1 Title Page

PHASE – I & II

Clinical Study Protocol

of

A Novel Covid-19 vaccine containing Receptor Binding Domain of SARS-CoV-2 * * *

Vaccine Manufactured By:
Biological E. Limited, Hyderabad, India.

Study/Trial Title:
A prospective open label randomised phase-I seamlessly followed by phase-II study to assess the safety, reactogenicity and immunogenicity of Biological E's novel Covid-19 vaccine containing Receptor Binding Domain of SARS-CoV-2 for protection against Covid-19 disease when administered intramuscularly in a two dose schedule (0, 28D) to healthy volunteers.

Study Code:	BECT062
Trial No.:	BECT/Covid-19-phase-I&II/062
Protocol No.:	BECT062/Covid-19-phase-I&II/CTP-01
Version No. & Date:	1.1 dated 07.10.2020
Amendment No. & Date:	1.0 dated 07.10.2020
Clinical Phase of Development:	Phase-I seamlessly followed by phase-2 study.
Investigational New Drug:	Biological E's novel Covid-19 vaccine

Sponsor Registered Office:
Biological E. Limited,
18/1&3, Azamabad,
Hyderabad - 500020, India.

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

Version History:
Summary of changes made to version 1.0 of the Study Protocol

Change Control – Version History:

Version No.	Date	Protocol No.
1.0	22.09.2020	BECT062/Covid-19-phase-I&II/CTP-01
1.1	07.10.2020	BECT062/Covid-19-phase-I&II/CTP-01

The current version 1.0 of the study protocol dated 22.09.20 is revised to version 1.1 to incorporate the recommendations of 'Subject Expert Committee (SEC) meeting to examine COVID-19 related proposal under accelerated approval process made in its 114th meeting held on 05.10.2020.

Changes Made to the Existing Protocol:

- As per the SEC minutes', protocol amended to start with 15 µg dose followed by 25 µg dose and the 50 µg dose sequentially in ascending approach to demonstrate 7-day safety of each formulation before proceeding to phase II study. No further changes have been made to the design of the study.

Study Centres: Multicentre (5) - All Centres will be within India only.

List of the Investigators:

Site Code	Name of the Investigator(s)	Institutional Affiliations And Site Locations
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Study Sponsor:

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

Central Laboratory Services:

Anti-SARS-CoV IgG antibody test, Neutralizing antibody (NAb) assay against live and/or pseudo typed SARS-CoV-2 virus & Interferon-Gamma Cytokine Levels (INF-γ) will be performed at any NABL and/or CAP accredited central laboratory in India.

Data Management & Statistical Services Support:

BE approved CRO/Data Management Organisation in India.

Study Monitoring & Safety Surveillance:

Clinical Development team,
Biological E. Limited,
18/1&3, Azamabad,
Hyderabad – 50020, Telangana. India.

PROTOCOL APPROVAL SHEET

Study/Trial Title:

A prospective open label randomised phase-I seamlessly followed by phase-II study to assess the safety, reactogenicity and immunogenicity of Biological E's novel Covid-19 vaccine containing Receptor Binding Domain of SARS-CoV-2 for protection against Covid-19 disease when administered intramuscularly in a two dose schedule (0, 28D) to healthy volunteers.

Study Code: BECT062

Trial No.: BECT/Covid-19-phase-I&II/062

Protocol No.: BECT062/Covid-19-phase-I&II/CTP-01

Version No. & Date: 1.1 dated 07.10.2020

PROTOCOL PREPARED BY:

Date: 07.10.20

(Signature)
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PROTOCOL REVIEWED BY:

G.V.S. Reddy

Date: 07.10.20

(Signature)
Mr. G.V. Subba Reddy
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Date: 07.10.20

(Signature & Date)
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PROTOCOL APPROVED BY:

Date: 07.10.20

(Signature)
Dr. Subhash Thuluva
Vice President – Clinical Development, BE Ltd.

INVESTIGATOR'S STATEMENT OF APPROVAL & COMPLIANCE

[The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and G.S.R. 227(E), ICMR and ICH guidelines in force at the time of execution].

