at Day 56 was 1286.80 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 852.03 : 1007.94 : 2262.74 : 1600.00]; the post/pre-vaccination geometric mean titres (GMT) was 10.15 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 6.22 : 17.96 : 10.08 : 11.99].

Phase II:

The GMC of IgG1 antibodies of the ATP population at screening was 75.10 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 97.37 : 66.97 : 70.13 : 70.39], and GMC of IgG1 antibodies at Day 56 was 2357.21 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 2386.66 : 1875.13 : 2758.31 : 2509.54]; the post/pre-vaccination geometric mean titres (GMT) was 31.39 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 24.51 : 28.00 : 39.33 : 35.65].

The GMC of IgG2 antibodies of the ATP population at screening was 87.13 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 80.79 : 95.91 : 84.09 : 88.16], and GMC of IgG2 antibodies at Day 56 was 469.07 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 441.08 : 420.55 : 410.03 : 650.39]; the post/pre-vaccination geometric mean titres (GMT) was 5.38 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 5.46 : 4.38 : 4.88 : 7.38].

Immunoglobulin G (IgG) antibody immune response - Fold Rise & GMFR

Overall:

A total of 331(92.7%) subjects reported ≥2 fold rise in the IgG1 antibodies against SARS-CoV-2 RBD antigen from Screening to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 78(87.6%) : 82(92.1%) : 89(98.9%) : 82(92.1%)], while 313(87.7%) subjects reported ≥4 fold rise in the IgG1 antibodies against SARS-CoV-2 RBD antigen from Screening to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 74(83.1%) : 76(85.4%) : 84(93.3%) : 79(88.8%)] and the Geometric Mean Fold Rise (GMFR) was 31.94 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 24.94 : 28.92 : 39.70 : 36.25].

A total of 290(81.2%) subjects reported ≥2 fold rise in the IgG2 antibodies against SARS-CoV-2 RBD antigen from Screening to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 68(76.4%) : 70(78.7%) : 72(80.0%) : 80(89.9%)], while 242(67.8%) subjects reported ≥4 fold rise in the IgG2 antibodies against SARS-CoV-2 RBD antigen from Screening to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 58(65.2%) : 59(66.3%) : 60(66.7%) : 65(73.0%)] and the Geometric Mean Fold Rise (GMFR) was 5.73 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 5.55 : 4.82 : 5.12 : 7.88].

Phase I:

A total of 33(94.3%) subjects reported ≥2 fold rise in the IgG1 antibodies against SARS-CoV-2 RBD antigen from Screening to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 10(90.9%) : 6(100.0%) : 6(100.0%) : 11(91.7%)], while 32(91.4%) subjects reported ≥4 fold rise in the IgG1 antibodies against SARS-CoV-2 RBD antigen from Screening to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 9(81.8%): 6(100.0%) : 6(100.0%) : 11(91.7%)] and the Geometric Mean Fold Rise (GMFR) was 37.49 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 28.21 : 45.25 : 45.25: 40.32].

A total of 34(97.1%) subjects reported ≥2 fold rise in the IgG2 antibodies against SARS-CoV-2 RBD antigen from Screening to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 10(90.9%) : 6(100.0%) : 6(100.0%) : 12(100.0%)], while

30(85.7%) subjects reported ≥4 fold rise in the IgG2 antibodies against SARS-CoV-2 RBD antigen from Screening to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 8(72.7%) : 6(100.0%) : 5(83.3%) : 11(91.7%)] and the Geometric Mean Fold Rise (GMFR) was 10.15 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 6.22 : 17.96 : 10.08 : 11.99].

Phase II:

A total of 298(92.5%) subjects reported ≥2 fold rise in the IgG1 antibodies against SARS-CoV-2 RBD antigen from Screening to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 68(87.2%) : 76(91.6%) : 83(98.8%) : 71(92.2%)], while 281(87.3%) subjects reported ≥4 fold rise in the IgG1 antibodies against SARS-CoV-2 RBD antigen from Screening to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 65(83.3%) : 70(84.3%) : 78(92.9%) : 68(88.3%)] and the Geometric Mean Fold Rise (GMFR) was 31.39 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 24.51 : 28.00 : 39.33 : 35.65].

A total of 256(79.5%) subjects reported ≥2 fold rise in the IgG2 antibodies against SARS-CoV-2 RBD antigen from Screening to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 58(74.4%) : 64(77.1%) : 66(78.6%) : 68(88.3%)], while 212(65.8%) subjects reported ≥4 fold rise in the IgG2 antibodies against SARS-CoV-2 RBD antigen from Screening to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 50(64.1%) : 53(63.9%) : 55(65.5%) : 54(70.1%)] and the Geometric Mean Fold Rise (GMFR) was 5.38 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 5.46 : 4.38 : 4.88 : 7.38].

Virus Neutralizing antibody assay response - Geometric Mean Concentrations (GMCs)

Overall:

The GMC for virus neutralizing antibody (VNA) against SARS-CoV-2 RBD antigen at screening was 5.99 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 5.97 : 5.90 : 6.55 : 5.52] and GMC for VNA against SARS-CoV-2 RBD antigen at Day 56 was 54.22 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 44.18 : 41.14 : 99.96 : 46.56]. The post/pre-vaccination geometric mean titres (GMT) were 9.05 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 7.40 : 6.97 : 15.26 : 8.43].

Phase I:

The GMC for virus neutralizing antibody (VNA) against SARS-CoV-2 RBD antigen at screening was 6.17 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 6.60 : 5.00 : 5.00 : 7.25] and GMC for VNA against SARS-CoV-2 RBD antigen at Day 56 was 56.29 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 22.70 : 17.22 : 89.26 : 145.13]. The post/pre-vaccination geometric mean titres (GMT) were 9.12 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 3.44 : 3.44 : 17.85 : 20.03].

Phase II:

The GMC for virus neutralizing antibody (VNA) against SARS-CoV-2 RBD antigen at screening was 5.97 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 5.90 : 5.97 : 6.70 : 5.24] and GMC for VNA against SARS-CoV-2 RBD antigen at Day 56 was 53.99

[BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 47.67 : 43.67 : 100.91 : 37.24]. The post/pre-vaccination geometric mean titers (GMT) were 9.04 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 8.08 : 7.32 : 15.06 : 7.11].

Virus Neutralizing antibody assay response - Fold Rise & GMFR

Overall:

A total of 171(56.8%) subjects reported ≥2 fold rise in the VNA against SARS-CoV-2 RBD antigen from Screening to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 45(57.7%) : 36(46.2%) : 50(64.1%) : 40(59.7%)], while 150(49.8%) subjects reported ≥4 fold rise in the VNA against SARS-CoV-2 RBD antigen from Screening to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 40(51.3%) : 34(43.6%) : 46(59.0%) : 30(44.8%)] and the Geometric Mean Fold Rise (GMFR) was 9.05 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 7.40 : 6.97 : 15.26 : 8.43].

Phase I:

A total of 17(56.7%) subjects reported ≥2 fold rise in the VNA against SARS-CoV-2 RBD antigen from Screening to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 3(37.5%) : 2(40.0%) : 4(66.7%) : 8(72.7%)], while 16(53.3%) subjects reported ≥4 fold rise in the VNA against SARS-CoV-2 RBD antigen from Screening to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 3(37.5%) : 2(40.0%) : 4(66.7%) : 7(63.6%)] and the Geometric Mean Fold Rise (GMFR) was 9.12 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 3.44 : 3.44 : 17.85 : 20.03].

Phase II:

A total of 154(56.8%) subjects reported ≥2 fold rise in the VNA against SARS-CoV-2 RBD antigen from Screening to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 42(60.0%) : 34(46.6%) : 46(63.9%) : 32(57.1%)], while 134(49.4%) subjects reported ≥4 fold rise in the VNA against SARS-CoV-2 RBD antigen from Screening to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 37(52.9%) : 32(43.8%) : 42(58.3%) : 23(41.1%)] and the Geometric Mean Fold Rise (GMFR) was 9.04 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 8.08 : 7.32 : 15.06 : 7.11].

Interferon Gamma (INF-γ) & IL-4 Cytokines

Two key cytokines were monitored in the clinical study, Interferon-gamma which represents Th1 biased T cell response and Interleukin-4 which represents Th2 biased T cell response. Average cytokine concentrations in the Active and Null supernatant samples collected from Day-0 and Day-56 time-points for all four cohorts is summarized in Table 37. As expected, the Active cytokine concentrations are low and close to the Null concentration for both INF-γ and IL-4 cytokines at Day-0. Significant increase is observed in Active INF-γ concentration for Day-56 samples for all cohorts with the highest concentration observed for the BECOV2B formulation. In comparison, low increase was observed in Active IL-4 concentration for Day-56 samples for all cohorts.

Exploratory Analysis:

Immunoglobulin G (IgG4) antibody immune response

Overall:

The GMC for IgG4 antibodies against SARS-CoV-2 RBD antigen at screening was 30.12 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 31.58 : 27.45 : 30.54 : 31.09] and GMC for IgG4 antibodies against SARS-CoV-2 RBD antigen at Day 56 was 59.09 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 56.64 : 49.61 : 75.79 : 57.08]. the post/pre-vaccination geometric mean titres (GMT) were 1.96 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 1.79 : 1.81: 2.48: 1.84].

Phase I:

The GMC for IgG4 antibodies against SARS-CoV-2 RBD antigen at screening was 29.29 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 36.49 : 28.06 : 28.06 : 25.00] and GMC for IgG4 antibodies against SARS-CoV-2 RBD antigen at Day 56 was 67.30 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 77.72 : 56.12 : 178.18 : 39.69]. the post/pre-vaccination geometric mean titres (GMT) were 2.30 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 2.13: 2.00: 6.35: 1.59].

Phase II:

The GMC for IgG4 antibodies against SARS-CoV-2 RBD antigen at screening was 30.21 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 30.94 : 27.41 : 30.73 : 32.17] and GMC for IgG4 antibodies against SARS-CoV-2 RBD antigen at Day 56 was 58.26 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 54.16 : 49.17 : 71.30 : 60.40]. the post/pre-vaccination geometric mean titres (GMT) were 1.93 [BECOV2D : BECOV2C : BECOV2B : BECOV2A :: 1.75 : 1.79 : 2.32 : 1.88].

Immunoglobulin G (IgG4) antibody immune response - Fold Rise & GMFR

Overall:

A total of 176(49.3%) subjects reported ≥2 fold rise in the IgG4 antibodies against SARS-CoV-2 RBD antigen from Screening to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 38(42.7%) : 40(44.9%) : 53(58.9%) : 45(50.6%)], while 94(26.3%) subjects reported ≥4 fold rise in the IgG4 antibodies against SARS-CoV-2 RBD antigen from Screening to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 20(22.5%): 22(24.7%): 31(34.4%): 21(23.6%)] and the Geometric Mean Fold Rise (GMFR) was 1.96 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 1.79: 1.81: 2.48: 1.84].

Phase I:

A total of 22(62.9%) subjects reported ≥2 fold rise in the IgG4 antibodies against SARS-CoV-2 RBD antigen from Screening to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 7(63.6%): 4(66.7%): 5(83.3%): 6(50.0%)], while 11(31.4%) subjects reported ≥4 fold rise in the IgG4 antibodies against SARS-CoV-2 RBD antigen from Screening to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 3(27.3%): 2(33.3%): 5(83.3%): 1(8.3%)] and the Geometric Mean Fold Rise (GMFR) was 2.30 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 2.13 : 2.00: 6.35: 1.59].

Phase II:

A total of 154(47.8%) subjects reported ≥2 fold rise in the IgG4 antibodies against SARS-CoV-2 RBD antigen from Screening to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 31(39.7%) : 36(43.4%) : 48(57.1%): 39(50.6%)], while 83(25.8%) subjects reported ≥4 fold rise in the IgG4 antibodies against SARS-CoV-2 RBD antigen from Screening to Day 56 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 17(21.8%) : 20(24.1%) : 26(31.0%) : 20(26.0%)] and the Geometric Mean Fold Rise (GMFR) was 1.93 [BECOV2D: BECOV2C : BECOV2B : BECOV2A :: 1.75 : 1.79 : 2.32 : 1.88].

Safety results: The combined safety data of Phase I and Phase II study showed that a total of 46 AEs [42 (11.67%) subjects] were reported within 7 days' post vaccination, of which 16 AEs were reported in 14 (15.56%) subjects of BECOV2D group, followed by 11 AEs reported in 11 (12.22%) subjects of BECOV2A group, 10 AEs reported in 8 (8.89%) subjects of BECOV2C group and 9 AEs reported in 9 (10.00%) subjects of BECOV2B group. Almost all the reported AEs were mild, except 1 AE of Pyrexia reported in 1 (1.11%) subject of BECOV2D group was of moderate severity.

None of the subject reported any AE within 120 minutes' post vaccination and none of the AE was of Grade 3 severity.

Of all reported 46 AEs, 26 AEs in 25 (6.94%) subjects were local and 7 AEs in 7 (7.78%) subjects were systemic. Of the reported local AEs [26 AEs in 25 (6.94%) subjects], majority of AEs were of injection site pain [22 AEs in 21 (5.83%) subjects], followed by Injection site swelling [3 AEs in 3 (0.83%) subjects]. The most commonly reported systemic AE was Pyrexia [8 AEs in 8 (2.22%) subjects], followed by Headache [6 AEs in 6 (1.67%) subjects], Myalgia [2 AEs in 2 (0.56%) subjects], and Urticaria [2 AEs in 2 (0.56%) subjects]. Only 1 AE of Chills was reported in 1 (0.28%) subject.

One unsolicited AE of Dyspepsia [1 (1.11%) subject] reported in BECOV2B group during risk period 2 was medically attended, of mild severity and unrelated to study medication.

For most of the AEs no action was taken, except for 6 AEs [6 (1.67%) subjects] of Pyrexia, 4 AEs [4 (1.11%) subjects] of Headache, 2 AEs [2 (0.56%) subjects] of Urticaria, and 1 AE [1 (0.28%) subject] of Dyspepsia, drug therapy was started.

During risk period 1, most commonly reported AEs were of General disorders and administration site conditions [25 AEs in 24 (6.67%) subjects], followed by 6 AEs [6 (1.67%) subjects] of nervous system disorders and 1 AE [1 (0.28%) subject] of Musculoskeletal and connective tissue disorders. During risk period 2, 9 AEs [9 (2.50%) subjects] of General disorders and administration site conditions were reported followed by 2 AEs [2 (0.56%) subjects] of Skin and subcutaneous tissue disorders, and 1 AE, each [1 (0.28%) subject, each] of Gastrointestinal disorders and Musculoskeletal and connective tissue disorders.

Of total 10 MAAEs, 9 systemic MAAEs were reported in 9 (2.50%) subjects, of which 3 MAAEs, each [3 (3.33%) subjects] were reported in BECOV2D and BECOV2C group followed by 2 MAAEs, each [2 (2.22%) subjects] in BECOV2A group and 1 MAAE [1 (1.11%) subject] in BECOV2B group. None of the reported MAAE was

serious. Majority MAAEs [4 MAAEs in 4 (1.11%) subjects] were of Pyrexia followed by 3 MAAEs of Headache [3 (0.83%) subjects].

A total of 7 (1.94%) subjects reported 8 cases of fever increment of ≥100.4°F after vaccination (Day 0 - Day 6), of which majority subjects [3 cases in 3 (3.33%) subjects] belong to the BECOV2A group; 3 cases [2 (0.56%) subjects] of fever of ≥101.3°F were reported after vaccination, while 1 case [1 (0.28%) subject] of fever of ≥102.2°F after vaccination was reported. Of the reported cases of fever increment, 5 cases [5 (1.39%) subjects] lasted for 24 hours; 6 of these cases [6 (1.67%) subjects] were of Grade 1. The maximum and minimum temperature recorded was 100.4:102.4°F; time of onset was 12 hours while time to resolution was 38 hours. Most of the cases of fever increment [5 cases in 5 (1.54%) subjects] were reported during risk period 1. The mean ± SD duration of fever (in days) after vaccination (Day 0 – Day 6) of total vaccinated group was 2.6 ± 1.51.

Phase I:

During the Phase I study, a total of 12 solicited AEs were reported in 11 (30.56%) subjects within 7 days post vaccination. Majority of AEs were reported in BECOV2D [6 AEs in 5 (41.67%)] and BECOV2A groups [5 AEs in 5 (41.67%) subjects] groups; 1 AE was reported in 1 (16.67%) subject of BECOV2B group. No adverse event was reported in any of the subject in BECOV2C group. All the reported AEs were of mild severity and were probably related to study treatment.

One systemic AE of Headache in 1 (30.56%) subject of BECOV2D group was medically attended, however it was not serious.

None of the subject reported any AE within 120 minutes post vaccination and none of the AE was serious, unsolicited or of Grade 3 severity.

Of the reported solicited AEs, 10 AEs in 10 (27.78%) subjects were local and 2 AEs in 2 (5.56%) subjects were systemic. Most commonly reported local AE was injection site pain [9 AEs in 9 (25.00%) subjects] in BECOV2D group [5 AEs in 5 (41.67%) subjects] and BECOV2A group [4 AEs in 4 (33.33%) subjects] followed by 1 AE of injection site erythema was reported in 1 (8.33%) subject of BECOV2A group. Two systemic AEs of Headache were reported in 2 (5.56%) subjects [1 subject each of BECOV2D and BECOV2B group].

For majority of reported AEs (11 AEs), no action was taken whereas, for 1 AE of Headache in 1 (8.33%) subject drug therapy was started.

Of reported 12 solicited AEs in 11 (30.56%) subjects, 11 AEs were reported during Risk period I while 1 AE was reported during Risk period 2.

Phase II:

During the Phase II study, a total of 34 AEs [31 (9.57%) subjects] were reported within 7 days post vaccination, of which 10 AEs were reported in 9 (11.54%) subjects of BECOV2D group, followed by 10 AEs reported in 8 (9.52%) subjects of BECOV2C group, 8 AEs reported in 8 (9.52%) subjects of BECOV2B group, and 6 AEs reported in 6 (7.69%) subjects of BECOV2A group. Almost all the reported AEs were mild,

except 1 AE of Pyrexia reported in 1 (1.28%) subject of BECOV2D group was of moderate severity.

None of the subject reported any AE within 120 minutes post vaccination and none of the AE was of Grade 3 severity.

Of all reported 34 AEs, 16 AEs in 15 (4.63%) subjects were local and 17 AEs in 16 (4.94%) subjects were systemic. Of the reported local AEs [16 AEs in 15 (4.63) subjects], majority of AEs were of injection site pain [13 AEs in 12 (3.70%) subjects], followed by Injection site swelling [3 AEs in 3 (0.93%) subjects]. The most commonly reported systemic AE was Pyrexia [8 AEs in 8 (2.4%) subjects], followed by Headache [4 AEs in 4 (1.23%) subjects], Myalgia [2 AEs in 2 (0.62%) subjects], and Urticaria [2 AEs in 2 (0.62%) subjects]. Only 1 AE of Chills was reported in 1 (0.31%) subject.

One unsolicited AE of Dyspepsia [1 (1.19%) subject] reported in BECOV2B group during risk period 2 was medically attended, of mild severity and unrelated to study medication.

For most of the AEs no action was taken, except for 6 AEs [6 (1.85%) subjects] of Pyrexia, 3 AEs [3 (0.93%) subjects] of Headache, 2 AEs [2 (0.62%) subjects] of Urticaria, and 1 AE [1 (0.31%) subject] of Dyspepsia, drug therapy was started.

During risk period 1, most commonly reported AEs were of General disorders and administration site conditions [16 AEs in 15 (4.63%) subjects], followed by 4 AEs [4 (1.23%) subjects] of nervous system disorders and 1 AE [1 (0.31%) subject] of Musculoskeletal and connective tissue disorders. Similarly, during risk period 2, 8 AEs [8 (2.47%) subjects] of General disorders and administration site conditions were reported followed by 2 AEs [2 (0.62%) subjects] of Skin and subcutaneous tissue disorders, and 1 AE, each [1 (0.31%) subject, each] of Gastrointestinal disorders and Musculoskeletal and connective tissue disorders.

Of total 9 MAAEs, 8 systemic MAAEs were reported in 8 (2.47%) subjects, of which 3 MAAEs [3 (3.57%) subjects] were reported in BECOV2C group followed by 2 MAAEs, each [2 (2.56%) subjects, each] in BECOV2D and BECOV2A group and 1 MAAE [1 (1.19%) subject] in BECOV2B group. None of the reported MAAE was serious. Majority MAAEs [4 MAAEs in 4 (1.23%) subjects] were of Pyrexia followed by 2 MAAEs, each of Headache [2 (0.62%) subjects] and Urticaria [2 (0.62%) subjects].

A total of 7 (2.16%) subjects reported 8 cases of fever increment of ≥100.4°F after vaccination (Day 0 - Day 6), of which majority subjects [3 cases in 3 (3.85%) subjects] belong to the BECOV2A group. Two (0.62%) subjects [1 each from BECOV2D and BECOV2A group] reported 3 cases of fever increment of ≥101.3°F after vaccination; 1 (1.28%) subject of BECOV2D group reported 1 case of fever increment of ≥102.2°F after vaccination. Of the reported cases of fever increment, most of the cases lasted for 24 hours [5 cases in 5 (1.54%) subjects], and most cases [6 cases in 6 (1.85%) subjects] of fever increment were of Grade 1. The maximum and minimum temperature recorded was 100.4:102.4°F; the time of onset was 12 hours while time to resolution was 38 hours. Most of the cases of fever increment [5 cases in 5 (1.54%) subjects] were reported during risk period 1. The mean (±SD) duration of fever (in days) after vaccination (Day 0 – Day 6) of total vaccinated group was 2.6 ± 1.51 days.

1.2.3. Proposed Dosage and Administration

The study vaccine should be administered intramuscularly in the deltoid muscle of muscle of the upper arm. Each study subject will receive a 0.5 mL dose of study vaccine. Two doses should be administered with 28 days interval between doses.

Please refer to the Investigator's Brochure for complete details on the pre-clinical studies conducted for the study vaccine.

1.2.4. Possible Side Effects and Contraindications

The most commonly reported solicited local adverse events (AEs) were injection site pain, redness and swelling.

The most commonly reported solicited systemic AEs were fever, headache, chills, myalgia, fatigue, urticaria, nausea and arthralgia.

Anaphylactic reactions to vaccines are extremely rare but have the potential to be fatal. The mainstay in the treatment of severe anaphylaxis is the prompt use of adrenaline, which can be lifesaving. It should be used at the first suspicion of anaphylaxis. As with the use of all vaccines the vaccinees should remain under observation for not less than 6 hours for possibility of occurrence of any rapid allergic reactions. *For more details, please refer to the Investigator's Brochure.*

Clinical experience has exceptionally recorded isolated reactions involving the CNS. These more serious reactions have however, not been directly linked to vaccination.

The study vaccine is contraindicated for use in individuals receiving corticosteroids, other immuno-suppressive drugs or undergoing radio-therapy, as they may not develop an optimal immune response. The study vaccine should not be given in febrile states, pregnancy, acute infectious diseases, leukaemia, severe anaemia and other severe diseases of the blood system, severe impairment of the renal function, decompensated heart diseases, following administration of gammaglobulin or blood transfusions or to subjects with potential allergies to vaccine components.

1.3. Study Rationale

SARS-CoV-2 belongs to the family Coronaviridae, which includes a large number of species capable of infecting various wild animals, some of which also affect humans. In humans, several coronaviruses are known to cause respiratory infections ranging from the common cold (20-30%) to more severe diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). The most recently discovered coronavirus causes coronavirus disease COVID-19.

The coronavirus COVID-19 pandemic is defining the global health crisis of our times and the greatest challenge humanity ever faced since World War Two. Since its emergence in Asia late last year, the COVID-19 has been spreading at a supersonic speed as a severe deadly disease, causing considerable anxieties at all levels and now reported on every continent except Antarctica. There are no drugs or other proven therapeutic options to prevent or treat COVID-19.

Current clinical management includes infection prevention, supportive medical care including supplemental oxygen and mechanical ventilator support when indicated. Since the number of people infected with COVID-19 continues to rise in alarming rate globally, the full extent and severity of this outbreak still remains unclear.

As the name suggests, the virus is novel, therefore humans have no natural immunity to it, and researchers must start from square one to develop a vaccine to educate the immune system to defending itself from the virus. Numerous pharma and academic institutes are racing to develop a vaccine against SARS-CoV-2 across the world, including India. Developing an effective and safe vaccine is urgently needed to prevent infection by severe acute respiratory syndrome (SARS)–associated coronavirus (SARS-CoV2). In the absence of a definite therapeutic drug, Indian regulatory authorities have kept an option open for an “emergency authorisation” of the vaccines that are undergoing clinical trials for use. Recently, COVID-19 vaccines have been granted permission for emergency use via Emergency Use Authorization (EUA) of US FDA and UK MHRA, including two mRNA-based vaccines from Moderna and Pfizer, and a chimpanzee adenoviral vector-based vaccine from Astrazeneca. A whole virion vaccine from Bharat Biotech, India has also received EUA from Indian regulator for use domestically in India.

The spike (S) protein of SARS-CoV-2 is the major inducer of neutralizing antibodies, and the receptor-binding domain (RBD) in the S1 subunit of S protein contains multiple conformational neutralizing epitopes. This suggests that recombinant proteins containing RBD and vectors encoding the RBD sequence can be used to develop safe and effective SARS vaccines. Biological E’s recombinant RBD antigen contains the major neutralizing epitopes in the S protein.

As a part of the global effort, Biological E. has initiated research towards development of a novel protein RBD subunit vaccine targeting this spike antigen of the novel corona virus-2. By preventing disease and reducing the need for treatment, vaccines help lower the risk of disease, antibiotic misuse and the development of drug resistance.

Based on literature, the receptor-binding domain (RBD) in the S1 subunit of the SARS-CoV-2 spike (S) protein is the most important target for developing a SARS vaccine. In particular, RBD of S protein contains the critical neutralizing domain (CND), which is able to induce highly potent neutralizing antibody response and cross-protection against divergent SARS-CoV strains. Furthermore, a RBD-based subunit vaccine is expected to be safer than other vaccines that may induce Th2-type immunopathology.

RBD, a fragment (≈193 aa residues) in the middle of S1 subunit of S protein, is responsible for virus binding to the receptor on target cells. The S2 subunit, which contains a putative fusion peptide and 2 heptad repeats (HR1 and HR2), is responsible for fusion between the viral and target cell membranes. Infection by SARS-CoV-2 is initiated by binding of RBD in the viral S protein S1 subunit to ACE2 on target cells. This forms a fusogenic core between the HR1 and HR2 regions in the S2 domain that brings the viral and target cell membranes into close proximity, which results in virus fusion and entry. This scenario indicates that the S protein may be used as a vaccine to induce antibodies for blocking virus binding and fusion.

Keeping this mechanism in view, Biological E developed a vaccine targeting the S1 subunit of the SARS-CoV-2 spike (S) protein. A phase-I seamlessly followed by phase-II clinical trial was conducted in India. This trial assessed the safety, tolerability, reactogenicity and immunogenicity of its novel protein RBD subunit vaccine to induce anti-SARS-CoV-2 IgG and neutralising antibodies for blocking virus binding and fusion thereby offering preventive protection.

As part of development of the vaccine candidate, immunogenicity studies were performed in mice. In those studies, addition of CpG 1018 to the formulation resulted in significant increase in overall immunogenicity. Based on this data, two concentrations of CpG 1018 were chosen for evaluation in Phase I/II study i.e. 500 and 250 mcg per dose in addition to RBD concentrations of 15, 25 and 50 mcg. Formulations BECOV2B and BECOV2C consisted of same RBD-antigen content of 25 mcg per dose but differed in CpG 1018 content and Aluminium Hydroxide Content i.e. CPG at 500 and 250 mcg/dose and Aluminium Hydroxide at 750 and 500 mcg/dose respectively.

Detailed comparison showed substantial increase in all immunogenicity parameters in BECOV2B-500 mcg formulation as compared to BECOV2C-250 mcg formulation; thus confirming the crucial role played by CpG 1018. Hence, to further enhance vaccine immunogenicity which will also increase vaccine efficacy and improve the consistency of immune response (narrowing of CI around GMT), CpG 1018 content of the formulation will be increased from 500 to 750 mcg per dose. In addition to observations from the Phase I/II studies, higher CpG content resulted in higher immunogenicity of Hepatitis-B Surface antigen in prior clinical studies and in proof of concept studies conducted for CORBEVAX formulations in mice.

Excellent safety profile observed for the current vaccine coupled with significant clinical experience associated with vaccines containing much higher CpG 1018 content provides assurance of similar safety profile for CORBEVAX containing 750 mcg of CpG per dose (reference : Heplisav-B product contains 3000 mcg of CpG 1018 per dose; Clover Biopharma protein sub-unit COVID19 vaccine that is in Phase III contains 1500 mcg of CpG 1018)

Formulation development studies have shown that the current formulation can handle additional CpG till 750 mcg/dose without any adverse impact on RBD or CpG adsorption to Alum or RBD antigenicity. This was confirmed by demonstration of comparable quality attributes in process validation batches conducted at 20 & 130L scale for the two formulations. These studies also indicate comparable stability profile for CORBEVAX formulations containing 500 and 750 mcg of CpG per dose.

This current Phase II study for demonstrating safety in a small sample size of N=100 which will seamlessly progress to Phase-III (N=1168) study which is aimed at demonstrating seroconversion rates of anti-SARS-CoV-2 neutralizing and IgG antibodies using a two-dose vaccination schedule (0, 28D).

2. STUDY OBJECTIVE AND ENDPOINTS

2.1. Study Objectives – Phase II

2.1.1. Primary Objective

- To assess the safety, tolerability and reactogenicity of two intramuscular doses of CORBEVAX vaccine in 18-55 years old (both inclusive) healthy adult males and non-pregnant female subjects.

2.1.2. Secondary Objectives

- To assess the immunogenicity of two intramuscular doses of SARS-CoV-2 COVID-19 vaccine, administered with a 28-day interval between doses, in 18-55 years old (both inclusive) healthy adult males and non-pregnant female subjects.

2.2. Study Endpoints – Phase II

2.2.1. Primary Endpoint

- Proportion of subjects with solicited adverse reactions/symptoms during first 60 minutes of post vaccination observation period and for subsequent 7 consecutive days (Day 0-6) captured through subject diary.
- Proportion of subjects with unsolicited adverse events (AEs) during the subsequent 28-day follow-up period after each dose.
- Serious adverse events (SAEs) and medically attended adverse events (MAAE) in all subjects at 6- and 12-months post 2nd dose.

2.2.2. Secondary Endpoints

- Anti-RBD IgG concentrations (GMC, Fold Rise, GMFR) at baseline, day 28, 42 and 56 and at 6 and 12 months post second dose.
- Anti-RBD IgG subclass assessment in terms of ratio of IgG1 to IgG4 titers at day 42 & day 56.
- Neutralizing antibody titre (GMT, Fold Rise, GMFR) against SARS-CoV-2 (Pseudovirus or wild type) at baseline, day 28, 42, 56 and at 6 and 12 months post second dose.
- Cell mediated immunity assessment in terms of cytokine expression from stimulated PBMCs (INF-γ, IL-4) at baseline and at day 42 (14 days' post-second dose) in a subset of subjects.

2.3. Study Objectives – Phase III

2.3.1. Primary Objective

- To assess the immunogenicity of two intramuscular doses of SARS-CoV-2 COVID-19 vaccine, administered with a 28-day interval between doses, in 18-

80 years old (both inclusive) healthy adult males and non-pregnant female subjects.

2.3.2. Secondary Objectives

- To assess the safety, tolerability and reactogenicity of two intramuscular doses of CORBEVAX vaccine in 18-80 years old (both inclusive) healthy adult males and non-pregnant female subjects.

2.3.3. Exploratory Objective

- Total IgG & neutralising antibodies at day 56 in a subset of subjects.
- Persistence of both virus neutralising and IgG antibodies at 6 months and 12 months post 2nd dose.
- Neutralising antibodies against UK, South Africa, Brazil, B.1.617 variants in a subset of population.

2.4. Study Endpoints – Phase III

2.4.1. Primary Endpoint

- Anti-RBD IgG antibodies and subclass assessment in terms of ratio of IgG1 to IgG4 anti-RBD titers at day 42 and proportion of subjects with ≥4-fold rise in IgG1 anti-RBD antibody titers at day 42 vs baseline.
- Neutralizing antibody titre against SARS-CoV-2 (Pseudovirus or wild type) at baseline and again at day 42.
- Immunogenicity in terms of GMC/T of anti-RBD IgG antibodies and neutralizing antibodies at baseline and again at day 42.
- Proportion of subjects seroconverted in terms of ≥2-fold & ≥4-fold rise in anti-RBD IgG antibodies and neutralizing antibodies by overall and by ≥4-fold rise in baseline seronegative subjects and ≥2-fold rise in baseline seropositive subjects along with their GMFR at day 42.
- Cell mediated immunity assessment in terms of cytokine expression from stimulated PBMCs (INF-γ, IL-4) at baseline and at day 42 (14 days' post-second dose) in a subset of subjects.

2.4.2. Secondary Endpoints

- Proportion of subjects with solicited adverse reactions/symptoms during first 60 minutes of post vaccination observation period and for subsequent 7 consecutive days (Day 0-6) captured through subject diary.
- Proportion of subjects with unsolicited adverse events (AEs) during the 28-day follow up period after each dose.
- Serious adverse events (SAEs), if any, during the entire study period.
- Medically attended adverse events (MAAE), during the entire study period.
- Safety follow-up visit for all subjects at 6- and 12-months post 2nd dose.

2.4.3. Exploratory Endpoints

- Anti-RBD IgG concentrations & Neutralizing antibody titre (GMC, Fold Rise, GMFR) and Anti-RBD IgG subclass assessment in terms of ratio of IgG1 to IgG4 titres at day 56 in a subset of subjects.
- Virus neutralising and IgG antibodies at 6 months and 12 months post 2nd dose in comparision with Day 42.
- Neutralising antibodies against UK, South Africa, Brazil, B.1.617 variants in a subset of population at Day 42.

Definitions to be considered for this protocol:

- Seronegative (SN) is defined as subjects with no detectable VNT antibody (below the lower limit of detection [LLOD]) or no quantifiable antibody (below the lower limit of quantification [LLOQ]).
- Seropositive (SP) is defined as subjects with detectable VNT antibody (above the lower limit of detection [LLOD]) or quantifiable antibody (above the lower limit of quantification [LLOQ]).
- Seroconversion is defined as proportion of subjects achieving ≥4-fold rise in VNT antibodies in baseline seronegative subjects and ≥2-fold rise in baseline seropositive subjects.

Note: In subjects with quantifiable VN antibody titre prior to vaccination, seroconversion is commonly predefined by a ≥2-fold-increase from pre- to post-vaccination as a measure of immunogenicity.

Note: The neutralisation test is the standard method used to confirm the presence of neutralizing antibodies against SARS-CoV-2.

3. STUDY DESIGN

3.1. Overview of the Study Design

This is a prospective, open-label, single arm, phase II seamlessly followed by Phase III clinical study design to evaluate the immunogenicity and safety of CORBEVAX vaccine for Protection Against COVID-19 Disease When administered to COVID-19-Negative Adult Subjects between18-80 years of age.

A total of 1268 male and non-pregnant female adult, from moderate to high-risk population with and without comorbidities will be enrolled across both phases of the study. Subjects must be RT-PCR negative to SARS-CoV-2 antigen from nasopharyngeal swab at the time of screening.

A total of 100 subjects, aged 18 to 55 years, will be enrolled in Phase II for safety assessment. Each enrolled subject will receive 0.5 mL dose of the study test vaccine intramuscularly in a 2-dose schedule with 28 days' interval between doses. In phase II of the study, there will be a total of 7 study visits for each subject. Subjects will initially be invited for a screening visit (Day -3 to -1) to assess the eligibility criteria set, day -3 to -1 prior to the 1st dose of vaccination. Prior to attending, they will receive written information about the study and will have adequate time to consider their

participation. At the screening visit, an attending physician will explain the study and answer any questions they may have regarding the study and implications of their participation. If the subject decides to take part, they will be asked to sign a consent form. The attending physician will then check whether the subject is eligible to take part. Day of the 1st vaccination will be considered as day 0. Subjects will receive the second dose of the study vaccine at Day 28 in the study. All subjects will then have follow-up visits at day 42, day 56, at 6 months (28+180) and at 12 months (28+365) post second dose. A whole blood sample of 10-20 mL will be collected intravenously at protocol-specified time points, as specified in the schedule of assessment table, by a trained nurse or a phlebotomist.

The interim immunogenicity data will be submitted to CDSCO. After submission of the interim immunogenicity data to the CDSCO, the enrolment will commence into phase III part of the study. The 100 subjects of phase II will continue to be followed up till 12 months for any SAEs and medically attended AEs.

A total of 1168 subjects, aged 18 to 80 years, will be enrolled in Phase III to receive BioE's study vaccine. Subjects will receive 0.5 mL dose of the test vaccine intramuscularly in a 2-dose schedule with 28 days' interval between doses. All subjects will be followed up to 12-months post the second dose. There would be a total of 7 study visits for each subject during the study period. Subjects will initially be invited for a screening visit (Day -3 to -1) to assess the eligibility criteria set, day -3 to -1 prior to the 1st dose of vaccination. Prior to attending, they will receive written information about the study and will have adequate time to consider their participation. At the screening visit, an attending physician will explain the study and answer any questions they may have regarding the study and implications of their participation. If the subject decides to take part, they will be asked to sign a consent form. The attending physician will then check whether the subject is eligible to take part. Day of the 1st vaccination will be considered as day 0. Subjects will receive the second dose of the study vaccine at Day 28 in the study. All subjects will then have follow-up visits at day 42, day 56, at 6 months (28+180) and at 12 months (28+365) post second dose. A whole blood sample of 10-20 mL will be collected intravenously at protocol-specified time points, as specified in the schedule of assessment table, by a trained nurse or a phlebotomist.