I have read the attached protocol and agree that it contains all the information necessary for the conduct the study. I agree to abide by all provisions set forth therein.

I agree to conduct this study in accordance with ICH - GCP & other local regulatory guidelines. I will initiate the study only after obtaining written approval by the appropriate Ethics Committee and Regulatory Authority (Drug Controller General of India), where applicable. I will obtain written informed consent, as applicable, from all study participants or their legally acceptable representative prior to performing any screening procedures.

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.

The attached protocol and related information is subject to the Confidentiality Agreement between Biological E. Limited and the investigator(s).

Investigator's Name:

_____

Investigator Signature: _____**Date:** _____

Site Name & Address:

_____

_____

_____

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2.1 Abbreviations

-	Minus
+	Plus
®	Registered
%	Percentage
+ve	Positive
-ve	Negative
<	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
CAP	College of American Pathologists
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	Case Report Form
CRO	Contract Research Organization
CTC	Common Toxicity Criteria

CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
DB	Direct Bilirubin
DAIDS	Division of AIDS
D&CA	Drugs & Cosmetics Act
DCF	Data Clarification Form
DCGI	Drug Controller General of India
DSMB	Data Safety Monitoring Board
'E'	Enrolment
GMFR	Geometric Mean Fold Rise
MERS	Middle East Respiratory Syndrome
EC	Ethics committee
ELISA	Enzyme-Linked Immunosorbent Assay
EIA	Enzyme Immune Assay
ENT	Ear, Nose & Throat
EPI	Expanded Programme of Immunization
°F	Fahrenheit
GCP	Good Clinical Practice
gm	Gram
GMT	Geometric Mean Titre
Hb	Haemoglobin
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HR1	Heptad repeats1
HR2	Heptad repeats2
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonization
ICMR	Indian Council of Medical Research
i.e.	That is
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IEC	Institutional Ethics Committee
IgG	Immunoglobulin G
INF-γ	Interferon-Gamma
IP	Indian Pharmacopeia, Investigational product
ITT	Intent-to-treat
IM	Intramuscular
IU	International Units
IV	Intravenous
IWRS	Interactive Web Response System
KFT	Kidney Function Test
kg	Kilogram
LAR	Legally Acceptable Representative

LFT	Liver Function Test
LLOQ	Lower Limit of Quantitation
LTD	Limited
MedDRA	Medical Dictionary for Regulatory Activities
MEIA	Micro-particle Enzyme immunoassay
Mg	Milligram
mL	Millilitre
MoH & FW	Ministry of Health and Family Welfare
n	Sub sample
N	Total sample
NAb	Neutralizing Antibody
NABL	National Accreditation Board for Laboratories
NaCl	Sodium Chloride
ND	Not Done
NS	Normal Saline
PC	Platelet Count
PCV	Packed Cell Volume
PHEIC	Public health emergency of international concern
PI	Principal Investigator
PP	Per-Protocol
'R'	Randomization
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
SIS	Subject Information Sheet
SNT	Serum Neutralization Test
SOP	Standard Operating Procedure
SP	Safety Population
TB	Total Bilirubin
TEAE	Treatment Emergent Adverse Event
TRF	Test Requisition Form
TT	Tetanus Toxoid
™	Trade Mark
TVC	Total vaccinated cohort
U	Units
ukn	Unknown
UPS	Uninterruptible Power Supply

v1	Version 1
VPI	Valid Professional Indemnity
WBC	White Blood Cell
WFI	Water for Injection
WHO	World Health Organization
WMA	World Medical Association

2.2 Background and Introduction

2.2.1 Background

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.

The first case of COVID-19 in India, which originated from China, was reported on 30 January 2020. As of 21 September 2020, the Ministry of Health and Family Welfare (MoH&FW) has confirmed a total of 55,62,663 cases, out of which 9,76,420 active cases, 44,97,867 recoveries and 88,965 deaths in the country [9]. India currently has the largest number of confirmed cases in Asia, [10] and has the second highest number of confirmed cases in the world [10].

2.2.2 General Introduction

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].