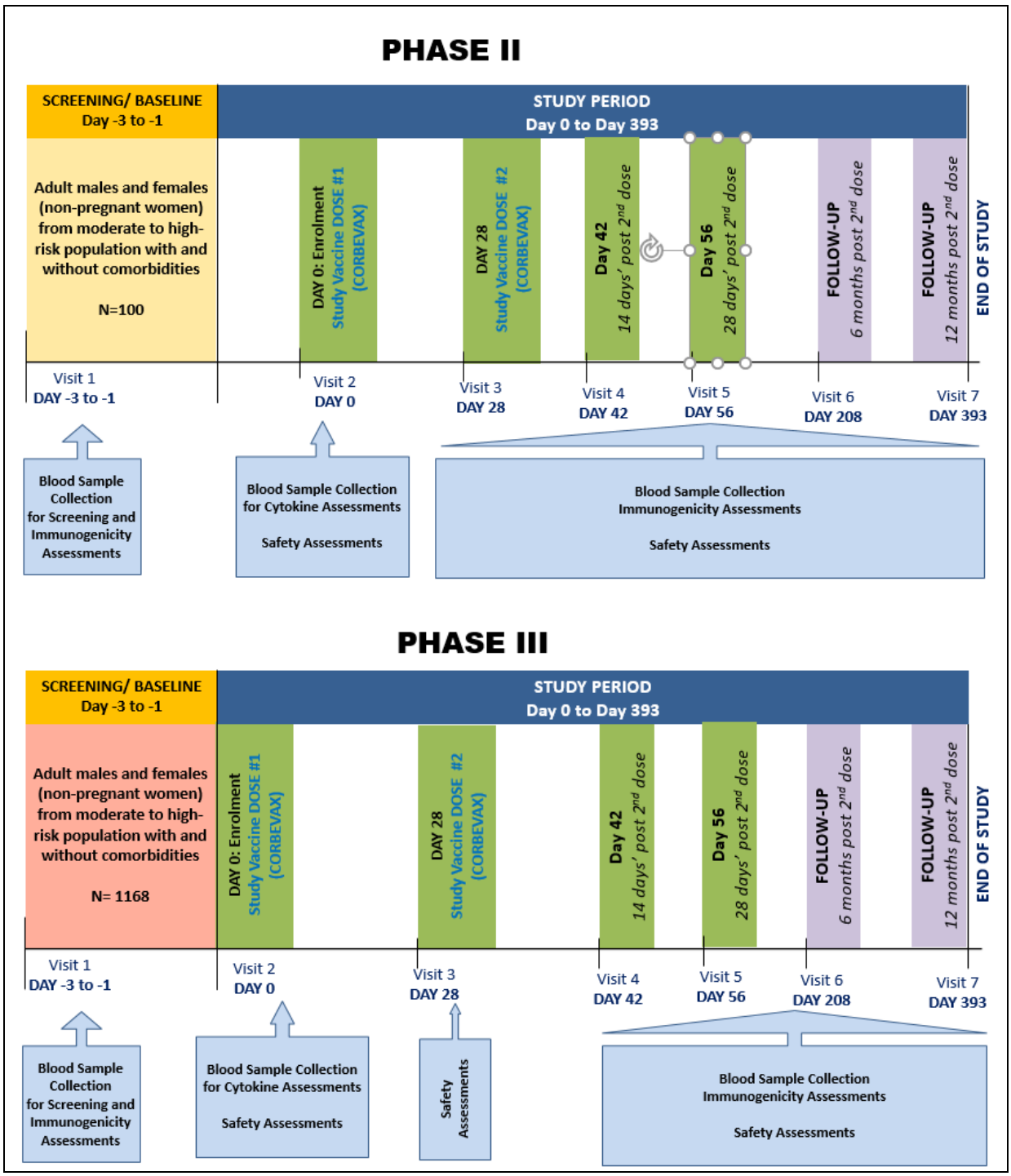
In both phases of the study, subjects will be asked to contact the study team if they develop any symptoms suggestive of COVID-19 at any point during the trial. Symptomatic subjects will be asked to present for an unscheduled visit to test for SARS-CoV-2 by RT-PCR. Dedicated isolation rooms at each study site will be kept for the enrolled clinical trial subjects, in case the subject diagnosed as COVID-19 positive throughout the study period.

Independent DSMB Review:

An independent data safety monitoring board (DSMB) setup, will review cumulative day 56 Phase-III safety data (up to 28 days post 2nd dose) at visit-5, for all the enrolled subjects in this Phase-II seamlessly followed by Phase-III study.

The study flow chart is provided in Figure 1 below.

Figure 1: Study Flow Chart



3.2. Study Duration

The duration of study participation for the subject is approximately 13 months i.e. 3 days for Screening followed by 1 months of 2 dose administration, and follow-up till 12 months post second dose.

3.3. Study Centres

The study will be conducted across approximately 15 study centres in India.

3.4. Blinding

This is a multicentre open-label, single-arm, study. Hence, no blinding will be applicable.

3.5. Randomization

This is a multicentre open-label, single-arm, study. Randomization is not applicable for this study.

3.6. Subject identification numbering system

In both phases of the study, each subject will be assigned a unique **'subject identification number'** as follows:

Phase II: A-xx-xxx

Phase III: B-xx-xxx

- A represents Phase II part of the study;
- B represents Phase III part of the study; and
- the first two digits will be the Site Number (xx) that stands unique for each centre (e.g.: 01, 02, 03, and so on), followed by
- next three digits (xxx) representing the subject number, given sequentially at the site i.e. 001, 002, 003, etc.

The subject will continue this unique identification number throughout the study. If a subject fail to qualify, his/her screening number will not be used for another subject. The voluntary informed consent is obtained from each subject or legally acceptable representative voluntary consent prior to screening.

3.6.1. Method of assigning treatments to subjects

Subjects who are screened, and meet all of the inclusion and none of the exclusion criteria and who have turned up for the Day 0 will be enrolled in the study. Day 0 is the day when the subject receives the first dose of the study vaccine. Each subject dosing visit will be registered in the IWRS.

3.7. Termination/Discontinuation/Modification of the Study

This study may be terminated at the discretion of the Regulatory Authority or the Sponsor if it becomes aware of any medical reasons for doing so, or for administrative reasons that the Sponsor deems appropriate. An Investigator may elect to discontinue or stop the study at his/her study centre for any reason including safety or low enrolment.

Study vaccination for any individual subject will be stopped if the subject experiences a possibly vaccine-related serious adverse event (SAE) or a possibly vaccine-related clinically significant non-serious adverse event (AE), which in the opinion of the Principal Investigator or Sponsor, warrants the discontinuation of the vaccination for the subject's well-being. The subject will continue to be part of the study despite the stoppage of vaccine dosing and will continue to provide all scheduled assessments per-protocol (see Section 4.3 for details).

4. SUBJECT ELIGIBILITY CRITERIA

4.1. Inclusion Criteria

Subjects must meet ALL of the following inclusion criteria to be included in this study.

Inclusion Criteria <u>ONLY</u> for Phase II:

1. Male or female (non-pregnant) subject between ≥ 18 to 55 years of age.
2. Subject seronegative to anti-SARS-CoV-2 antibody prior to enrolment.

Inclusion Criteria <u>ONLY</u> for Phase III:

1. Male or female subject between ≥ 18 to 80 years of age.

Inclusion Criteria for Phase II and Phase III:

1. Subject or their legally acceptable representative (LAR) is willing to provide a written informed consent for voluntary participation in the study.
2. Subject, in the opinion of the investigator, has ability to communicate and willingness to comply with the requirements of the protocol.
3. Subject is virologically seronegative to SARS-CoV-2 infection as confirmed by RT-PCR prior to enrolment.
4. Subject is seronegative to HIV 1 & 2, HBV and HCV infection prior to enrolment.
5. Subject is considered of stable health as judged by the investigator, determined by medical history and physical examination.
6. Female subject of child bearing potential must have a negative urine pregnancy test (UPT), and willingness to avoid becoming pregnant through use of an effective method of contraception or abstinence from the time of study enrolment until six weeks after the last dose of vaccination in the study.

7. Male subject, who is sexually active, must agree to use double-barrier contraception (e.g. condom with spermicide) with his female partner during the study period. Male subject should also agree to avoid semen donation or providing semen for in-vitro fertilization during the study duration.
8. Subject agrees not to participate in another clinical trial at any time during the total study period.
9. Subject agrees to refrain from blood donation during the course of the study.
10. Subject agrees to remain in the town where the study centre is located, for the entire duration of the study.

4.2. Exclusion Criteria

Exclusion criteria for Phase II and Phase III:

Subjects who meet ANY of the following criteria will NOT BE ELIGIBLE for this study.

1. History of vaccination with any investigational or approved vaccine against COVID-19 disease.
2. Subject living in the same household as that of any active COVID-19 positive individual at the time of enrolment.
3. History of receipt of any licensed vaccine within 1 month prior to screening, likely to impact on interpretation of the trial data (e.g., influenza vaccines);
4. Subjects with any clinically significant abnormal haematology and biochemical laboratory parameters tested at screening as judged by the investigator.
5. Subjects with Body temperature of ≥100.4°F (>38.0°C) or symptoms of an acute illness at the time of screening or prior to vaccination.
6. Pregnant women, nursing women or women of childbearing potential who are not actively avoiding pregnancy during the study.
7. Subjects with known current or chronic history of any of the following conditions, likely to affect participation in the study:
    - severe psychiatric conditions;
    - any bleeding disorder (e.g. factor deficiency, coagulopathy or platelet disorder);
    - allergic disease or reactions likely to be exacerbated by any component of the study vaccine (BE CORBEVAX vaccine);
    - neurological illness, and any other serious chronic illness requiring hospital specialist supervision.
8. Subjects requiring chronic administration (defined as more than 14 days in total) of immunosuppressant (e.g. corticosteroids, cytotoxic drugs or antimetabolites, etc.) or other immune-modifying drugs (e.g. interferons) during the period starting six months prior to the first vaccine dose including use of any blood products.
    - For corticosteroids, this will mean prednisone ≥0.5 mg/kg/day, or equivalent.
    - Inhaled and topical steroids are allowed.

- Receipt of prohibited concomitant medication that may jeopardize the safety of the participant or interpretation of the data.

9. Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
10. Any medical condition that in the judgment of the investigator would make study participation unsafe.
11. Planned use of any investigational or non-registered product other than the study vaccine during the trial period or 3 months prior to enrolment.
12. Current or planned participation in prophylactic drug trials for the duration of the study.
13. Individuals who are part of the study team or close family members of individuals conducting the study.

4.3. Criteria for Discontinuation or Withdrawal of Subjects

The Subject/LAR will be informed that they are free to withdraw their consent from either phase of the study at any time without stating the reason.

Pre-mature withdrawal of the subject from the study may occur, if:

- The subject/LAR withdraws consent from either phase of the study.
- Failure of the subject or legally acceptable representative for whatever reason to comply with key requirements of the protocol and the study procedures/assessments
- Subjects who drop out.
- Death of the subject.

Pre-mature discontinuation (of study vaccine) for the subject in the study may occur, if:

- The subject develops signs and symptoms of COVID-19. The clinical manifestations of COVID-19 range from fever, cough, fatigue or malaise, sore throat, shortness of breath and less common symptoms such as headache, nausea and diarrhoea. The most common abnormalities in vital signs are increased temperature and tachypnoea.
    - If the subject develops COVID-19 infection between 1st and 2nd dose, the 2nd dose will be deferred till 1 to 3 months' post-recovery at the discretion of the Investigator.
    - If the subject develops COVID-19 after the 2nd dose, the subject will still continue to be in the study for safety follow-up (*unless only if the subject withdraws consent*).

- The subject suffers from a significant disease or undergoes surgery during the course of the study.
- The subject experiences serious adverse events and discontinuation would be in the best interest of the subject as per the Investigator.
- Discontinuation from the vaccination is considered by the Investigator to be in the subject's best interest.

Note: Pre-mature discontinuation of study vaccine will not lead to drop-out or withdrawal of the subject from the study, unless as per the criteria for pre-mature withdrawal listed above. The study visits, assessments, and safety follow-up as per the schedule of assessments should be completed for all subjects discontinued for study vaccine but continued in the study till the end of study visit.

A subject who returns for the concluding visit foreseen in the protocol is considered to have completed the study. For drop-out definition, please see section 4.4.

The discontinuation/withdrawal of a subject from the study must be immediately reported to the CRO/Sponsor Staff.

Subjects who are enrolled and dosed, but discontinued or withdrawn will not be replaced in this study.

4.4. Screening Failure and Dropout of Subjects

Applies to both, Phase II and Phase III of the study

Screened failure: All subjects who sign an informed consent (via ICF) but fail to meet any of the eligibility criteria or withdraw consent prior to enrolment, or do not turn up for enrolment, being eligible in the study will be considered as screening failures. The reason for screen failure will be documented. Re-screening of these subjects is not allowed.

The definition of dropout:

A 'drop-out' is defined as any subject who did not come back for the concluding visit foreseen in the protocol. A subject who returns for the concluding visit foreseen in the protocol is considered to have completed the study in spite of his/her missing a visit.

Dropout cases management: Dropouts will not be replaced. Investigators will make at least 3 attempts to contact those subjects who do not return for scheduled visits or follow-up. Information gathered will be described on the study conclusion page of the eCRF and on medication/adverse event form as required.

It will be specified on the Study Conclusion page of the eCRF as which of the following possible reasons were responsible for dropout of the subject from the study:

1. Serious adverse event
2. Non-serious adverse event
3. Protocol violation (specify)
4. Consent withdrawal, not due to an adverse event
5. Migration from the study area
6. Lost to follow-up
7. Other (specify)

5. STUDY PROCEDURES

5.1. Overview of Study Visits – Phase II

There would be a total of 7 study visits for each subject during the Phase II study period on stipulated time points as below:

- VISIT 1: Screening Baseline (Day -3 to -1)
- VISIT 2: Study Vaccine Dose #1 (Day 0)
- VISIT 3: Study Vaccine Dose #2 (Day 28)
- VISIT 4: Follow-up – 14 days post 2nd dose (Day 42)
- VISIT 5: Follow-up – 28 days post 2nd dose (Day 56)
- VISIT 6: Follow-up – 6 months post 2nd dose (Day 208)
- VISIT 7: Follow-up – 12 months post 2nd dose (Day 393)

Subjects will initially be invited for a screening visit (Day -3 to -1) to assess the eligibility criteria set, day -3 to -1 prior to the 1st dose of vaccination. Prior to attending, they will receive written information about the study and will have adequate time to consider their participation. At the screening visit, an attending physician will explain the study and answer any questions they may have regarding the study and implications of their participation. If the subject decides to take part, they will be asked to sign a consent form. The attending physician will then check whether the subject is eligible to take part.

All the subjects will undergo a screening visit up to 3 days prior to enrolment. Eligible subjects will be enrolled in the study to receive the first dose of the study vaccine. The day of the 1st vaccination will be considered as Day 0 in the study. The subject will be followed up at 7 days (day 0 – day 6), post the first dose. Subjects will receive the second dose of the study vaccine at Day 28 in the study. All subjects will then have follow-up visits at day 42, day 56, at 6 months (28+180) and at 12 months (28+365) post second dose.

Please refer to Section 5.2 below for a detailed description of visit-wise assessments to be done throughout the study.

Please refer to the Phase II Schedule of Assessments provided in Section 5.3 below for detailed information on study assessments and timepoints.

Details of study assessments and parameters to be recorded are presented in Section 6 below.

5.2. Observations by Visit – Phase II

5.2.1. Visit 1: Screening Baseline [Day -3 to -1]

- Written informed consent [Prior to any study-related procedures]
- Assignment of subject identification number and registration in IWRS
- Evaluation of inclusion/exclusion criteria
- Demographic details
- Vaccination history; medical and surgical history; prior medications
- Vital signs [body temperature, Pulse rate, blood pressure, respiratory rate]
- History-directed physical examination
- Height and weight measurements
- Real-time Reverse transcriptase polymerase chain reaction (RT-PCR) using nasopharyngeal swab
- Blood sample collection (20 mL) for immunogenicity assessment
    - *Anti-SARS-CoV-2 IgG antibody estimation*
    - *Anti-SARS-CoV-2 IgG subclasses IgG1 & IgG4 estimation*
    - *SARS-CoV-2 virus neutralising Antibody (NAb) estimation*
- Laboratory assessments – Haematology & Biochemistry; Serology for HIV 1&2, HBV and HCV
- Urine pregnancy test – only for females of child-bearing potential

5.2.2. Visit 2: Study Vaccine Dose-1 [Day 0]

- Re-confirmation inclusion/exclusion criteria
- Registration of Enrolment visit in IWRS
- Vital signs [body temperature, Pulse rate, blood pressure, respiratory rate]
- History-directed physical examination
- Check contraindications and warnings and precautions before administration of study vaccine dose
- Blood sample collection (10 ml) for cellular immunity assessment via ELISPOT or TrueCulture method
- Dose #1: Study Vaccine administration (0.5mL IM; deltoid muscle)
- Post-vaccination observation for 60 minutes
- Concomitant medications recording

- Subject diary distribution and training
- Adverse event (AE) recording and reporting instructions
    - Recording of solicited local and general AEs within 7 days post-vaccination
    - Recording of non-serious (unsolicited) AEs, serious AEs (SAEs) and medically attended AEs

5.2.3. Visit 3: Study Vaccine Dose-2 [Day 28]

- Registration of subject visit in IWRS
- Vital signs [body temperature, Pulse rate, blood pressure, respiratory rate]
- History-directed physical examination
- Check contraindications and warnings and precautions before administration of study vaccine dose
- Urine pregnancy test – only for females of child-bearing potential
- Blood sample collection (10 mL) for immunogenicity assessment
    - *Anti-SARS-CoV-2 IgG antibody estimation*
    - *SARS-CoV-2 virus neutralising Antibody (NAb) estimation*
- Dose #2: Study Vaccine administration (0.5mL IM; deltoid muscle)
- Post-vaccination observation for 60 minutes
- Concomitant medications recording
- Subject diary retrieval, and distribution of new diary and training
- Adverse event (AE) recording and reporting
    - Recording of solicited local and systemic AEs within 7 days post-vaccination
    - Recording of solicited AEs, unsolicited AEs, serious AEs (SAEs) and medically attended AEs

5.2.4. Visit 4: Follow-up - 14 days post 2nd dose [Day 42]

- Vital signs [body temperature, Pulse rate, blood pressure, respiratory rate]
- History-directed physical examination
- Blood sample collection (20 mL) for immunogenicity assessment
    - *Anti-SARS-CoV-2 IgG antibody estimation*
    - *Anti-SARS-CoV-2 IgG subclasses IgG1 & IgG4 estimation*
    - *SARS-CoV-2 virus neutralising Antibody (NAb) estimation*
    - *Cellular immunity assessment via ELISPOT or TrueCulture method*

- Concomitant medications recording
- Diary review/retrieval and re-distribution of diary and training
- Adverse event (AE) recording and reporting
    - Recording of solicited AEs, unsolicited AEs, serious AEs (SAEs) and medically attended AEs

5.2.5. Visit 5: Follow-up - 28 days post 2nd dose [Day 56]

- Vital signs [body temperature, Pulse rate, blood pressure, respiratory rate]
- History-directed physical examination
- Blood sample collection (20 mL) for immunogenicity assessment
    - *Anti-SARS-CoV-2 IgG antibody estimation*
    - *Anti-SARS-CoV-2 IgG subclasses IgG1 & IgG4 estimation*
    - *SARS-CoV-2 virus neutralising Antibody (NAb) estimation*
- Laboratory assessments – Haematology & Biochemistry
- Concomitant medications recording
- Diary retrieval
- Adverse event (AE) recording and reporting
    - Recording of unsolicited AEs, serious AEs (SAEs) and medically attended AEs

5.2.6. Visit 6: Follow-up - 6 months post 2nd dose [Day 208]

- Vital signs [body temperature, Pulse rate, blood pressure, respiratory rate]
- History-directed physical examination
- Blood sample collection (10 mL) for immunogenicity assessment
    - *Anti-SARS-CoV-2 IgG antibody estimation*
    - *SARS-CoV-2 virus neutralising Antibody (NAb) estimation*
- Recording of AEs, serious AEs (SAEs) and medically attended AEs

5.2.7. Visit 7: Follow-up – 12 months post 2nd dose [Day 393]

- Vital signs [body temperature, Pulse rate, blood pressure, respiratory rate]
- History-directed physical examination
- Blood sample collection (10 mL) for immunogenicity assessment
    - *Anti-SARS-CoV-2 IgG antibody estimation*
    - *SARS-CoV-2 virus neutralising Antibody (NAb) estimation*
- Recording of AEs, serious AEs (SAEs) and medically attended AEs

5.3. Study Schedule of Assessments (SOA) – Phase II

Data to be collected during the conduct of the study and their corresponding time points are specified in the schedule of assessments (SOA) Table below:

SCHEDULE OF ASSESSMENTS [PHASE II]							
VISIT	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**
DAY	**Day -3 to -1**	**Day 0**	**Day 28 (+4)**	**Day 42 (+4)**	**Day 56 (+4)**	**Day 208 (+14)**	**Day 393 (+14)**
Assessments and Time Points	**Screen baseline**	**Dose-1**	**Dose-2**	**Follow-up**	**Follow-up**	**Follow-up**	**Follow-up**
Signed Informed consent	●						
Allocate subject identification number (Screening number) and registration in IWRS	●						
Inclusion/exclusion criteria evaluation	●	●					
Collect demographic data	●						
Record vaccination history	●						
Record personal medical history	●						
History directed physical examination	●	●	●	●	●	●	●
Check contraindications and warnings and precautions before vaccination		●	●				
Record body temperature	●	●	●	●	●	●	●
Record other vital signs (Pulse, BP, Respiratory rate)	●	●	●	●	●	●	●
Measure/record height and weight	●						
Record any concomitant medications/vaccinations	●	●	●	●	●	●	●
Only baseline screening against HIV 1&2, HBV and HCV	●						

SCHEDULE OF ASSESSMENTS [PHASE II]							
VISIT	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**
DAY	**Day -3 to -1**	**Day 0**	**Day 28 (+4)**	**Day 42 (+4)**	**Day 56 (+4)**	**Day 208 (+14)**	**Day 393 (+14)**
Assessments and Time Points	**Screen baseline**	**Dose-1**	**Dose-2**	**Follow-up**	**Follow-up**	**Follow-up**	**Follow-up**
Urine Pregnancy test in females only	●		●				
Real time RT-PCR nasopharyngeal swab)	●						
Immunogenicity assessments							
Blood sample collection	● (20 ml)	● (10 ml)	● (10 ml)	● (20 ml)	● (20 ml)	● (10 ml)	● (10 ml)
Haematology & Biochemistry parameters	●				●		
Anti-SARS-CoV-2 IgG antibody estimation	●		●	●	●	●	●
Anti-SARS-CoV-2 IgG subclasses IgG1 & IgG4 estimation	●			●	●		
SARS-CoV-2 virus neutralising Antibody (NAb) estimation	●		●	●	●	●	●
Cellular immunity assessment via ELISPOT or TrueCulture method		●		●			
Vaccine administration (0.5mL IM; deltoid muscle)		●	●				
60 minutes post-vaccination observation		●	●				
Safety Assessments							
Distribution of diary		●	●				

SCHEDULE OF ASSESSMENTS [PHASE II]							
VISIT	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**
DAY	**Day -3 to -1**	**Day 0**	**Day 28 (+4)**	**Day 42 (+4)**	**Day 56 (+4)**	**Day 208 (+14)**	**Day 393 (+14)**
Assessments and Time Points	**Screen baseline**	**Dose-1**	**Dose-2**	**Follow-up**	**Follow-up**	**Follow-up**	**Follow-up**
Recording of solicited local and systemic AEs within 7 days post-vaccination after each dose		●	●	●			
Recording of unsolicited AEs		●	●	●	●		
Return of diary *Diary to be reviewed and re-distributed at Day 42 for recording of AEs*			●	●	●		
Recording of SAEs and medically attended AEs		●	●	●	●		
Safety follow up after Day 56 for any SAEs and medically attended AEs for 12 months post 2nd dose						●	●

5.4. Overview of Study Visits – Phase III

There would be a total of 7 study visits for each subject during the study period on stipulated time points as below:

- VISIT 1: Screening Baseline (Day -3 to -1)
- VISIT 2: Study Vaccine Dose #1 (Day 0)
- VISIT 3: Study Vaccine Dose #2 (Day 28)
- VISIT 4: Follow-up – 14 days post 2nd dose (Day 42)
- VISIT 5: Follow-up – 28 days post 2nd dose (Day 56)
- VISIT 6: Follow-up – 6 months post 2nd dose (Day 208)
- VISIT 7: Follow-up – 12 months post 2nd dose (Day 393)

Subjects will initially be invited for a screening visit (Day -3 to -1) to assess the eligibility criteria set, day -3 to -1 prior to the 1st dose of vaccination. Prior to attending, they will receive written information about the study and will have adequate time to consider their participation. At the screening visit, an attending physician will explain the study and answer any questions they may have regarding the study and implications of their participation. If the subject decides to take part, they will be asked to sign a consent form. The attending physician will then check whether the subject is eligible to take part.

All the subjects will undergo a screening visit up to 3 days prior to enrolment. Eligible subjects will be enrolled in the study to receive BioE's test vaccine. The day of the 1st vaccination will be considered as Day 0 in the study. Subjects will receive the second dose of the study vaccine at Day 28 in the study. All subjects will then have follow-up visits at day 42, day 56, at 6 months (28+180) and at 12 months (28+365) post second dose.

Please refer to Section 5.5 below for a detailed description of visit-wise assessments to be done throughout the study.

Please refer to the study's Schedule of Assessments provided in Section 5.6 below for detailed information on study assessments and timepoints.

Details of study assessments and parameters to be recorded are presented in Section 6 below.

5.5. Observations by Visit – Phase III

5.5.1. Visit 1: Screening Baseline [Day -3 to -1]

- Written informed consent [Prior to any study-related procedures]
- Assignment of subject identification number and registration in IWRS
- Evaluation of inclusion/exclusion criteria
- Demographic details
- Vaccination history; medical and surgical history; prior medications
- Vital signs [body temperature, Pulse rate, blood pressure, respiratory rate]
- History-directed physical examination
- Height and weight measurements
- Blood sample collection (20 mL) for immunogenicity assessment
    - *Anti-SARS-CoV-2 IgG antibody estimation*
    - *Anti-SARS-CoV-2 IgG subclasses IgG1 & IgG4 estimation*
    - *SARS-CoV-2 virus neutralising Antibody (NAb) estimation*
- Real-time Reverse transcriptase polymerase chain reaction (RT-PCR) using nasopharyngeal swab
- Laboratory assessments – Haematology & Biochemistry; Serology for HIV 1&2, HBV and HCV
- Urine pregnancy test – only for females of child-bearing potential

5.5.2. Visit 2: Study Vaccine Dose-1 [Day 0]

- Re-confirmation inclusion/exclusion criteria
- Registration of Enrolment visit in IWRS
- Vital signs [body temperature, Pulse rate, blood pressure, respiratory rate]
- History-directed physical examination
- Check contraindications and warnings and precautions before administration of study vaccine dose
- Blood sample collection (10 ml) for cellular immunity assessment via ELISPOT or TrueCulture method
- Dose #1: Study Vaccine administration (0.5mL IM; deltoid muscle)
- Post-vaccination observation for 60 minutes
- Concomitant medications recording
- Subject diary distribution and training
- Adverse event (AE) recording and reporting

- Recording of solicited local and general AEs within 7 days post-vaccination
- Recording of non-serious (unsolicited) AEs, serious AEs (SAEs) and medically attended AEs

5.5.3. Visit 3: Study Vaccine Dose-2 [Day 28]

- Registration of subject visit in IWRS
- Vital signs [body temperature, Pulse rate, blood pressure, respiratory rate]
- History-directed physical examination
- Check contraindications and warnings and precautions before administration of study vaccine dose
- Urine pregnancy test – only for females of child-bearing potential
- Dose #2: Study Vaccine administration (0.5mL IM; deltoid muscle)
- Post-vaccination observation for 60 minutes
- Concomitant medications recording
- Subject diary retrieval and distribution of new diary and training
- Adverse event (AE) recording and reporting
    - Recording of solicited local and systemic AEs within 7 days post-vaccination
    - Recording of solicited AEs, unsolicited AEs, serious AEs (SAEs) and medically attended AEs

5.5.4. Visit 4: Follow-up - 14 days post 2nd dose [Day 42]

- Vital signs [body temperature, Pulse rate, blood pressure, respiratory rate]
- History-directed physical examination
- Blood sample collection (20 mL) for immunogenicity assessment
    - *Anti-SARS-CoV-2 IgG antibody estimation*
    - *Anti-SARS-CoV-2 IgG subclasses IgG1 & IgG4 estimation*
    - *SARS-CoV-2 virus neutralising Antibody (NAb) estimation*
    - *Cellular immunity assessment via ELISPOT or TrueCulture method*
- Concomitant medications recording
- Diary review/retrieval and re-distribution of diary and training
- Adverse event (AE) recording and reporting
    - Recording of solicited local and systemic AEs within 7 days post-vaccination

- Recording of solicited AEs, unsolicited AEs, serious AEs (SAEs) and medically attended AEs

5.5.5. Visit 5: Follow-up - 28 days post 2nd dose [Day 56]

- Vital signs [body temperature, Pulse rate, blood pressure, respiratory rate]
- History-directed physical examination
- Blood sample collection (20 mL) for laboratory assessments & immunogenicity assessment
  - Haematology & Biochemistry
  - *Anti-SARS-CoV-2 IgG antibody estimation*
  - *Anti-SARS-CoV-2 IgG subclasses IgG1 & IgG4 estimation*
  - *SARS-CoV-2 virus neutralising Antibody (NAb) estimation*
- Concomitant medications recording
- Diary review and retrieval
- Adverse event (AE) recording and reporting
  - Recording of solicited AEs, unsolicited AEs, serious AEs (SAEs) and medically attended AEs

5.5.6. Visit 6: Follow-up - 6 months post 2nd dose [Day 208]

- Vital signs [body temperature, Pulse rate, blood pressure, respiratory rate]
- History-directed physical examination
- Blood sample collection (10 mL) for immunogenicity assessment
  - *Anti-SARS-CoV-2 IgG antibody estimation*
  - *SARS-CoV-2 virus neutralising Antibody (NAb) estimation*
- Recording of AEs, serious AEs (SAEs) and medically attended AEs

5.5.7. Visit 7: Follow-up – 12 months post 2nd dose [Day 393]

- Vital signs [body temperature, Pulse rate, blood pressure, respiratory rate]
- History-directed physical examination
- Blood sample collection (10 mL) for immunogenicity assessment
  - *Anti-SARS-CoV-2 IgG antibody estimation*
  - *SARS-CoV-2 virus neutralising Antibody (NAb) estimation*
- Recording of AEs, serious AEs (SAEs) and medically attended AEs

5.6. Study Schedule of Assessments (SOA) – Phase III

Data to be collected during the conduct of the study and their corresponding time points are specified in the schedule of assessments (SOA) Table below:

SCHEDULE OF ASSESSMENTS [PHASE III]									
VISIT	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	*Interim Clinical Study Report*	**Visit 6**	**Visit 7**	*Clinical Study Report*
DAY	**Day -3 to -1**	**Day 0**	**Day 28 (+4)**	**Day 42 (+4)**	**Day 56 (+4)**		**Day 208 (+14)**	**Day 393 (+14)**	
Assessments and Time Points	**Screen baseline**	**Dose-1**	**Dose-2**	**Follow-up**	**Follow-up**	*v1.0*	**Follow-up**	**Follow-up**	*v2.0*
Signed Informed consent	●								
Allocate subject identification number (Screening number) and registration in IWRS	●								
Inclusion/exclusion criteria evaluation	●	●							
Collect demographic data	●								
Record vaccination history	●								
Record personal medical history	●								
History directed physical examination	●	●	●	●	●		●	●	
Check contraindications and warnings and precautions before vaccination		●	●						

SCHEDULE OF ASSESSMENTS [PHASE III]									
VISIT	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	*Interim Clinical Study Report*	**Visit 6**	**Visit 7**	*Clinical Study Report*
DAY	**Day -3 to -1**	**Day 0**	**Day 28 (+4)**	**Day 42 (+4)**	**Day 56 (+4)**		**Day 208 (+14)**	**Day 393 (+14)**	
Assessments and Time Points	**Screen baseline**	**Dose-1**	**Dose-2**	**Follow-up**	**Follow-up**	*v1.0*	**Follow-up**	**Follow-up**	*v2.0*
Record body temperature	●	●	●	●	●		●	●	
Record other vital signs (Pulse, BP, Respiratory rate)	●	●	●	●	●		●	●	
Measure/record height and weight	●								
Record any concomitant medications/vaccinations	●	●	●	●	●		●	●	
Only baseline screening against HIV 1&2, HBV and HCV	●								
Urine Pregnancy test in females only	●		●						
Real time RT-PCR nasopharyngeal swab)	●								
Immunogenicity assessments									
Blood sample collection	● (20 mL)	● (10 mL)		● (20 mL)	● (20 mL)		● (10 mL)	● (10 mL)	
Haematology & Biochemistry parameters	●				●				

SCHEDULE OF ASSESSMENTS [PHASE III]									
VISIT	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	*Interim Clinical Study Report*	**Visit 6**	**Visit 7**	*Clinical Study Report*
DAY	**Day -3 to -1**	**Day 0**	**Day 28 (+4)**	**Day 42 (+4)**	**Day 56 (+4)**		**Day 208 (+14)**	**Day 393 (+14)**	
Assessments and Time Points	**Screen baseline**	**Dose-1**	**Dose-2**	**Follow-up**	**Follow-up**	*v1.0*	**Follow-up**	**Follow-up**	*v2.0*
Anti-SARS-CoV-2 IgG antibody estimation	●			●	●		●	●	
Anti-SARS-CoV-2 IgG subclasses IgG1 & IgG4 estimation	●			●	●				
SARS-CoV-2 virus neutralising Antibody (NAb) estimation	●			●	●		●	●	
Cellular immunity assessment via ELISPOT or TrueCulture method		●		●					
Vaccine administration (0.5mL IM; deltoid muscle)		●	●						
60 minutes post-vaccination observation		●	●						
Safety Assessments									
Distribution of diary		●	●						
Recording of solicited local and systemic AEs within 7 days		●	●	●					

SCHEDULE OF ASSESSMENTS [PHASE III]									
VISIT	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	*Interim Clinical Study Report*	**Visit 6**	**Visit 7**	*Clinical Study Report*
DAY	**Day -3 to -1**	**Day 0**	**Day 28 (+4)**	**Day 42 (+4)**	**Day 56 (+4)**		**Day 208 (+14)**	**Day 393 (+14)**	
Assessments and Time Points	**Screen baseline**	**Dose-1**	**Dose-2**	**Follow-up**	**Follow-up**	*v1.0*	**Follow-up**	**Follow-up**	*v2.0*
post-vaccination after each dose									
Recording of unsolicited AEs		●	●	●	●				
Return of diary *- Diary to be reviewed and re-distributed at Day 42 for recording of AEs*			●	●	●				
Recording of SAEs and medically attended AEs		●	●	●	●				
Safety follow up after Day 56 for any SAEs and medically attended AEs for 12 months post 2nd dose							●	●	

6. STUDY ASSESSMENTS

All study assessments should be performed at the stipulated study visits as described in the schedule of assessments for Phase II (Section 5.3) and Phase III (Section 5.6) of the study. Details of Assessments and data to be collected are described in this section.

6.1. Demographic Data

The following basic demographic data of the subject will be recorded:

- Subject Initials
- Mailing address and other contact details will be recorded only in the source document during the baseline after obtaining informed consent form.
- Date of birth; age
- Gender
- Nationality; ethnic community; race
- Social history – education; occupation; employment; income; marital status & children
- Body weight (kgs)
- Height (cms)

6.2. Medical History

- Subject record of vaccinations along with occupational history, family history, etc. will be recorded during the baseline after obtaining written informed consent.
- Pre-existing or current medical conditions
- Comorbidities
- Previous Surgeries
- Any history of known disorders or other communicable diseases will be ascertained through relevant past history.
- Presence of any infectious disease in the family shall be asked on this screening day.
- Serological screening test for HIV, HBV and HCV infections will be done only once at baseline.
- Previous and ongoing medications

6.3. General, Physical & Systemic Examination

All subjects will undergo physical and systemic examination. Information will be collected on the subject's current health status, including history of any current illnesses. A complete physical examination of head & neck, eyes, ear, nose, throat cardiovascular, respiratory, gastrointestinal, genitourinary, musculoskeletal,

neurological, endocrine, metabolic, haematopoietic/lymphatic, skin and psychiatric and any other systems will be recorded.

6.4. Vital Signs

Following data related to vital signs and physical examination of the subject will be recorded:

- Body temperature in ºF (°Fahrenheit)
- Pulse rate (beats per minute)
- Respiratory rate (breaths per minute)
- Systolic blood pressure (mm Hg)
- Diastolic blood pressure (mm Hg)

NOTE: Normal *vital signs defined as pulse rate of ≥60 to ≤100 bpm; blood pressure systolic of ≥90 mm Hg and <140 mm Hg; diastolic ≥ 60 mm Hg and <90 mm Hg; body temperature <100.4 ºF prior to enrolment.*

Patients will be provided a non-returnable digital thermometer, free of cost, as part of the study to record oral body temperature; and a transparent scale to measure injection site reactions like redness, swelling and pain.

6.5. Concomitant Medications Recording

At each study visit, the Investigator will enquire with the subject or subject's legally acceptable representative about any concomitant medication taken. Concomitant medication (if any), starting from Day 0 until the end of the trial, will be recorded in the source document including details of trade name and/or generic name of the medication, indication, total daily dose, route of administration, start and end dates of treatment.

6.6. Routine Laboratory Assessments

All laboratory assessments will be performed at the stipulated study visits as described in the schedule of assessments for Phase II (Section 5.3) and Phase III (Section 5.6) of the study.

Haematology

- Haemoglobin level (Hb)
- Red blood cell count (Total RBC count)
- White blood cell count (WBC count)
- Differential count (viz., Neutrophils, Lymphocytes, Eosinophils,
- Basophils and Monocyte count)
- Haematocrit % (PCV)
- Platelet count (PC)

Biochemistry

- Liver Function Tests (LFT)

- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Alkaline Phosphatase (AP)
- Total bilirubin (TB)
- Direct (conjugated) bilirubin (DB)
- Total protein
- Albumin Globulin Ratio

- Kidney Function Tests (KFT)
  - Serum Creatinine levels (SC)
  - Blood Urea Nitrogen (BUN)
- Urine Pregnancy test – only for females of child bearing potential (as judged by the PI)

Serology for HIV 1&2, HBV and HCV (only at screening visit)

6.7. Immunogenicity Assessments

All immunogenicity assessments as indicated below will be performed at the stipulated study visits as described in the schedule of assessments for Phase II (Section 5.3) and Phase III (Section 5.6) of the study.

6.7.1. Real time RT-PCR

A nasopharyngeal swab will be collected at Screening for reverse transcription polymerase chain reaction (RT-PCR) testing, for detection of SARS-CoV-2 specific RNA in clinical samples.

RT-PCR will be performed at the accredited local laboratory of the study centre.

6.7.2. Immune Serology

The blood samples' collection is described in section 6.8 below. The following immunogenicity assessments will be performed at stipulated time points in the study:

- Anti-SARS-CoV-2 IgG antibody titres
- Anti-SARS-CoV-2 IgG antibody subclasses (IgG1 & IgG4 only)
- Neutralizing antibody (NAb) assay against SARS-CoV-2 virus (pseudo and / or wild type)
- Cytokine expression from stimulated PBMCs via ELISPOT method or Trueculture. Interferon-Gamma Cytokine Levels (INF-γ) - to assess the Th1 response and IL-4 cytokine levels – to assess for the Th2 response pre and post vaccination time points.

6.8. Collection of Blood Samples

Instructions for Handling

Wherever laboratory materials are provided by the Sponsor/or sponsor assigned laboratory, it is mandatory that all clinical samples be collected using exclusively with the laboratory materials supplied in the appropriate manner. The use of other laboratory materials without sponsor's consent could result in the exclusion of the subject from analysis if found inappropriate. The Investigator must ensure that his/her personnel under his/her supervision comply with this requirement.

Collection of Blood Samples

Sufficient quantity of blood (10 to 20 mL) will be collected intravenously by a qualified study nurse at all protocol specified time points from the enrolled subjects required for immunogenicity assessment, Haematology & Biochemistry Parameters as specified in the schedule of assessments or Phase II (Section 5.3) and Phase III (Section 5.6) into appropriate vacutainer for analysis of the parameters as defined in Laboratory manual.

Serum will be separated by centrifugation at 3500 rpm for 10 to 15 minutes at room temperature. The separated serum will be aspirated out and transferred into pre-labelled supplied cryovials with precision. The sera containing cryovials will be stored between -20 to -80^{0}C (deep freezer component of a normal refrigerator or preferably into a deep freezer) and temperature will be monitored periodically. The laboratory personnel involved in the study at each site shall keep sufficient quantity of serum sample for each subject for Anti-SARS-CoV-2 IgG antibody estimation titres estimation.