2.2.3 Preclinical and Clinical experience

A. Single Dose Acute Toxicity Study Reports

i) STUDY NO: 20/0166

Study title: Single Dose Acute Toxicity Study of SARS-CoV-2 (Covid-19) Vaccine with AH+Co-Adjuvant in Sprague Dawley Rats by Intramuscular Route.

Summary:

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).

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 up to 0.5 mL/rat following single dose of intramuscular administration under conditions tested.

B. Repeat Dose Toxicity Study Reports

i) STUDY NO: 20/0167

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

Summary:

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 analyzed. This study will provide a rational basis for toxicological risk assessment in humans

Conclusion:

Study under progress.

ii) STUDY NO: 20/0168

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

Summary:

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 analyzed. This study will provide a rational basis for toxicological risk assessment in humans

Conclusion:

Study under progress.

2.3 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.

To date, there is no vaccine and no specific antiviral medicine to prevent or treat COVID-19. 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.

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.

Developing an effective and safe vaccine is urgently needed to prevent infection by severe acute respiratory syndrome (SARS)–associated coronavirus (SARS-CoV2). 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 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 and proposes a phase-I seamlessly followed by phase-II clinical trial in India to assess 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.

3 Study Objectives

3.1 Trial Objectives & Endpoints at Phase-I Study:

3.1.1 Primary Objective

» Primary objective at each of the dose strengths, starting from lower to higher, is to assess the safety, tolerability and reactogenicity of single intramuscular dose of the Covid-19 vaccine administered to 18-55 year-old healthy adult volunteers of either gender.

- A DSMB review of “post 7-days safety data” for 12 subjects from each of the dose strengths before seamlessly proceeding to phase-II.
- However, all 12 subjects in each of the dose strengths will receive their second dose 28 days after first dose and continue to be followed up for safety and immunogenicity at day 56 and later till 12 months post 2nd dose.

3.1.2 Secondary Objective

» To assess the immunogenicity of two intramuscular doses of the adsorbed 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 volunteers.

3.1.3 End Points

3.1.3.1 Primary Endpoint (s)

» Safety, tolerability and reactogenicity after each dose of Covid-19 vaccine in in terms of:

- any adverse reactions within 2 hours of immediate post vaccination period;
- any solicited symptoms within 7 consecutive days after each dose captured through subject diary;

- any unsolicited adverse events during 28 days after each dose of study vaccination;
- Serious and other medically attended adverse events in all study participants at 6 months and 12 months post 2nd dose.

3.1.3.2 Secondary Endpoint(s)

» Immune response after each dose of Covid-19 vaccine in in terms of:

➢ IgG antibodies against SARS-CoV-2 RBD antigen at baseline, 28, 42, 56 days and again at 6 months and 12 months post 2nd dose.

- Seroconversion rates in terms of proportion of subjects with ≥4-fold increase in IgG antibodies from baseline.
- Geometric mean concentrations and Geometric mean fold rise in IgG titres from baseline.
- IgG antibody subclasses (IgG1 & IgG2) against SARS-CoV-2 RBD at baseline and again at Day 56 will be presented.

➢ Virus neutralizing antibody (NAb) assay against SARS-CoV-2 virus at baseline, 28, 42, 56 days and again at 6 months and 12 months post 2nd dose.

- Seroconversion rates in terms of proportion of subjects with ≥4-fold increase in neutralizing antibodies from baseline.
- Geometric mean titres and Geometric mean fold rise in neutralizing antibodies from baseline.

➢ Interferon-gamma cytokine levels at baseline, Day 28 and again at Day 56.

Independent DSMB Review:

An independent data safety monitoring board (DSMB) setup for this purpose will review 7 days' diary data after 1st dose at visit-3 (Day 7), in first 12 subjects from each of the three dose strengths.

1. First DSMB: In first 12 subjects from BECOV2D (15 µg/dose)
2. Second DSMB: In first 12 subjects from BECOV2B & BECOV2C (25 µg/dose)
3. Third DSMB: In first 12 subjects from BECOV2A (50 µg/dose)

Based on the positive recommendation from DSMB after 7-day safety review of respective dose strengths, the study will move seamlessly into phase-II by continuing enrolling balance subjects in the respective groups.

A fourth DSMB review occurs 28 days' post 2nd dose for all the subjects at the end of phase II.

The phase-I seamlessly followed by phase-II of the protocol will help to select the right candidate for further clinical evaluation into next phase.

3.2 Trial Objectives at Phase-II Study:

3.2.1 Primary Objective(s):

» To assess the immunogenicity of two intramuscular doses of Covid-19 vaccine, administered with a 28-day interval between two doses, in 18-65 year-old healthy adults of either gender in each of the groups.

3.2.2 Primary End-points(s):

» Immunogenicity in all the groups in terms of:

➢ Virus neutralizing antibody (NAb) assay against SARS-CoV-2 virus at baseline, 28, 42, 56 days and again at 6 months and 12 months post 2nd dose.

- Seroconversion rates in terms of proportion of subjects with ≥4-fold increase in neutralizing antibodies from baseline.
- Geometric mean titres and Geometric mean fold rise in neutralizing antibodies from baseline.

3.2.3 Secondary Objective(s):

» To assess the safety, tolerability and reactogenicity of two intramuscular doses of Covid-19 vaccine, administered with a 28-day interval between doses, in 18-65 year-old healthy adult volunteers of either gender in each of the groups.

3.2.4 Secondary Safety End-point(s):

» Safety, tolerability and reactogenicity after each dose of Covid-19 vaccine in terms of:

- any adverse reactions within 2 hours (first 120 min) of immediate post vaccination period;
- any solicited symptoms within 7 consecutive days after each dose captured through subject diary;
- any unsolicited adverse events during 28 days after each dose of study vaccination;
- Serious and other medically attended adverse events in all study participants at 6 months and 12 months post 2nd dose.

3.2.5 Secondary Immunogenicity End-point(s):

➢ IgG antibodies against SARS-CoV-2 RBD antigen at baseline, 28, 42, 56 days and again at 6 months and 12 months post 2nd dose.

- Seroconversion rates in terms of proportion of subjects with ≥4-fold increase in IgG antibodies from baseline.
- Geometric mean titres and Geometric mean fold rise in IgG titres from baseline.
- IgG antibody subclasses (IgG1 & IgG2) against SARS-CoV-2 RBD at baseline and again at Day 56 will be presented.

➢ Interferon-gamma cytokine levels at baseline, Day 28 and again at Day 56.

4 Study Design

4.1 Overview of The Study Design

This is a phase-I seamlessly followed by phase-II, open label, randomized trial to assess safety, tolerability, reactogenicity and immunogenicity of the Biological E's 4 candidate vaccine formulations for preventive protection against COVID-19 disease in adult volunteers of either gender between 18-55 years of age in Phase-I and 18-65 years of age in phase-II.

The aim of this phase-I seamlessly followed by phase-II is to select a preferred vaccine formulation among the 4 candidate formulations based on overall safety and immunogenicity considerations.

A total of 12 subjects from each of the dose strengths would be enrolled at phase-I for safety assessment. An independent DSMB will review the 7 days' safety data post 1st dose of vaccination from 12 subjects enrolled in each of the dose strengths at this phase I. Based on favourable outcome from DSMB, the study will seamlessly proceed to phase-II. Meanwhile, these 12 subjects from each dose strength will also receive their second dose and will be followed up till 12 months for any SAEs and medically attended AEs.

The sample size at these phases is given below:

A) Phase-I study (n=36 [12 subjects from each of the dose strengths])

B) Phase-II study (n=324)

At each of these phases, a 0.5mL dose of the candidate Covid-19 vaccine will be administered as per their group assignment, via an intramuscular injection into the deltoid muscle of the non-dominant arm in a 2-dose schedule with 28 days' interval between doses. In case of anatomical features and/or medical indication preventing vaccination in the required side (left/right), the vaccine could be administered in other side/arm.