A small sample of serum shall be used for testing presence of HIV, HBV or HCV infections at baseline.

The central laboratory or any other authorized courier contact person should be informed prior to pick up the sample for analysis and reporting. A properly filled electronic or a paper-based test requisition form (TRF) should accompany each test sample as provided.

The serum samples will be collected by the sponsor assigned courier agency or by the representatives of the central laboratory assigned with the task, with prior intimation to respective sites. Analysis of Anti-SARS-CoV-2 IgG and or SNT antibody titre estimation will be performed by standardised methods as per the kit specifications and as per the relevant SOPs of the laboratory performing the test.

For detailed processes and procedures, the site should refer the Central Laboratory Manual.

6.9. Safety Assessments

The safety assessments for both phases of the study include solicited and unsolicited, non-serious and serious adverse events (AEs) and medically attended AEs reported in the study from the time of first dose of the vaccine.

6.9.1. Adverse Events

Definition:

An AE is any untoward medical occurrence in a subject administered an investigational product, whether or not related to this treatment. Abnormalities already existing before the first administration of the investigational product are not considered as AEs, but need to be documented as medical history. All new abnormalities or any exacerbation in intensity or frequency (worsening) of a pre-existing condition during or after the first vaccination have to be documented as AEs.

This definition includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, or drug interaction or the significant worsening of the disease under investigation that is not recorded elsewhere in the eCRF under specific efficacy assessments. Anticipated day-to-day fluctuations of pre-existing conditions, including the disease under study (if applicable) that does not represent a clinically significant exacerbation need not be considered adverse events. However, discrete episodes of chronic conditions occurring during a study period will be reported as adverse events in order to assess changes in frequency or severity. All conditions, which are pre-existing prior to study drug administration, will be recorded in the past medical history section on the subject's source document and the case report form (eCRF).

Over-dosage of study vaccine without resulting in abnormal findings, worsening of the study disease if expected, and hospitalization on admission due to study disease will not be considered as an adverse event. Baseline assessment will be performed immediately prior to the study medication administration in all groups, and signs and symptoms will be recorded on the source document and transcribed on to the eCRF subsequently. If these signs and symptoms continue and worsen during the follow-up period, they will then be considered as adverse events and recorded in the adverse event section of the source document and the information is then transcribed to eCRF. The adverse event definition outlined above applies to both solicited and unsolicited symptoms.

Solicited symptoms are the symptoms that are most likely to occur following study drug administration or as a result of the underlying medical condition. Solicited local and systemic reactions will be recorded differently. They will be followed-up for total duration of the study starting immediately following vaccine administration until 7 days after each dose of vaccination.

Local and systemic reactions, if any, will be scored by severity (mild, moderate, severe and life threatening) and the erythema and swelling or induration by the maximum diameter per day. All unsolicited adverse events (AEs) and MAAEs will be recorded for the entire study duration, as appropriate.

The WHO defines ***adverse event following immunization (AEFI)*** as an any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine.

Medically attended adverse events **(**MAAEs) are adverse events with medically-attended visits that are not routine visits for physical examination or vaccination, such as (i) visits for hospitalization, (ii) an emergency room visit, or (iii) an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason.

6.9.1.1. Solicited Adverse Events

The list of ***solicited local AEs*** along with their intensity grading is given in the following table:

Local (injection-site) Adverse Events	Intensity grade	Parameter
Pain (tenderness) at injection site**	0	Absent
	1	Pain causing no or minimal limitation of use of limb
	2	Pain causing greater than minimal limitation of use of limb
	3	Pain causing inability to perform usual social & functional activities
	4	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Redness (erythema) at injection site**	0	None
	1	2.5 to <5.0 cm in diameter. AND Symptoms causing no or minimal interference with usual social & functional activities
	2	≥5.0 to <10.0 cm. OR Symptoms causing greater than minimal interference with usual social & functional activities.
	3	≥10.0 cm. OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities.
	4	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Swelling or Induration at injection site**	0	None
	1	2.5 to <5.0 cm in diameter. AND Symptoms causing no or minimal interference with usual social & functional activities
	2	≥5.0 to <10.0 cm. OR Symptoms causing greater than minimal interference with usual social & functional activities.
	3	≥10.0 cm. OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms

		causing inability to perform usual social & functional activities.
	4	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)

The list of ***solicited systemic AEs*** along with their intensity grading is given in the following table

Systemic Adverse Events	**Intensity grade**	**Parameter**
Fever* (Pyrexia)	0	<100.4ºF (< 38.0ºC)
	1	100.4 ºF to 102.2°F [38.0°C to 39.0°C]
	2	102.3 ºF to 104°F [≥ 39.0°C to 40°C]
	3	> 104.0°F (> 40.0°C) for ≤ 24 hours
	4	> 104.0°F (> 40.0°C) for > 24 hours
Headache	0	Absent
	1	Symptoms causing no or minimal interference with usual social & functional activities
	2	Symptoms causing greater than minimal interference with usual social & functional activities
	3	Symptoms causing inability to perform usual social & functional activities
	4	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function
Chills**	0	Absent
	1	Symptoms causing no or minimal interference with usual social & functional activities
	2	Symptoms causing greater than minimal interference with usual social & functional activities
	3	Symptoms causing inability to perform usual social & functional activities
Myalgia** (Generalized muscle pain)	0	Absent
	1	Muscle pain causing no or minimal interference with usual social & functional activities
	2	Muscle pain causing greater than minimal interference with usual social & functional activities
	3	Muscle pain causing inability to perform usual social & functional activities
	4	Disabling muscle pain causing inability to perform basic self-care functions
Arthralgia** (Generalized joint pain)	0	Absent
	1	Joint pain causing no or minimal interference with usual social & functional activities
	2	Joint pain causing greater than minimal

		interference with usual social & functional activities
	3	Joint pain causing inability to perform usual social & functional activities
	4	Disabling joint pain causing inability to perform basic self-care functions
Fatigue** (feeling tired) or malaise	0	Absent
	1	Symptoms causing no or minimal interference with usual social & functional activities
	2	Symptoms causing greater than minimal interference with usual social & functional activities
	3	Symptoms causing inability to perform usual social & functional activities
	4	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Nausea**	0	None
	1	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake
	2	Persistent nausea resulting in decreased oral intake for 24 to 48 hours
	3	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)
	4	Life-threatening consequences (e.g., hypotensive shock)
Urticaria*	0	Absent
	1	Urticarial lesions covering <10% Body Surface Ares (BSA); topical intervention indicated
	2	Urticarial lesions covering 10 - 30% BSA; oral intervention indicated.
	3	Urticarial lesions covering >30% BSA; IV intervention indicated.
Anaphylaxis (Anaphylactic Reaction)	0	None
	1	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated
	2	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated
	3	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated
	4	Potentially life-threatening symptoms causing inability to perform basic self-care functions

		with intervention indicated to prevent permanent impairment, persistent disability

- ***Solicited COVID-19 disease symptoms***

The following COVID-19 symptoms will also be solicited throughout the study period to check for SARS-CoV-2 infection. Subjects will be asked to contact the study team if they develop any symptoms suggestive of COVID-19 at any point during the trial. Symptomatic subjects will be asked to present for a visit to test for SARS-CoV-2 by RT-PCR.

Adverse Event	Intensity grade	Parameter
Fever* (Pyrexia)	0	<100.4ºF (< 38.0ºC)
	1	100.4 ºF to 102.2°F [38.0°C to 39.0°C]
	2	102.3 ºF to 104°F [≥ 39.0°C to 40°C]
	3	> 104.0°F (> 40.0°C) for ≤ 24 hours
	4	> 104.0°F (> 40.0°C) for > 24 hours
Cough*	0	Absent
	1	Mild symptoms; Non-prescription intervention Indicated
	2	Moderate symptoms; Medical intervention indicated; limiting instrumental Activities of Daily Living (ADL)
	3	Severe symptoms-Limiting self-care Activities of Daily Living (ADL)
Chills**	0	Absent
	1	Mild sensation of cold; shivering; chattering of teeth
	2	Moderate tremor of the entire body; narcotics indicated
	3	Severe or prolonged, not responsive to narcotics
Myalgia** (Generalized muscle pain)	0	Absent
	1	Muscle pain causing no or minimal interference with usual social & functional activities
	2	Muscle pain causing greater than minimal interference with usual social & functional activities
	3	Muscle pain causing inability to perform usual social & functional activities
	4	Disabling muscle pain causing inability to perform basic self-care functions
Fatigue** (feeling tired) or malaise	0	Absent
	1	Symptoms causing no or minimal interference with usual social & functional activities
	2	Symptoms causing greater than minimal interference with usual social & functional activities
	3	Symptoms causing inability to perform usual social & functional activities

	4	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Nausea**	0	None
	1	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake
	2	Persistent nausea resulting in decreased oral intake for 24 to 48 hours
	3	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)
	4	Life-threatening consequences (e.g., hypotensive shock)
Diarrhoea**	0	Absent
	1	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period
	2	Persistent episodes of unformed to watery stools OR Increase of 4 – 6 stools over baseline per 24-hour period
	3	Bloody diarrhoea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated
	4	Life-threatening consequences (e.g., hypotensive shock)
Vomiting **	0	None
	1	Intervention not indicated
	2	Outpatient IV hydration; medical intervention indicated
	3	Tube feeding, Total Parenteral Nutrition (TPN), or hospitalization indicated
	4	Life-threatening consequences
Sore throat**	0	None
	1	Mild pain
	2	Moderate pain; limiting instrumental Activities of Daily Living (ADL)
	3	Severe pain; limiting selfcare ADL; limiting ability to swallow
Dyspnoea (Shortness of breath or difficulty in breathing)**	0	None
	1	Shortness of breath with moderate exertion
	2	Shortness of breath with minimal exertion; limiting instrumental ADL
	3	Shortness of breath at rest; limiting self-care ADL
	4	Life-threatening consequences; urgent intervention indicated
Loss of taste (ageusia)	0	None

	1	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated
	2	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated
	3	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated
	4	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability
Expectoration	0	None
	1	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated
	2	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated
	3	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated
	4	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability
Abdominal Discomfort	0	None
	1	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated
	2	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated
	3	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated
	4	Potentially life-threatening symptoms causing inability to perform basic self-care functions

		with intervention indicated to prevent permanent impairment, persistent disability
Rhinorrhoea (congestion or runny nose)	0	None
	1	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated
	2	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated
	3	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated
	4	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability
Loss of smell (Anosmia)	0	None
	1	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated
	2	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated
	3	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated
	4	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability

***Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events - Corrected Version 2.1 July 2017.*

**=Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 Published: November 27, 2017 (v5.0: November 27, 2017).*

**=Fever is defined as the endogenous elevation of at least one measured body temperature of ≥ 38°C (≥ 100.4°F). The value of ≥38°C is accepted as reflecting an abnormal elevation of temperature, irrespective of device, anatomic site, age, or environmental conditions.*

6.9.1.2. Un-solicited Adverse Events

Any other (unsolicited) adverse event reported at any time in the study after the second dose.

The intensity up to the maximum will be recorded according to the following guidelines:

The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table.

PARAMETER	**DEFINITION**
GRADE-0	----
GRADE-1 - MILD	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated
GRADE-2 - MODERATE	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated
GRADE-3 - SEVERE	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated
GRADE-4 - LIFE THREATENING	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Unsolicited symptoms include any symptoms, other than the solicited symptoms, which are less likely to occur (<3%). These events were considered intercurrent diseases and not related to the administration of study drug.

The nature of each unsolicited event, start and end date, outcome, maximum intensity and relationship to treatment administration will be assessed and recorded in the adverse event section of the eCRF. Adverse events already documented in the eCRF, i.e. at a previous visit and designated, as ‘ongoing’ will be reviewed at subsequent visits, as necessary.

6.9.1.3. Serious Adverse Events (SAEs)

As per WHO, a serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires or prolongs subject's hospitalization.
- Results in persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions).
- Results in a congenital anomaly/birth defect.
- Requires intervention to prevent permanent impairment or damage.
- Is an important and significant medical event that may not be immediately life threatening or resulting in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

In addition, a pre-existing event or condition that results in hospitalization should be recorded on the Medical History page of eCRF. If the onset of an event occurred before the subject entered the trial (e.g., any pre-planned hospitalization for conditions like cosmetic treatments or for non-emergency routine visits for a pre-existing condition), the hospitalization would not lead to an AE being classified as serious unless, in the view of the investigator, hospitalization was prolonged as a result of participation in the clinical trial or was necessary due to a worsening of the pre-existing condition.

6.9.1.4. Unexpected Adverse Drug Reactions/Events

An adverse drug reaction/event (ADR/ADE) whose nature, severity, specificity, or outcome is not consistent with the term or description used in the local/regional product labelling (e.g. Package Insert or Summary of Product Characteristic or the Investigator Brochure if it is a candidate vaccine) should be considered unexpected. When the investigator is uncertain whether an ADR/ADE is expected or unexpected, the ADR/ADE should be treated as unexpected.

An expected ADR with a fatal outcome should be considered unexpected unless the local/regional product labelling specifically states that the ADR might be associated with a fatal outcome.

"Class ADRs" should not automatically be considered to be expected for the subject drug. "Class ADRs" should be considered expected only if described as specifically occurring with the product in the local/regional product labelling.

6.9.2. Adverse event evaluation

The causality assessment for each adverse event should be done as per the description below:

A. Related:

- **Very likely/certain:** A clinical event with a plausible time relationship to vaccine administration and which cannot be explained by concurrent disease or other drugs or chemicals.

- **Probable:** A clinical event with a reasonable time relationship to vaccine administration; is unlikely to be attributed to concurrent disease or other drugs or chemicals.
- **Possible:** A clinical event with a reasonable time relationship to vaccine administration, but which could also be explained by concurrent disease or other drugs or chemicals.

B. Unrelated:

- **Unlikely:** A clinical event whose time relationship to vaccine administration makes a causal connection improbable, but which could be plausibly explained by underlying disease or other drugs or chemicals.
- **Unrelated:** A clinical event with an incompatible time relationship and which could be explained by underlying disease or other drugs or chemicals.
- **Unclassifiable:** A clinical event with insufficient information to permit assessment and identification of the cause.

6.9.3. Classification of Adverse Events

The AEs are classified as either expected or unexpected:

- **Expected**: an AE that is listed in the Investigator's Brochure & or in the study protocol.
- **Unexpected:** an AE which is not listed in the current Investigator's Brochure & or in the study protocol or it differs because of greater severity or greater specificity.

Outcome

- Recovered/ resolved
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

NOTE: A subject's death per se is not an event, but an outcome. The event which resulted into subject's death must be fully documented and reported, even in case the death occurs within four weeks after test drug treatment end, and without respect of being considered treatment-related or not.

6.9.4. Actions Taken for Adverse Events

AEs requiring therapy must be treated with recognized standards of medical care to protect the health and well-being of the subject. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment of an emergency situation. The action taken by the Investigator must be clearly documented.

Action Taken

a) in general	b) on the study vaccine
▪ none	▪ no action regarding study drug
▪ drug therapy started	▪ First dose withheld / Second dose withheld
▪ test performed (e.g. local laboratory)	▪ Study drug definitely stopped

The investigator will follow-up each AE until it is resolved or until the medical condition of the subject is stable and all relevant follow-up information will be reported to the sponsor.

6.9.5. Documentation of Adverse Events

Adverse events will be continually monitored for, or asked about during all visits. The occurrence of all adverse events will be documented in the CRF with the following type of information where appropriate:

1. Reason for reporting
2. When the adverse event first occurred (date and time)
3. Nature of adverse event (diagnosis, description, and confirmatory tests)
4. Intensity of the adverse event
5. Relationship to Investigational product
6. Counter-measures
7. How long the adverse event persisted. Whether the event was once or intermittent (ideally each occurrence of an adverse event will be reported. However, certain adverse events may occur frequently, such as vomiting or diarrhoea, and it is more sensible to record these as a single event with an intermittent periodicity if the intervals are less than 24 hours.)
8. Outcome
9. Relevant medical history
10. Concomitant medications

All subjects experiencing adverse events, whether considered associated with the use of the Investigational product or not, will be monitored until symptoms subside and any clinically relevant changes of laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report will be supplied, if possible. All findings will be reported in the subject's file (source document).

6.9.6. Reporting of Adverse events

The period of observation for adverse events starts from the time the subject receives the first vaccination dose.

NOTE: Subjects will be provided a transparent scale to measure injection site reactions like redness, swelling and pain.

The subject diary will be used by the subject for recording any adverse events experienced at any time during the study.

All study subjects will be observed at site for at least 60 minutes after vaccination for evidence of immediate reactions and in particular for symptoms of allergic phenomena (such as rashes or other allergic manifestations). In both phases of the study, each subject/LAR will be instructed to complete a diary for 7 consequent days (Day 0 to Day 6) following first dose of vaccination, and thereafter till the next visit for the 2nd dose of vaccination at Day 28. Post the second dose, a new diary will be distributed and the subject/LAR will be instructed to complete the diary for 7 consequent days and for any other AE; which will be retrieved by the PI at visit 4 (Day 42) for data collection. The diary will be re-distributed to the subject and retrieved on Day 56 (visit 5). All Serious Adverse Events (SAEs) and medically attended AEs if any, will be collected and documented until the end of the study.

All adverse events occurring within the study period, regardless of severity, will be monitored and medically managed by the investigator until resolution. All subjects experiencing adverse events - whether considered associated with the use of the study vaccine or not - must be monitored until symptoms subside and any clinically significant abnormal laboratory values if identified, have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report should be supplied, if possible. All findings must be reported on an "Adverse Events" eCRF page and on the "Serious Adverse Event" form as applicable, where necessary. All findings in subjects experiencing adverse events must be reported also in the subject's medical records.

When a reportable AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.

Any serious adverse event (SAE) occurring after the single dose vaccination until study end will be reported to the Sponsor, Independent Ethics Committee/Institutional Review Board (IEC/IRB) and the licencing authority within 24 hrs of the occurrence of the SAE. The Sponsor and investigator after due analysis are responsible for the reporting of any unexpected or serious AEs to the IEC/IRB, Head of the Institute and the licencing authority within 14 days. All adverse events will be followed up until resolution or until the end of the study whichever is earlier. The site investigator will make a decision as to the severity of the event and whether there was a causal relationship to the vaccination.

Safety and data monitoring will be carried out as per current ICH GCP, Indian GCP guidelines and G.S.R. 227(E), as applicable. The principal investigator will report safety issues to IEC/IRB and the sponsor periodically and as per regulatory requirement, until follow up visit of last subject.

SAE reporting should be preferably done by email or as requested by the BE. SAEs can be reported by emailing the scanned report or by phone to Drug Safety Physician

with sponsor. The SAE report data elements should be as per the sponsors and G.S.R. 227(E) requirements.

The email ID and phone number of the Drug Safety Physician is given below:

Email: pharmacovigilance@biologicale.com

Phone: +91 40 71216242 (Landline)

Mobile: +91 7893611762 (Drug Safety Physician – Dr. Vijay. Y, (M.D., Pharmacology)

All efforts should be made to collect the safety data from all subjects who are withdrawn from the trial. A complete evaluation should be recorded at the time of the subject's withdrawal, including an explanation of why the subject is withdrawing from the study where possible.

6.9.7. Special Procedures for SAEs And Complications

When complications or events occur which are not tolerable, it is for the Investigator to decide for that subject whether to continue the subject in the study and/or treat the subject.

6.9.8. Classification of action when an unexpected adverse event occurs

1. Study Vaccine discontinued/ interrupted and reintroduced / administration completed prior to SAE (Serious Adverse Event).
2. Adverse event treated by medication or other form of treatment
3. Concomitant medication changed/not changed

6.9.9. Notifications of Serious Adverse Events

If an unexpected or serious adverse event occurs (including death, irrespective of the cause) during the study period regardless of their relationship to Investigational product, the Investigator shall report to Licensing Authority, IEC/IRB, and the Sponsor within 24 hours of occurrence of the event, by email/fax or telephone, the receipt of the AE to be confirmed by a telephone call with the sponsor. The Investigator shall also leave a paper trail documenting that the adverse event has been properly reported. This paper trail will include keeping a log of phone calls to the sponsor and the IEC/IRB, with each call annotated with time and summary of the discussion.

The notification must be sent to the address or email, which is provided in the central files of the study and in the Investigator's files. The following minimal information must be communicated with the first notification of a serious adverse event:

1. Subject's study identification number
2. Subject's initials (subject's name is not to be communicated for reasons of confidentiality)

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

The Investigator will be requested to submit a report, which includes a description of the serious adverse 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 are to identify the subject by the unique subject identifier, and not by the subject's name or address.

The sponsor 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, if brought to the notice of the Investigator at any time after cessation of study medication, must be reported to the sponsor.

A. Responsibilities of the Investigator(s)

Investigator(s) shall report all serious and unexpected adverse events to the Sponsor or his representative, whosoever had obtained permission from the Licensing Authority for conduct of the clinical trial, and the Ethics Committee that accorded approval to the study protocol, within twenty-four (24) hours of their occurrence.

The report of the serious adverse event, after due analysis shall be forwarded by the Investigator to Licensing Authority, Sponsor, the Chairman of the Ethics Committee and the Head of the Institution as per the table 5 of the third schedule given in the G.S.R 227(E) where the trial has been conducted within fourteen (14) days of occurrence of the serious adverse event.

Investigator shall provide information to the clinical trial subject through informed consent process as per table 3 of third schedule, GSR 227(E) about the essential elements of the clinical trial and the subject's right to claim compensation in case of trial related injury or death. He shall also inform the subject or his/her nominee(s) of their rights to contact the sponsor or his representative who-so-ever had obtained permission from the licensing authority for conduct of the clinical trial for the purpose of making claims in the case of trial related injury or death.

The PI informs the Sponsor within 24 hours after occurrence of the event. All information available on the event (hospital records, lab tests, discharge summaries, etc.) are forwarded to the Sponsor so that they can determine whether the SAE is unexpected or expected and the reporting outcome of the SAE to the concerned. As additional information becomes available on the SAE, it should be forwarded to the Sponsor.

All study site staff members are responsible for communicating reports of any AE and/or SAE to the PI.

The PI/Sub or Co-Investigator and/or study coordinator are responsible for reviewing with the subject's all AE information during protocol specified study visits.

The PI is responsible for accurate and timely recording/documenting of AE in the eCRF and reporting of AE to the IEC/IRB and the Sponsor.

The PI and/or study coordinator are responsible for recording all new clinical events, exacerbation, and/or deterioration of any existing clinical condition, occurring after a study subject has entered the study, on the appropriate form. They will also provide follow-up information on all AE, until resolution or as mentioned in the protocol.

B. Responsibilities of the Ethics Committee

In case of serious adverse event occurring to the clinical trial subject, the Ethics Committee shall forward it's report on the serious adverse event after due analysis, along with its opinion on the financial compensation, if any, to be paid by the Sponsor or his representative, whosoever had obtained permission from the Licensing Authority for conducting the clinical trial, to the Licensing Authority within thirty (30) days of the receiving the serious adverse event report.

C. Responsibilities of the Sponsor

Any report of serious adverse event occurring in clinical trial, after due analysis shall be forwarded by the sponsor to the Licensing Authority, the Chairman of the Ethics Committee and the head of the institution where the trial has been conducted within fourteen (14) days of receiving the serious adverse event report.

The Sponsor is responsible for a complete and accurate investigation, reporting and timely submission of AE reports to the DCGI or any other regulatory body.

The Sponsor is responsible for advising the PI that all Serious Adverse Events (SAE) and Investigational New Drug safety reports must be reported immediately.

The Sponsor's medical team will review all AE reports. It is the Sponsor's responsibility to follow the progression of all SAE until resolution or appropriate end points are reached and determine whether a SAE is unexpected and associated with the drug.

The PI and/or study coordinator are responsible for reviewing all AE information with the subject during study visits.

6.9.10. Treatment of Adverse Events

Treatment of any adverse event is at the sole discretion of the Investigator(s) and according to current ICH-Good Clinical Practice & Indian GCP guidelines. All applied measures as well as the follow-up will be recorded in the eCRF of the subject.

6.9.11. Dropout or Withdrawal of Subjects from The Study due to Adverse Events

Please also refer to section 4.3 and 4.4 for withdrawal or dropout of subjects from the study.

Any vaccinated subject who has an adverse reaction to study medication that threatens his/her well-being will be monitored for resolution of the adverse event and ***will continue to be monitored on the protocol schedule*** until completion of the study.

The Investigator will evaluate any subject who demonstrates a significant deterioration in his/her clinical status. Evidence that would suggest such deterioration includes:

a) Subjective increase in symptomatology

b) Worsening laboratory parameters.

The Investigator will be requested to submit a report, which includes a description of the serious adverse 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 are to identify the subject by the unique subject identifier, and not by the subject's name or address.

The sponsor 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, if brought to the notice of the Investigator at any time after cessation of study medication, must be reported to the sponsor.

6.9.12. Subject Diary

Diaries will be completed by the subjects or subject's LAR. The study staff to record safety information (concomitant medications, local and systemic reaction, AE and SAE) occurring post 7 days of each vaccination and at stipulated time points.

According to ICH-GCP E6 (R2) guidelines (1.52), subject's diary is a "Source Document". It is an investigator responsibility to ensure that data on the diary correspond to the real health status of subject and to accurately transcribe data from the Diary to the eCRF.

All symptoms (local and systemic tolerability) including the body temperature will be measured after vaccination will be assessed by the subject, subject's LAR by checking for presence of the symptoms listed in the diary. The diary assessments will occur preferably at the same time each day, starting from the day of vaccination, for a total of 7 consecutive days (Day 0 to Day 6) following each dose of vaccination. The subject diary will be verified by the investigator at the subject's next visit to the study site and any missing information would be updated after proper interrogation. When re-

distributing diary to subject on day 42 (for both, phase II and III), a copy of diary can be collected as part of source data until diary returned during next scheduled visit. These data will then be entered into the eCRF by the investigator or his authorized delegate. The investigator will additionally assess the severity of the reported local reaction and the severity and relationship of reported systemic reactions according to the above tables.

In case the diary is not available, the study staff will document the reasons for the missing documents on the comment section of the source document and eCRF will be completed with UNK for all assessments. Nevertheless, if a SAE occurred it must be recorded in SAE form and in the adverse event section of eCRF.

7. INVESTIGATIONAL PRODUCTS: THE STUDY VACCINES

7.1. Study Vaccines Description, Dosage and Administration

The investigational product (IP) or Test vaccine for Phase II and Phase III is the CORBEVAX Vaccine, referred to as the 'Study Vaccine' in this protocol. Please refer to section 1.2 for more details.

Study Vaccine(s) Dosage and Administration

- A 0.5 mL per dose of the study vaccine will be given intramuscularly in a two-dose schedule (Day 0 & Day 28).

Composition: RBD Antigen (25 µg) + Aluminium Hydroxide (750 µg) +CpG 1018 (750 µg).

CORBEVAX Vaccine formulation:

Each dose of 0.5 mL Study Vaccine Contains:

Component Details	Quantity per 0.5mL	Function
RBD antigen of SARS-CoV-2 (COVID-19)[1]	25 µg	Immunizing Agent
Aluminium Hydroxide gel as Al^{+++}	750 µg	Adjuvant
CpG 1018	750 µg	
Buffer (Tris and NaCl in WFI)	q.s to 0.5 mL	Formulation Buffer

[1] *Produced in Pichia pastoris (Yeast)*

CORBEVAX Vaccine formulation:

- **Manufactured by:** Biological E. Limited, India.
- **Indication:** For active immunization of at-risk persons to prevent COVID-19.
- **Usage & Storage:** The vaccine should be visually inspected for any particulate matter prior to administration.

- **Dose:** 0.5mL of ready-to-use formulation by Intra-muscular injection. Two doses to be administered with 28 days interval between doses.
- **Dosage Regimen:** Each study subject will receive a 0.5 mL dose of investigational vaccine intramuscularly. The preferred site for injection is the deltoid muscle of the upper arm.
- **Presentation:** This would be a transparent glass vial containing 0.5mL.
- **Storage:** The vaccine should be stored at a temperature between +2°C and +8°C. DO NOT FREEZE.
- **Shelf life:** Do not use beyond the "Retest date" specified on the label.
- **Precaution:** As with any other parenteral drug products it will be inspected visually for particulate matter and discoloration prior to administration. This investigational vaccine will not be used if particulate matter or discoloration is found.

7.1.1. Rationale for dose selection

Four vaccine formulations were tested in Phase I/II study to analyse the immunogenicity via multiple parameters. All formulations contained the same antigen i.e. Receptor Binding Domain (RBD) protein. Both humoral immune response and cellular immune response were analysed at key time-points in the study to determine the optimum formulation.

The humoral immune response was assessed by measurement of total anti-RBD antibody concentration, anti-RBD IgG1, IgG2, IgG4 titres and pseudovirus neutralization titres in the sera samples collected at specified time-points.

The total anti-RBD antibody concentration measured by ELISA showed similar trends for all four formulations. All four cohorts had similar GMC's at Day-0 which increased moderately till Day-28 representing low immune response after first dose that is as per expectations. The GMC's increased substantially at Day-42 and formed a plateau at Day-56 showing significant and stable immune response post 2nd dose of vaccination. Within the four cohorts, formulation BECOV2B, showed the highest immune response in terms of overall GMC's and Geometric Mean Fold Rise when Day-42 and Day-56 antibody concentrations were compared to those observed at the Day-0 time point.

Vaccine induced antibodies are expected to neutralize the SARS-CoV-2 virus. These titres were measured by neutralization of a Pseudovirus (mimicking SARS-CoV-2 virus-Wuhan strain). Different dilutions of the sera samples were mixed with the PSV stock to enable antibody-mediated virus neutralization and then the mixture was incubated with a specific cell line expressing ACE-2 receptor to assess the residual virus activity. The sera dilutions that demonstrate 50% of reduction in virus replication were calculated and reported as Neutralization Titer-50% i.e. NT_{50}. Most of the subjects had NT_{50} below assay detection level (reported as NT_{50} =5) and only about 10% of subjects across all cohorts had low detectable levels of neutralization titres at the Day-0 time point and thus all cohorts had similar GMT's at Day-0. In the interim

analysis, significant increase in the neutralization titres were observed for the BECOV2B formulation at Day-56. Other three formulations had slightly lower increase in the GMT's and corresponding GMFR's. The Day-56 GMT for the BECOV2B formulation compares very well with a large convalescent plasma panel (n = 273) GMT of 126.

Detailed comparison showed substantial increase in all immunogenicity parameters in BECOV2B-500 mcg formulation as compared to BECOV2C-250 mcg formulation; thus confirming the crucial role played by CpG 1018. Formulation development studies have shown that the current formulation can handle additional CpG till 750 mcg/dose without any adverse impact on RBD adsorption to Alum or RBD antigenicity. Thus, increase of CpG 1018 in the vaccine from 500 to 750 mcg will result in higher immunogenicity and provide a more consistent response than what has been observed in Phase I/II study for the BECOV2B formulation. Excellent safety profile observed for the current vaccine coupled with significant clinical experience associated with vaccines containing much higher CpG 1018 content provides assurance of similar safety profile (reference : Heplisav-B product contains 3000 mcg of CpG 1018 per dose; Clover Biopharma protein sub-unit COVID19 vaccine that is in Phase III contains 1500 mcg of CpG 1018).

7.1.2. Intramuscular Route for administration

Use an antimicrobial wipe to cleanse the injection site and allow the skin to dry. Allowing the skin to dry completely may help to reduce discomfort as the medication is being injected. Proper injection technique requires rapid insertion of the needle through the skin after a brief caution to the subject or subject's his/her legally acceptable representative. Before vaccination, the skin over the site should be cleansed with a suitable germicide. The vaccine will be administered intramuscularly into deltoid muscle of the upper arm by qualified and trained study personnel for both treatment groups. No other route of administration will be allowed except the route specified in this protocol. Aspiration of the plunger may be required before injection to ensure that the needle is not in a blood vessel.

Note: Suggestion for injections by intramuscular route (IM) route - There is some suggestion in the literature that the injection technique may contribute to the severity of local reactions, including abscess formation at the injection site, as a result of the antigen seeding the needle track. The following precautions have been suggested.

1. Administer by deep intramuscular injection by IM route.
2. Inject slowly so as to allow the injected material to disperse instead of coming up the needle track.

As with all injectable vaccines, appropriate medical treatment should always be readily available, as per the age of the subject, in case of anaphylactic reactions following the administration of the study vaccine. Under no circumstances shall the study drugs be administered by any other route other than those specified in this approved protocol.

This visit at Day 28 constitutes the 'Study Vaccine Administration Day' for all the enrolled subjects. The second dose of Biological E's COVID-19 vaccine will be

administered through IM route in the deltoid muscle, as per the treatment group assigned through IWRS. No other route of administration will be permitted except as specified in this protocol.

7.2. Study Vaccine Dose Modifications OR Dose Delays

No change in the prescribed dosing schedule will be permitted at any time during the study period, except for:

- If the subject develops COVID-19 infection between 1st and 2nd dose, the 2nd dose will be deferred till 1 to 3 months' post recovery at the discretion of the Investigator.

7.3. Possible Drug Interactions OR Overdose

No known drug interactions for these study vaccines.

There is no specific information available for the overdose of study vaccine. There is no possibility of an overdose as the vaccine candidate is provided in single dose vials. However, there is no known specific treatment required in case of overdose. In case of a suspected overdose, the Investigator must treat the subject symptomatically as per the best of his/her clinical judgment. The subjects may be hospitalized for observation and appropriate supportive treatment should be given as per the Investigator's clinical judgment.

7.4. Packaging and Labelling of Investigational Products

The study vaccine will be made available in single dose (0.5 mL) vials by Biological E. Ltd., to the study sites.

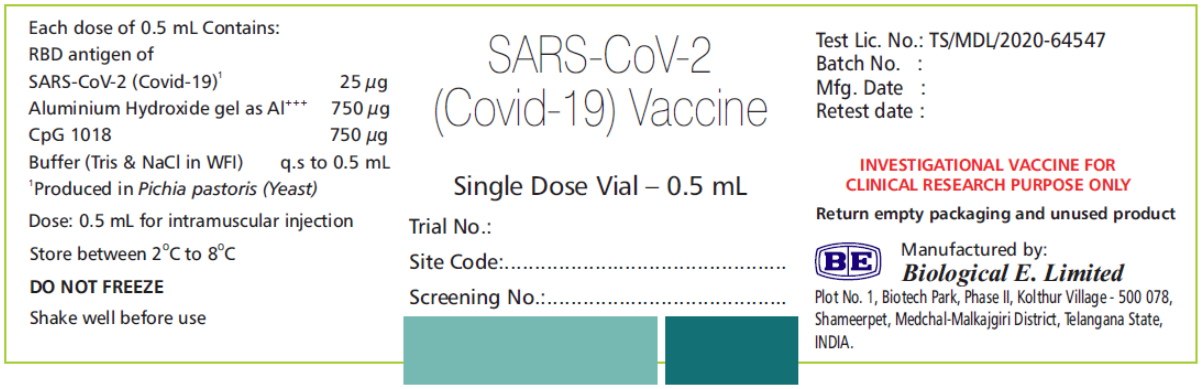
The Investigational product label shall be in compliance with local regulations where applicable. Blinding is not applicable as this an open label study.

The vial label will contain reference to the study trial number the name of Investigational product with quantity, form and administration route, date of manufacture and retest date, name and address of the sponsor, and that the Investigational product for clinical research purpose only, and any other text required by the local regulatory authorities.

7.4.1. Specimen Labels – Study Vaccine Vials

The Study Test Vaccine vial will be supplied in a single dose presentation as mentioned below:

Single dose TEST Vacine vial – 0.5 mL



7.5. Handling & Storage of Study Product

Biological E Limited will supply the vaccines to the investigational site. All the Investigational products will be shipped under controlled temperature through standard courier to each of the study sites. A temperature logger will be used for recording the temperature during transport. Temperature will be monitored during the shipment. The investigator should acknowledge receipt of the study vaccines. Upon receipt, investigator or designee should ensure study vaccines are received in good condition. The investigator shall inform immediately the sponsors of any shipment temperature out of range.

The vaccines at the site must not be used before the appropriate shipping conditions have been checked and confirmed. Study vaccine will be labelled and will comply with the legal requirements of India. Study vaccines must be handled properly and stored in a secure location to which only the investigator or designee have access.

All study vaccines must be stored in a safe, locked, and secure place with no access by unauthorized personnel. They must be kept in the refrigerator (+2°C to +8°C) and must not be frozen. Storage temperature should be monitored every day. Access to a back-up refrigerator in case of power failure/breakdown is necessary.

Vaccines that have been stored differently from the sponsor's recommendations or in case of temperature excursion, study drug must not be used unless the sponsor provides written authorization for use. In the event that the use cannot be authorized, vaccine supply must be replaced with fresh stock supplied by the sponsor.

The investigator should ensure that the vaccines delivered to the site are used only in accordance with the approved protocol. Monitoring of vaccine accountability will be performed by the study monitor during site visits.

The investigator should maintain an accurate record of investigational product delivery to the site, the inventory at the site, the administration to the subjects, and the return to the sponsor, or destruction, of study vaccines. At the conclusion, and as appropriate during the course of the study, the investigator will return to the sponsor, or destroy at study site (as per sponsor requirements and SOP) all used and unused study vaccines, packaging and supplementary labels, if any. If the unused study vaccines are disposed at the site, the investigator should provide a copy of the site's procedure for destruction of material and documentation of the destruction.

7.6. Dispensing and Return of Study Vaccines

All study products will be stored and administered by the Investigator designated qualified medical personnel. Investigational clinical supplies must be received by a designated person at the study site, handled and stored properly. These will not be delivered by BE Ltd until all required documentation is present at the site (Ethics Committee approval, signed contract and protocol, regulatory authority approval where required).

All study drugs must be stored in a safe and locked place with no access for unauthorized personnel. They must be kept in the refrigerator at 2ºC to 8ºC (35º - 46ºF) and must not be frozen. Storage temperature will be monitored on day-to-day basis and a log to this effect needs to be maintained. It is advisable to have a back-up refrigerator in case of power failure. If any discrepancy in the package arises, this must be communicated immediately to the sponsor / study site and vice-versa.

7.7. Investigational Product Accountability

The Investigator may assign some or all of the Investigator's duties for drug accountability to an appropriate individual (e.g. study nurse or authorized designee) who is under supervision of the Investigator.

The Investigator or appropriate individual is obliged to keep sufficient documentation of the delivery, use, and destruction or return of unused, used, or partially-used packages of investigational products. The documentation must include date, quantity, subject number, batch/lot/serial number or other identification number, expiry/use by date, and the means to identify the subject to whom it was administered.

The Investigator will maintain records that document adequately, that the subjects were provided the dose specified in the protocol and reconcile all Investigational products received for the study. Before any investigational product is destroyed, the Investigator must allow the Study Monitor to perform drug reconciliation. Once reconciliation is done then the study vaccines may be destroyed at the study site or brought back to the sponsor. The entries in the eCRF will be compared with the returned and residual Investigational products, with clarification of any discrepancies or inconsistencies.

7.8. Replacement of Unusable / Broken / Misplaced Study Medication

In addition to the study vaccine quantities required, additional units of investigational vaccine will be provided to replace unusable, broken or lost vials, if any, for each site. The Investigator, in the event of breakage or misplacement shall report to study monitor and use the additional units provided.

In the event of replacement, it shall be documented both in the source document and also on the additional comments section of the eCRF.