Volunteers will initially be invited for a screening visit (Day -3). 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 volunteer decides to take part, they

will be asked to sign a consent form. The attending physician will then check whether the volunteer is eligible to take part. This will involve taking a medical history and performing a physical examination as deemed necessary, collecting blood sample for estimation of haematology, biochemistry, anti-SARS-CoV-2 RBD IgG and serum neutralising antibodies, serological tests to rule out HIV, HBV and HCV infections (only once at screening), urinary pregnancy test negativity for women (before 1st dose and again before 2nd dose) along with measuring of vital signs viz., respiratory rate, pulse rate, blood pressure and body temperature.

A) Phase-I Study Procedures (N=36):

A total of 12 healthy RT-PCR and anti-SARS-CoV-2 antibodies negative volunteers will be screened and enrolled into each of the dose strengths, as per eligibility criteria set in the trial.

Covid-19 Vaccine with Alum & CpG 1018 as adjuvants (Total n= 36):

1. Dose Strength-1 with 15µg/dose (BECOV2D); n=12
2. Dose Strength-2 with 25µg/dose (BECOV2B & BECOV2C); n=12
3. Dose Strength-3 with 50µg/dose (BECOV2A); n=12

An independent DSMB would review the safety, tolerability and reactogenicity data seven days after first dose of vaccination. Based on favourable outcome, the study would seamlessly progress into phase-II. All the participants at this phase will continue to receive their second dose (Day 28) after DSMB clearance and will be followed up parallel for 6 months and 12 months after 2nd dose of vaccine administration.

There would be a total of 8 visits for each participant during the study. There is a pre-vaccination screening visit (day -3 to -1) to assess the eligibility criteria set, day -3 to -1 prior to the 1st dose of vaccination. Day of the 1st vaccination will be considered as day 0. All participants will be invited to follow-up visits at day 7, 28, 42, 56 and again at 6 months (28+180) and 12 months (28+365) post second dose. A time window of +4 days is allowed from visit-3 to visit-6 and a time window of 14 days will be allowed for the visit-7 and visit-8 respectively to ensure participant compliance to the visits. A whole blood sample of 5-15 mL will be collected intravenously at each of the protocol specified time points, as specified in the schedule of time and event table, by a trained nurse or a phlebotomist.

Participants will be asked to contact the study team if they develop any symptoms suggestive of COVID-19 at any point during the trial. Symptomatic participants will be asked to present for a 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.

Safety monitoring: The seamless phase-I part of the study will be overseen by an DSMB. A data & safety monitoring board (DSMB) with independent group of

experts will be constituted before initiation of any study related procedures at phase-I. The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. The primary responsibilities of the DSMB are to 1) review and evaluate the accumulated study data for participant safety, study conduct and progress, and 2) to make recommendations to sponsor concerning the continuation, modification, or termination of the trial as per the protocol defined time points. The DSMB will consider study-specific data as well as relevant background knowledge about the disease, test agent, or study population under study.

The first DSMB safety review will be at visit-3 (day 7) after the 7 days' diary data post 1st dose is gathered and tabulated, in all the dose strengths. Based on the positive recommendation at each of the dose strengths, the study will seamlessly move to phase-II for further screening and enrolment. The fourth DSMB review occurs 28 days' post 2nd dose for all the subjects enrolled at the end of phase-II. There will be a further follow-up at 6 months and 12 months post 2nd dose with a scheduled out-patient visit in the trial.

Safety surveillance:

- Each subject will be observed for at least 120 minutes following the administration of the study vaccine with appropriate medical treatment readily available in case of anaphylaxis or any other adverse reaction.

- All AEs and SAEs will be recorded and reported until the end of the phase-1 study. During the vaccination visits at day 0 and day 28, a diary card will be provided to the subject or the Legally Acceptable Representative to record any local and systemic symptoms experienced after each vaccination.

- Solicited local and general AEs will be collected during seven consecutive post-vaccination days (Day 0 – Day 6) and unsolicited AEs, if any, until day 56 and for any serious AEs until the end of the phase-I study (12 months post 2nd dose).

- Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures, are essential and required for study conduct.
- Holding rules have been predefined to guide the evaluation of safety during the study.
- Any single event (solicited symptom, AE and SAE) that are relevant for the holding rules described must be reported to the Sponsor within 24 hours.
- If the investigator becomes aware of a holding rule being met, he/she will suspend vaccination at his/her site and will inform the Sponsor Biological E. immediately who would then suspend vaccination at the other sites and inform the DSMB immediately.

- If the Sponsor becomes aware of a holding rule being met, the Sponsor will suspend further vaccination in all sites and will inform the DSMB immediately. All safety information available up to the time of suspension will be shared with the DSMB for their review and recommendation whether to stop, modify or continue the conduct of the study.
- Participants will be asked to contact the study team if they develop any symptoms suggestive of COVID-19 at any point during the trial. Symptomatic participants will be asked to present for a visit to test for SARS-CoV-2 by RT-PCR method.
- The 7-day safety results for the first 12 subjects in each of the dose strengths will be submitted to DSMB.
- The GO criteria to move into phase II will be conditional on the favorable outcome of a safety evaluation based on safety data from all the 12 vaccinated subjects in each of the dose strengths, collected up to the day 7 post first dose in Phase I. Until the outcome of the DSMB safety evaluation is reported in writing, further vaccinations and enrolments will be effectively on hold.
- The recommendation of the DSMB will be notified to the investigator(s), and to the Institutional Ethics Committee (IEC) before proceeding seamlessly into phase-II

The final responsibility to decide whether or not the trial should be stopped permanently rests with the Sponsor, after having considered all the safety information available and the recommendation of DSMB. If the trial is stopped, a letter indicating the reasons for stopping the study will be sent to the IEC via the investigator, and to the National Regulatory Authority (DCGI) via the Sponsor.

The study will be conducted in accordance with the WMA's Declaration of Helsinki, International Conference on Harmonization, Good Clinical Practice, Belmont Principles, and other applicable regulatory and clinical requirements. The study protocol and its associated documents will be reviewed and approved by the Institutional ethics committees of the respective study sites.

B) Phase-II Study Procedures (N=324):

A total of 324 healthy RT-PCR and anti-SARS-CoV-2 antibodies negative participants will be enrolled, as per eligibility criteria set in the phase II trial, with subjects randomised into one of the 4 groups. All participants having an average actual study duration of 56 days (until visit-5) and will be followed up further for 6 months (visit-6) and 12 months (visit-7) after the second dose as a scheduled out-patient visit.