7.9. Study Vaccine Compliance

Compliance with study vaccine will be assessed through vaccination records and accountability logs maintained by the Investigator and his team.

The vaccine administered to each subject must be recorded and reconciled with the study product and compliance records. Vaccine dosing dates including dates for any delays and/or discontinuations will also be recorded in the CRF.

7.10. Concomitant Medications

Any treatment other than those prohibited below may be administered during Phase II and III of this study. All concomitant medications that were taken by or being administered to the subject during both the phases of the study except for over-the-counter vitamins and dietary supplements should be recorded in the case report form (CRF).

7.10.1. Prohibited Medications

Through both phases of the study, the following medications are prohibited and the Sponsor must be notified if a participant receives any of these prohibited medications. The use of the following concomitant medications and/or vaccines, however, will not definitively require withdrawal of the participant from the study, but may determine a participant's eligibility to receive a second dose or evaluability in the per-protocol analysis set.

- If a participant receives a prohibited concomitant medication, the investigator in consultation with the Sponsor will evaluate any potential impact on receipt of study intervention based on time the medication was administered, the medication's pharmacology and pharmacokinetics, and whether the medication will compromise the participant's safety or interpretation of the data.
- Glucocorticoids at a dose ≥ 20 mg/day of prednisone or equivalent given daily or on alternate days for ≥ 14 consecutive days during the study period.
    - *Note:* Inhaled topical, or localized injections of corticosteroids (e.g., intra-articular or intrabursal administration) are permitted.

- Any other systemically administered drugs with significant immunosuppressive activity, such as azathioprine, tacrolimus, cyclosporine, methotrexate, or cytotoxic chemotherapy during the study period.
- Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after each study vaccination.

7.10.2. Permitted Medications

Participants may take concomitant medications prescribed by their primary care provider for management of chronic medical conditions and/or for health maintenance.

- Primary care providers, or where appropriate investigators, should prescribe appropriate concomitant medications or treatments deemed necessary to provide full supportive care and comfort during the study.
- Participants who develop COVID-19 after receiving study intervention should be treated with approved medications and interventions according to standard of care.
    - Unless the subject withdraws consent; the subject does not need to be withdrawn, and can continue with safety follow up till 12 months.
    - If the subject develops COVID-19 infection between 1st and 2nd dose, the 2nd dose will be deffered till 1 to 3 months' post recovery at the discretion of the principal Investigator.
- Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are permitted.

8. ETHICS AND REGULATORY CONSIDERATIONS

8.1. Regulatory Approval

This study is to be conducted according to the ethical principles that have their origin in the Declaration of Helsinki adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975; 35th WMA General Assembly, Venice, Italy, October 1983; 41st WMA General Assembly, Hong Kong, September 1989; 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996; 52nd WMA General Assembly, Edinburgh, Scotland, October 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); 59th WMA General Assembly, Seoul, October 2008; 64th WMA General Assembly, Fortaleza, Brazil, October 2013.

ICH GCP is a standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical studies that provides assurance that the

data and reported results are credible and accurate, and that the rights, integrity and confidentiality of the study subjects are protected.

This study also complies with GCP norms prescribed under G.S.R. 227(E), Indian Good Clinical Practice (GCP); The New Drugs and Clinical Trials Rules 2019 of CDSCO (Central Drugs Standard Control Organization), Ministry of health and family welfare, Government of India; the ethical guidelines for biomedical research on human participants, ICMR (Indian Council of Medical Research (2017).

The Sponsor will obtain regulatory approval from the Indian Authorities in accordance with applicable laws and requirements prior to initiating a study site/centre in India.

The Study protocol and related information will be posted on India's clinical trial registry - ctri.nic.in - before subject enrolment is started.

8.2. Trial Investigators

The Investigator is the person responsible for the conduct of the study at the study site. If a team of individuals at the study site conducts the study, then the Investigator is the responsible leader of the team and may be called the Principal Investigator. A Co-Investigator is any individual member of the clinical study team designated and supervised by the Investigator at a study site to perform critical study-related procedures and/or to make important study-related decisions (e.g., associates, residents, research fellows). The Investigator must maintain a delegation log/list of appropriately qualified persons to whom she/he has delegated significant study-related duties, which must be specified.

The trial Investigator(s) should possess appropriate qualifications, training and experience and should have access to such investigational and treatment facilities as are relevant to the proposed trial protocol. A qualified physician, who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical decisions.

The medical care given to, and medical decision made on behalf of subjects will always be the responsibility of a qualified trial physician. Each individual involved in conducting the study will 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 IEC/IRB have given, signed and dated approval of the protocol, written informed consent and other written information to be provided to the subject or LAR, and subject recruitment procedures (e.g. advertisements, if any). See section 8.3 for more details.

The Investigator will ensure that he/she has sufficient time to conduct and complete the study and has adequate staff and appropriate facilities which are available for the duration of the study and also ensure that other studies do not divert essential subjects or facilities away from the study at hand.

The responsibilities of the Investigator:

1. To submit an up-to-date curriculum vitae and other credentials to Sponsor (BE Ltd) and where required to relevant authorities;

2. To obtain necessary clearance from the site IEC/IRB;

3. To prepare and maintain adequate case histories designed to record observations and other data pertinent to the study;

4. To conduct the study in compliance with the protocol and appendices;

5. To co-operate with the representative of sponsor (BE Ltd) in the monitoring process of the study and in resolution of queries about the data.

A copy of the responsibilities is held in the Central files at the sponsor / designated CRO. Study related medical decisions and obtaining written informed consent are the responsibilities the Investigator or his/her authorised delegate. Curriculum Vitae and/or other relevant documents evidencing the qualifications of the Investigator and Co-Investigators are required before the study can commence at the site. When personnel changes are made, the relevant documentation has to be brought up-to-date and brought to the notice of Biological E Ltd./CRO before the new member of the team can perform critical and/or significant study-related activities.

8.3. Ethical Review

Independent Ethics Committee/Institutional Review Board's (IEC/IRB) approval will be sought at each participating centre, prior to the initiation of the study.

The Investigator (or Sponsor, where applicable) is responsible for ensuring that this protocol, the ICF, and any other information that will be presented to potential subjects (e.g. advertisements or information that supports or supplements the informed consent) are reviewed and approved by the appropriate IEC/IRB. The Investigator agrees to allow the IEC/IRB direct access to all relevant documents. The IEC/IRB must be constituted in accordance with all applicable regulatory requirements. The Sponsor will provide the Investigator with relevant document(s)/data that are needed for IEC/IRB review and approval of the study. Before study drugs can be shipped to the centre, the Sponsor must receive copies of the IEC/IRB approval, the approved ICF, and any other information that the IEC/IRB has approved for presentation to potential subjects.

The IEC/IRB will evaluate the ethical, scientific, and medical appropriateness of the study. If the protocol, the ICF, or any other information that the IEC/IRB has approved for presentation to potential subjects is amended during the study, the Investigator is responsible for ensuring that the IEC/IRB reviews and approves, where applicable, these amended documents. The Investigator must follow all applicable regulatory requirements pertaining to the use of an amended ICF including obtaining IEC/IRB approval of the amended form before new subjects consent to take part in the study using that version of the form. Copies of the IEC/IRB approval of the amended ICF/other information and the approved amended ICF/other information must be forwarded to the Sponsor promptly.

8.4. Informed Consent Procedure

Informed consent is a process by which a subject/or his/her or legally acceptable representative voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated.

The principles of informed consent in the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013), (essential elements of informed consent) in the G.S.R. 227(E) and the ICH-GCP (E6-R2) guidelines will be implemented before any protocol-specified procedures or interventions are carried out. Information will be given in both oral and written form whenever possible and deemed appropriate.

Both the subject information sheet as well as the Informed Consent Form should have been approved by the ethics committee and furnished to the Licensing Authority. Any changes in the informed consent documents should be approved by the ethics committee and submitted to the Licensing Authority before such changes are implemented.

The written consent document will embody the elements of informed consent as described in the Declaration of Helsinki and will also comply with local regulations. This form will be read to the subject, but, in any event, the Investigator will give the subject or legally acceptable representative adequate opportunity to read it before the consent form is signed.

Subjects or legally acceptable representative will be informed about the aims, expected benefits, possible risks (including a statement that the particular treatment or procedure may involve risks to the subject which are currently unforeseeable) and procedures of the research study. They will also be informed of alternative procedures.

Subject or subject's legally acceptable representative will receive an explanation as to whether any compensation and any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained. They will be informed whom to contact (e.g. the Investigator) for answers to any questions relating to the research project. The subject or legally acceptable representative must be informed that participation is voluntary and that they are free to withdraw from the study for any reason at any time, without penalty or loss of benefits to which they are otherwise entitled.

The extent of the confidentiality of subject records will be defined, and subjects or legally acceptable representative will be informed that applicable data protection legislation will be complied with. Subjects or subject's legally acceptable representative will be informed that the monitor(s), auditor(s), authorised representatives of IEC/IRB and regulatory/licensing authority(ies) will be granted direct / remote access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or subject's legally acceptable representative is authorizing such access.

The consent form generated by BE LTD/CRO, must be approved along with the protocol, and any other necessary documentation by the IEC/IRB and be acceptable to the Sponsor. Consent forms will be in a language fully comprehensible to the prospective subject or subject's legally acceptable representative. Informed consent will be documented by the use of a written consent form approved by the IEC/IRB and signed and dated by the subject or subject's legally acceptable representative, and by the person who conducted the informed consent discussion. The signature confirms that the consent is based on information that has been understood. The Investigator for possible inspection by Regulatory Authorities and/or Sponsor's/CRO external audit team will keep each subject's original signed informed consent form on file. The subject or subject's legally acceptable representative will receive a copy of the signed and dated written informed consent form and any other written information provided, and will receive copies of any signed and dated consent form updates and any amendments to the written information provided to them.

If the subjects or subject's legally acceptable representative has signed an informed consent form and subsequently found not to be eligible for the study depending upon the eligibility criteria, the investigator must complete that part of the source document that includes the subject's basic demographic information and the reason for excluding the subject from the study.

A separate Informed Consent Document will be applicable for each, Phase II and Phase III of the study.

8.5. Risk/benefit Assessment

A. Risks of receipt of CORBEVAX Vaccine Candidate

- Risk of no clinical protection against COVID-19 after 14 - 28 days post 2nd dose.
- Vaccine-enhanced disease
- Risk of pregnancy
- Risks of accidental disclosure of private medical information
- Risks of phlebotomy

B. Potential Benefits of Vaccine Participation

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

Rescue Medication and Risk Management

- Local reactions and systemic events, including body temperature will be reported by Subject or the LAR for 7 consecutive days after vaccination using a subject diary.

- Local reactions at the injection site such as pain, redness and swelling or induration are expected to occur. Commonly expected systemic adverse events may include Fever, headache, chills, myalgia, fatigue or malaise, urticaria, nausea and arthralgia. Rare adverse reactions like anaphylaxis may also occur.

- Since this is an investigational vaccine, subjects participating in this study may or may not be protected against SARS Coronavirus-2 through this vaccination.

- Individuals with altered immune-competence, if enrolled, may have reduced antibody responses to immunization with any COVID-19 vaccine. Severe allergic reaction (e.g., anaphylaxis) to any component of investigational vaccine will be an absolute contraindication. Epinephrine and other appropriate agents used to manage immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur following administration of the investigational vaccine.

- Management with antihistamines and/or hydrocortisone are not recommended in the emergency management of anaphylaxis in primary care. They should be considered, however, in the further management of anaphylaxis by appropriately trained staff.

9. STUDY MONITORING & QUALITY CONTROL

9.1. Study Monitoring

Monitoring is a process of overseeing the progress of a study, and of ensuring that the:

- rights, safety and well-being of subjects are protected;

- the study is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures, ICH-Good Clinical Practice guidelines and applicable regulatory requirements; and

- study data is accurate, complete and verifiable from source data.

Before the study starts, the monitor will ensure that the study site has sufficient capacity and equipment for performing the study. Sponsor/CRO will perform the monitoring of the site at regular intervals depending on the progress of the study. The Investigator will permit the monitors at agreed appointments to check and verify the study documentation (source data verification) including the eCRF and other

information. Corrections, amendments or clarifying statements will be made by the Investigator whenever necessary.

The monitor shall write a report after each visit. The sponsor and the investigators are responsible, according to ICH-GCP and local regulatory guidelines, for assuring proper study conduct as regards protocol adherence and validity of the data recorded on the eCRFs. The monitors will review the records and activities for maintenance of complete, legible, well-organized, and easily retrievable data. In addition, the monitors will train the site personnel on all applicable regulation concerning the clinical evaluation of an investigational drug, as laid down in ICH GCP guidelines.

The investigator agrees to allow the monitor access to the study drug dispensing and storage area and to all clinical data of the study subjects for the above purposes and agrees to assist the monitor in these activities. The investigator accepts that the monitor will visit the clinic/hospital at regular intervals or will contact the site remotely to review and verify the data collected. The monitor will regard all information, which is supplied to him or her as strictly confidential. The monitoring visits are for the purpose of verifying adherence to the protocol and for completeness and exactness of data entered in the case report forms and drug inventory forms. The monitor will verify eCRF entries by comparing them with the clinic/practice raw data, which will be made available for this purpose. Adequate time and space for these visits should be made available by the investigator.

9.2. Audits

For the purpose of compliance with ICH-GCP guidelines and regulatory agency guidelines, it may be necessary for licencing authority to conduct a site audit. This may occur at any time from start to conclusion of the study or even after that.

An audit is a systematic and independent examination of study related activities and documents to determine whether the evaluated study related activities were conducted, and the data recorded, analysed and accurately reported according to the protocol & Standard Operating Procedures, ICH-GCP and applicable regulatory requirements. Auditors are independent of the clinical study and its performance.

When an Investigator signs the protocol, he also agrees to permit Drug Regulatory Agency audits, providing direct access to source data/documents. Furthermore, if an Investigator refuses an inspection, his data will not be accepted in support of a New Drug Registration and/or Application.

BE Ltd has a substantial investment in clinical studies. Having the highest quality data is pivotal and studies are essential aspects of vaccine development. Where possible, BE Ltd will outsource clinical compliance audit of investigational sites. The external audit team will assess the quality of data with regard to accuracy, adequacy and consistency. In addition, external audit team assures that BE Ltd sponsored studies are in accordance with the ICH-Good Clinical Practices and that relevant regulations/guidelines are being followed.

To accomplish these functions, the external audit team selects investigational sites to audit. These audits usually take 1 to 2 days. BE Ltd audits entail review of sponsor

documents supporting the adequacy and accuracy of eCRF, review of documentation, and checks on vaccine accountability. BE Ltd audit, therefore, helps prepare an Investigator for a possible regulatory agency inspection as well as assuring BE Ltd validity of the database across investigational sites.

The Auditor will be especially interested in the following items

1. Log of visits from the Sponsor's/CRO's representative;
2. IEC/IRB approval;
3. Study medication accountability;
4. Approved study protocol and amendments;
5. Informed consent of the subjects (written or witnessed oral consent);
6. Medical records supportive of source document data;
7. Reports to the IEC/IRB and the Sponsor;
8. Record retention.

9.3. Inspection

Inspection is an act by regulatory authorities of conducting an official review of the documents, facilities, records and other resources that are deemed by the authorities to be related to the clinical study and that may be located at the study site, at Biological E. Limited or at other facilities deemed appropriate by the regulatory authorities. The Investigator is obliged to co-operate with any inspection.

9.4. Quality Assurance

The Clinical Research team of BE Ltd/CRO is responsible for implementing and maintaining quality assurance and quality control systems with written Standard Operating Procedures (SOP) where needed. BE Ltd/CRO is also responsible for ensuring that all parties involved with the study agree to direct/remote access to all study related sites, source data and documents, and reports for the purposes of monitoring and auditing that may be conducted by it or by other regulatory authorities. The documentation of the study will be adequate for reconstruction of the course of events (audit trail).

The sponsor/designated CRO will maintain a close liaison with the Investigator and staff to clarify problems that may arise during the study, and to ensure that the investigation is being carried out according to the Protocol, ICH-GCP and applicable local regulatory requirements. The study will be monitored throughout by the responsible monitor in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and the progress of the study. The monitoring will consist of visits before the study is initiated, when the centre is initiated, at appropriate intervals during the study and at the end of the study. The monitoring will include also communications via telephone, letter and remote monitoring.

9.5. Investigator's File

The Investigator will keep files of essential documents related to the study trial. These files must at least contain either in original or as a copy of the following:

1. Signed, original copy of the protocol and all amendments
2. Letter of approval from the IEC/IRB and any other correspondence
3. A copy of the IEC/IRB membership list
4. Original signed and stamped IEC/IRB-approved consent form, and copies of CRFs
5. Regulatory authority approval, authorization, or notification where applicable
6. The informed consent form being used and other information given to the subject
7. Documentation of corrections to the CRFs
8. Certificate of insurance and/or indemnity
9. Updated and signed copies of curriculum vitae and or other relevant documentation evidencing the qualification of the Investigator and co-Investigator(s)
10. Study personnel and specimen of signatures with list of function and delegated study-related activities
11. Investigator's brochure for candidate vaccine(s) and/or Package insert / Summary of Product Characteristics for licenced vaccines.
12. Relevant contracts affecting the performance of the study at the Investigator's site (financial agreement)
13. Certification, accreditation, validation or evidence of quality control of medical, laboratory or technical facilities
14. Normal values/ranges for medical, laboratory or technical procedures
15. Names and addresses of persons to be notified in case of a serious adverse event
16. Documentation of serious adverse events: discharge letters, reports of diagnostic or therapeutic procedures
17. Notification by Biological E. Limited and/or Investigator to regulatory authority(ies) and IECs/IRBs of serious adverse events and of other safety information as required
18. All study-related correspondence and communication between Sponsor and Investigator (including minutes, visit report of study initiation, and newsletters)
19. Site Visit log
20. Telephone contact log

21. Screening and enrolment log
22. Shipping/couriering records for Investigational medicinal products and other study related materials
23. Accountability of Investigational medicinal products and other study related material
24. Working sheets and additional instructions, if any, for handling study materials
25. Copies of final (study close-out) reports to the IEC/IRB and/or regulatory agencies
26. Summary of study results

The Investigator's files must be available at all monitoring visits and also during an audit or inspection. Biological E. Limited will inform the Investigator in writing of the need for record retention and will notify the Investigator when the study-related records are no longer required.

10. DATA HANDLING AND RECORD KEEPING

A Data Management Plan (DMP) or equivalent will be defined and data processing will be conducted accordingly by the Sponsor or the contract research organization. Database lock will occur once quality control procedure, and quality assurance procedures have been completed. Portable Document Format (PDF) files of the eCRFs will be provided to the Investigators at the completion of the study, if applicable.

Data will be captured in standardized format according to the study centre's standard operating procedures and the procedures specified in the study documentation. A Code of Federal Regulations Title 21, Part 11-compliant electronic data capture system will be used for this study, as applicable. The eCRFs will be produced by the contract research organization for each subject.

10.1. Confidentiality

Permission for direct / remote access to subject's data will be sought in writing by the Investigator and from the subject or subject's legally acceptable representative as part of the informed consent procedure. This gives permission to examine, analyse, verify and reproduce any records and reports that are important to the evaluation of the study. Any party (e.g., domestic and foreign regulatory authorities, monitors and auditors) with direct / remote access must take all reasonable precautions within the constraints of the applicable regulatory requirements to maintain the confidentiality of the subject's identities and Sponsor's proprietary information.

It is the Site Monitor's responsibility to verify that each subject or subject's legally acceptable representative has consented in writing for direct / remote access. It is to be ensured by the Investigator that documents that are given to BE LTD (sponsor) or its representatives do not contain the name or address of the subject, or other information that would affect the anonymity of the subject (apart from his initials). However, study monitor will check all source documents which contain all subject information.

Note: Subject or subject's legally acceptable representative will be informed that the monitor(s), auditor(s), IEC/IRB, and the regulatory authority(ies) will be granted direct / remote access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject is authorizing such access.

The aims and content of this study, and the results thereof are confidential and are not to be transmitted to a third party in any form or fashion. All persons involved in the study are bound by this confidentiality clause.

The Investigator will agree that all information communicated by the Sponsor directly or through a site monitor is the exclusive property of the Sponsor and shall ensure that the same shall be kept strictly confidential and shall not be disclosed by any person to any third party without the prior written consent of the Sponsor. The Investigator shall communicate the results of the study promptly to the Sponsor.

10.2. Ownership of Data

All rights and interests world-wide in any inventions, know-how or other intellectual or industrial property rights, which arise during the course of and/or as a result of the clinical study which is the subject of this Protocol or which otherwise arise from the information or materials supplied under this Agreement, shall be assigned to, rest in and remain the sole property of Biological E. Limited, Hyderabad, India.

10.3. Medical Coding Procedures

The medical coding of the study data, as appropriate, will be performed by sponsor approved data management organisation or any other sponsor approved contract research organisation once the database is synchronized. Adverse events and medical history will be coded using medical dictionary for regulatory activities (MedDRA) or any other currently used. Concomitant medication will be coded using the WHO Drug Dictionary Enhanced. No other free text data will be coded unless and until specified by Biological E. Limited or in the approved data management plan. Any modifications in version of the dictionaries used will be recorded and sponsor is notified accordingly.

10.4. Source Documents

Source data are defined as all information related to clinical findings, observations, or other activities in the study, written down in original records or certified copies of original records. The investigator will permit trial-related monitoring, audits, IEC/IRB review and regulatory inspections, by providing direct access to source data/records. Source records should be preserved for the maximum period of time permitted by local regulations.

At least the following data will be documented in the source records:

- Date of subject's study entry and termination, study identification
- Documentation of informed consent procedure

- Date of each study visit and study related correspondence
- Medical History, demographic data
- Any examination findings
- Laboratory test reports
- Adverse events
- Concomitant medication intake
- Early withdrawal date and withdrawal reason, if applicable
- Dosing dates
- Subject identification numbers
- Completed subject diaries.

All procedures to be performed for eCRF will be in compliance with the requirements of the study protocol and as per the Standard Operating procedures (SOPs) setup by the Contract Research Organisation (CRO) to which the clinical data management (CDM) activity is outsourced by the sponsor.

The Clinical Data Management (CDM) is intended to establish a standard plan on how the data for the designated study will be acquired and processed - from receiving final protocol to database lock.

After all the data clarifications were resolved, a clean file will be declared and documented after the final checking with respect to the overall consistency and evaluability of the data and after the resolution of all known and unclear issues. Following the declaration of clean file, the database will be locked.

10.5. Case Report Forms

Electronic case report forms (eCRF) will be used to record all of the information required by the protocol to be reported for each study subject. The Sponsor will provide the access of eCRF to the Investigator. Only validated information from the source document will be transcribed into the eCRFs. Separate instructions on how to access and use the electronic CRFs, will be provided to the site staff including necessary access to authorised personnel and relevant training both to the sponsor and site staff.

When subsequent corrections or additions to the entries in the eCRF are deemed necessary, they will be listed in the electronic Data Capture System. This will be sent to the Investigator requesting him/her to confirm or make the correction, or enter additional or missing data as required. This will be performed directly on the eCRF with the Investigator's access. The monitor should lock all the data with his access after the respective clarifications are closed.

All clinical documentation and data arising from the study is to be archived by the Investigator for a minimum period of 15 years or as per local regulatory requirements or as informed by the sponsor from time-to-time. Signatures must be hand-written by

the Investigator or delegated person; stamping is not allowed. Subject identification number shall begin as A (phase II) or B (phase III) - two-digit site number, three-digit sequential subject number i.e. A-01-001, A-01-002, etc. for Phase II part of the study, and B-01-001, B-01-002, etc. for Phase III part of the study.

When a subject completes a visit, it is anticipated that the relevant sections of the source document be completed by the Investigator (or designated staff) immediately as the data is available. The data must be captured directly on to the source document. The same must be transcribed on the eCRF. This also applies to potential study subjects who were screened but not enrolled.

As soon as the subject has completed/withdrawn from the study and the eCRF is completed, the principal Investigator or designated physician(s) under his/her supervision will complete the study completion information pages of the CRF to confirm that they have reviewed the data and that the data is complete and accurate.

The Clinical Study Monitor (sponsor) will review completed eCRFs, and if errors are detected may necessitate clarification and/or correction of such errors by the Investigator. The Investigator will assist in clarification or correction of errors detected after study finalization after them being brought to their attention. Any questions or comments related to the eCRF will be directed to the assigned Site Monitor.

10.5.1. Screening Evaluation

INSTRUCTIONS

Please read the instructions carefully – Please record and complete the following for all subjects (based on relevance to that age group/sub-group) at screening:

1. Inclusion/exclusion criteria
2. Demographic data
3. Medical History
4. General & Physical examination
5. Vital Signs (Body temperature, Pulse, respiratory rate & Blood pressure)
6. Systemic examination
7. Haematology & Biochemistry
8. Tests for determination of HIV 1 & 2, HBV and HCV infection status only once at baseline visit.
9. Urine pregnancy spot test for female subjects of childbearing potential once at baseline and again at Day 28.
10. Immunological assays (IgG antibody, INF-γ cytokine levels, IL-4 & Neutralizing antibodies)
11. Study vaccine administration
12. Dispensation of subject Diary and its training to the Subject or LAR.

13. Concomitant medications if any
14. All Adverse events
15. Severity of symptoms as reported by the subject or LAR and the causality assessment of AEs as judged by the investigator

10.5.2. Other Documentation

Clinical documentation relevant to the study includes all records in any form (including, but not limited to written, electronic, magnetic, and optical records, scans, X-rays and electrocardiograms) that describe or record the methods, conduct and/or results of the study, the factors affecting the study and the actions taken. Source data, are all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study.

Source data will be captured in source documents, which comprise clinical documentation, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments and data and records arising from other departments such as the pharmacy, laboratory and medico-technical departments).

Clinical Data Management services including statistical analysis and statistical report writing will be outsourced to a sponsor approved Contract Research Organisation (CRO).

10.6. Protocol Amendments

Changes to the protocol during the study will be documented as 'amendments'. These will form an integral part of the protocol and will be signed by the relevant personnel in Biological E. LTD and by the Investigators. Amendments, which affect subject's safety or welfare, must always be submitted to the relevant IEC/IRB and/or to the licensing authority for obtaining written approval before implementation.

Protocol amendments if become necessary before initiation or during the course of a clinical trial, all such amendments should be notified to the Licensing Authority in writing along with the approval by the ethics committee which has granted the approval for the study. No deviations from or changes to the protocol should be implemented without prior written approval of the ethics committee and the Licensing Authority except when it is necessary to eliminate immediate hazards to the trial Subject(s) or when change(s) involve(s) only logistic or administrative aspects of the trial. All such exceptions must be immediately notified to the ethics committee as well as to the Licensing Authority. Administrative and/or logistic changes in the protocol should be notified to the Licensing Authority within 30 days.

Any changes in the final protocol shall be added as an addendum/appendix at the end of the protocol and subsequently, a revised protocol version number shall be given to the main protocol. The revised protocol shall be submitted to the investigator at each site for submission/notification to the respective IEC/IRB. The amendments shall be

appropriately communicated to regulatory authorities as per sponsor's SOPs and applicable regulations in force.

The Investigator will not implement any deviation from, or changes of the protocol, without agreement by Biological E. LTD and prior review and documented approval/favourable opinion of the appropriate IEC/IRB, except where necessary to eliminate an immediate hazard to the subjects, or when the changes involve only logistical or administrative aspects of the study.

Amendments that affect the treatment of the subject require a new information sheet to be written with the relevant change incorporated. When subjects are currently undergoing study procedures and these procedures are altered due to the amendment then the subject must be asked to consent again.

10.7. Protocol Deviations

Inclusion of subjects not satisfying the enrolment criteria will be subject to prior discussion with the sponsor and written approval from the sponsor. Subjects developing exclusion criteria during the study need not necessarily be withdrawn except for safety reasons; other exceptions need prior discussion and information to the sponsor.

All major protocol deviations will be listed in the study report and assessed as to their influence on the quality of study analysis. The IEC/IRB will be informed of all major protocol changes by the investigator in accordance with the Ethics Committee's established procedures.

No deviations from the protocol of any type will be made without complying with all the Ethics Committee's established procedures in accordance with applicable regulations. Final decisions on all protocol violations reported will be done in a data review meeting prior to database lock.

Emergency deviations: When a deviation occurs in an emergency situation, such as when a departure from the protocol is required to protect the life or physical well-being of a subject, the sponsor and the reviewing IEC/IRB must be notified as soon as possible, but in no event later than 5 days after the emergency occurs.

Major, non-emergent deviations without prior approval: A planned deviation that is non-emergent and represents a major change in the protocol as approved by the IEC/IRB must be submitted as a change/amendment in research. The IEC/IRB must approve the request before the proposed change is implemented. If a major, non-emergent deviation occurs without prior IEC/IRB approval the event is considered non-compliance. Non-compliance must be reported to the IEC/IRB promptly. A Principal Investigator's failure to report promptly any major, non-emergent deviation for which the Principal Investigator (PI) did not obtain prior approval is itself an incident of non-compliance. Incidents of non-compliance will be managed in accordance with the Organization guidelines.

Protocol deviations that are only minor or administrative: Minor or administrative protocol deviations are defined as those which do not "affect the scientific soundness of the research plan or the rights, safety, or well-being /welfare of human subjects." If

a protocol deviation occurs which meets this definition, the deviation should be reported to the sponsor as soon as it is detected. Reporting to IEC/IRB is not required for these deviations. Examples of minor or administrative deviations could include: follow up visits that occurred outside the protocol required time frame because of the subject's schedule, or blood samples obtained at times close to but not precisely at the time points specified in the protocol.

Prior approval protocol deviations that involve a prior approval from Sponsor &/or IEC/IRB: A prior approval from the sponsor of all planned deviations, including administrative and minor deviations by principal investigator is mandatory. Planned deviations requested must also be submitted for IEC/IRB review as a "change in research" and approved by the IEC/IRB prior to instituting any planned deviations.

10.8. Premature Study Termination

The ethics committee, Regulatory Authorities, or the Sponsor may prematurely terminate the study, if the perception of the benefit/risk becomes unfavourable for the continuation of the study. If the study is prematurely terminated or suspended for any reason, the Investigator will i) promptly inform the subject or legally acceptable representative, ii) will assure appropriate therapy and follow-up for the subjects, iii) inform the regulatory authorities and ethics committee (where appropriate) and the Institution where the study is being performed. A decision to cease the study either by the regulatory body or ethics committee or by the sponsor is binding on the Investigator.

11. STATISTICS

Complete details regarding statistical analysis and interpretations will be provided in the Statistical Analysis Plan.

11.1. Sample Size Determination

The sample size estimate is based on results from human trials using a similar protein subunit-based vaccine (Yang et al. March, 2021). [20]

To evaluate immunogenicity, the following hypotheses will be tested:

- Seroconversion co-primary endpoint

$$H_0: \theta_{sc} - \mu_{sc} \leq \delta_{sc}$$
$$H_1: \theta_{sc} - \mu_{sc} > \delta_{sc}$$

where:

θ_{sc} = Estimated seroconversion rate in the cohort (assumed to be 71%),

μ_{sc} = Population background seroconversion rate (assumed to be 15%),

δ_{sc} = Superiority margin of 60% (based on human trials with similar vaccines),

α = 0.025 (one-sided test for superiority),

β = 90% power.

A total sample size of 1268 is required (n=100 at Phase-II and n=1168 at Phase-III) for this endpoint, assuming a 10% drop-out rate.

Based on this, the study will need to demonstrate that the peak seroconversion rate induced by vaccination is greater than 60% to be considered a success.

All data will be summarised descriptively, by visit/time point where possible. Safety data will be summarised by System Organ Class and Preferred term. Serious adverse events will be summarised separately.

In addition to the analysis for the primary endpoints, immunogenicity data will be analysed using generalised linear regression models for longitudinal data. Data will also be presented graphically, where applicable.

All data will be listed.

Interim Clinical study report will be generated on day 56 completion for all subjects enrolled. Updated Final clinical study report will be generated on completion of 12 months follow-up period.

11.2. Analysis Populations

Apart from the analysis sets described below, additional analysis sets may be described in the full statistical analysis plan.

11.2.1. Full Analysis Set (FAS)

Subjects who provided informed consent for participation will be considered in the full analysis set.

11.2.2. Intent-to-treat (ITT) Set

All subjects from the FAS who have received two (both) the doses of the study vaccine will be considered in the ITT population. Subjects will be analysed as randomised, irrespective of which treatment they received.

11.2.3. Per Protocol (PP) Set

All subjects form the IIT set without any major protocol deviations will be considered for PP Set.

11.2.4. Safety Set

All subjects from the FAS who received at least one dose of the study vaccine will be considered for the Safety Population.

11.3. Statistical Analysis Methods

All data will be summarised descriptively, by visit/timepoint where possible. Safety data will be summarised by System Organ Class and Preferred term. Safety data will be summarised by System Organ Class and Preferred term. Serious adverse events, related adverse events, adverse events leading to death or withdrawal, solicited

adverse events, and medically attended adverse events will all be summarised separately. In addition, adverse events will also be summarised by severity. The full analysis will be described in a prospective statistical analysis plan that will be finalised prior to database lock.

11.3.1. Primary Endpoint Analysis

- Neutralising antibody co-primary endpoint

Data will be log-transformed prior to obtain a log-normal distribution, which will be used for all statistical analyses. For reporting purposes and to test the hypothesis above, results will be back transformed. The peak neutralising GMT for each participant will be used to determine point estimates and confidence intervals. These results will be used to test the relevant hypothesis.

- Seroconversion co-primary endpoint

The point estimates and Confidence Intervals of the proportion of participants at each time point that seroconverted will be determined. The timepoint of the peak point estimate will be used to test the relevant hypothesis described above.

11.3.2. Secondary Endpoints Analyses

In addition to the descriptive statistics, immunogenicity data will be analysed using generalised linear regression models, where applicable, for longitudinal data. Data will also be presented graphically, where applicable. For all immunogenicity endpoints, descriptive statistics will be presented for each treatment group, as well as the difference between treatment groups. Where antibody titers are reported, instead of the difference, the ratio of log-transformed antibody titers will be reported. In addition, changes from baseline at each visit will also be presented. Antibody titers will be log-transformed prior to determining descriptive statistics, of which exponentiated values will be reported. Antibody titer data will not be log-transformed to estimate fold increases.

11.3.3. Statistical Analysis Software

All the statistical analysis will be conducted by CRO using SAS® 9.4 or higher.

12. INSURANCE AND INDEMNITY

Insurance

Biological E. Limited will ensure that the insurance or its equivalent for this study has been arranged prior to its commencement and a copy of the same will be held in the central files at sponsor (BE LTD) and also at the study site. All the study subjects will be suitably insured covering the entire duration of the study.

The insurance limit and determination of the quantum of compensation is dependent on the terms outlined in the insurance contract and will comply with the current G.S.R. 227(E) regulations.

Indemnity

Valid Professional Indemnity (VPI) cover will be provided to the investigator(s) for a mutually agreed amount.

The insurance company will insure and also indemnify or otherwise compensate the insured, in accordance with, and subject to the terms and conditions of the insurance &/or indemnity Policy, and in consideration of payment of premium to the insurance company for the period of Insurance. The proposal made to the Insurance company, by, or on behalf of the insured (Biological E. Limited) in writing shall be the basis of the contract. Provided that this policy shall be invalid unless it has been signed by the authorised official of the insurance company.

The indemnity limit and determination of the quantum of compensation is dependent on the terms outlined in the insurance contract and will comply with the current G.S.R 227 (E) regulations.

13. FINANCE

The study is Sponsored by Biological E Limited. Contracts will be prepared between the relevant parties (Investigator/CRO/etc.) setting out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters, and shall comply with all local and national rules and regulations.

14. DATA ARCHIVAL

At the end of the study, the Investigator will be instructed to archive the study documents as per the agreed archival policy with BE LTD. BE will retain these according to applicable regulations and laws.

15. STUDY REPORT

Biological E Ltd. Or the assigned CRO will prepare a Clinical Study Report (CSR), integrating the medical and statistical aspects based on the clean final TLFs provided by the data management team. The Investigators will be provided with a copy of the summary of the final CSR.

16. PUBLICATION POLICY

The Sponsor shall retain the title and the right to publish all documentation, records, raw data, specimens or other work product generated pertaining to the Study (“Data”) conducted by site (site includes the Investigator and the Institution) as defined in the applicable protocol or study plan or study agreement. The site shall maintain confidentiality and not disclose or divulge such Data to any third party. However, the site may seek permission to publish such Data for limited purpose and such Data may be published by the site only upon receipt of prior written approval from the Sponsor.

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18. VERSION HISTORY AND SUMMARY OF CHANGES

Change Control – Version History:

Version No.	Date	Protocol No.
1.0	14 Apr 2021	BECT/COVID-19-PHASE-III/069
2.0	30 Apr 2021	BECT/COVID-19-PHASE-III/069
2.1	13 May 2021	BECT/COVID-19-PHASE-III/069

Version 2.0 of the study protocol dated 30 Apr 2021 is revised to version 2.1 to remove comparator arm from Phase-III study design.

SUMMARY OF CHANGES FROM VERSION 2.0 TO VERSION 2.1

The following table provides a summary of changes (**Substantial/Major**) made in the amended protocol Version 2.1 date 13 May 2021 from the previous Version 2.0 date 30 April 2021.

Protocol Section	Summary of Changes made from Version 2.0 to Version 2.1
Title	'*A Prospective, Open-label, Single-arm, Phase II Seamlessly Followed by a Randomized, Observer-blind, Active Comparator-controlled, Phase III Clinical Study to Evaluate the Immunogenicity and Safety of Biological E's CORBEVAX Vaccine for Protection Against COVID-19 Disease When Administered to COVID-19-Negative Adult Subjects'* ***Changed to*** *A Prospective, multicentre, Phase II Seamlessly Followed by Phase III Clinical Study to Evaluate the Immunogenicity and Safety of Biological E's CORBEVAX Vaccine for Protection Against COVID-19 Disease When Administered to COVID-19-Negative Adult Subjects.*
Synposis	Day-7 visit in Phase II, followed by DSMB clearance to proceed to Phase III has been removed. Submission of Immunogenicity data of Phase II to CDSCO and proceed to Phase III has been included. Phase III design has been modified from active-controlled study to single arm study.

Protocol Section	**Summary of Changes made from Version 2.0 to Version 2.1**
Schedule of Assessments	Day 7 visit in Phase II has been removed
Study Objectives and Endpoints	Phase III objectives and endpoints revised to remove comparision with control vaccine.
Study Design	Phase III design has been revised from observer blind active-comparator design to single arm design.
Study Procedures	Visits and Assessments updated to reflect requirements for Phase II and Phase III of the study.
Investigational Products	Updated from: Phase II – Test: Biological E's COVID-19 Vaccine, CORBEVAX Phase III – Test: Biological E's COVID-19 Vaccine, CORBEVAX Control: Bharat Biotech's COVID-19 Vaccine, COVAXIN™ Updated to: Phase II – Test: Biological E's COVID-19 Vaccine, CORBEVAX Phase III – Test: Biological E's COVID-19 Vaccine, CORBEVAX
DSMB review	Updated from: DSMB meeting was scheduled after Day 7 assessments and proceed to Phase III. Updated to: DSMB meeting is scheduled after Day 56 of Phase III to cumulatively review safety data of the Phase-II seamlessly followed by Phase-III study
All OTHER SECTIONS	Minor edits and relevant alignment is done to reflect the revised study design from phase II by III active-comparator, observer blind study (version 2.0) to phase II by III single arm study (version 2.1).

19. APPENDICES

APPENDIX - I

List of Investigators