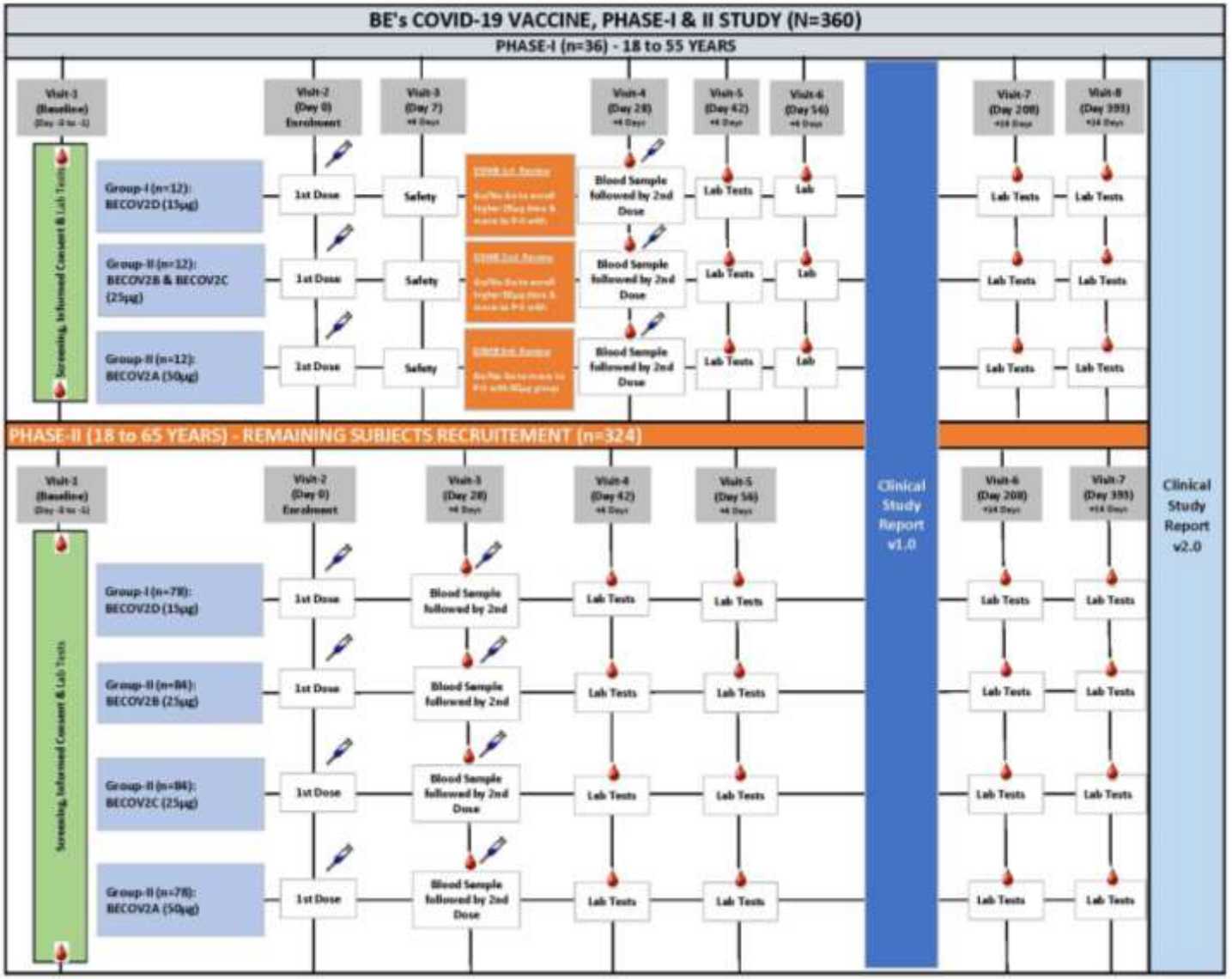
Covid-19 Vaccine with Alum & CpG 1018 as adjuvants (Total N=324):
1. Formulation-1 (BECOV2D); n=78 subjects
2. Formulation-2 (BECOV2B); n=84 subjects
3. Formulation-3 (BECOV2C); n=84 subjects
4. Formulation-4 (BECOV2A); n=78 subjects

There would be a total of 7 visits for each participant during the study at this phase II. There is a pre-vaccination screening visit (day -3 to -1 day) to assess the eligibility criteria set, 3 days prior to the 1st dose of vaccination. Day of the 1st vaccination will be considered as day 0.

All participants will be invited to follow-up visits at day 28, 42, 56, 208 (28+180) and day 393 (28+365) respectively. A time window of +4 days is allowed from visit-3 to visit-5 and a time window of 14 days will be allowed for the visit-6 and visit-7 respectively to ensure participant compliance to the visits.

The enrolled study participants will be asked to contact the study team if they develop any symptoms suggestive of COVID-19 at any point during the trial. Symptomatic participants will be asked to present for a visit to test for SARS-CoV-2 by RT-PCR by a trained nurse or a phlebotomist. 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.

4.2 Schematic Diagram of Phase-I & II Study Design



5 Study Population

Total sample size at phase-I seamlessly followed by phase-II study would be 360 subjects, out of which 36 subjects would be enrolled at phase-I (18-55 years) study and 324 subjects would be enrolled at phase-II (18-65 years) study.

For the purposes of data analysis, two subsets of vaccinated subjects shall be identified: Total vaccinated cohort (TVC) for safety assessment and the According to Protocol (ATP) cohort for immunogenicity assessment.

5.1 Sample Size

Phase-I study:

This open label randomised phase-I study is primarily designed to descriptively assess the safety, tolerability, reactogenicity and immunogenicity of Biological E's Covid-19 vaccine in 18-55 year-old healthy adult volunteers of either gender. The sample size for the study is not based on power computations, as this is a first-in-human study primarily to assess the safety, tolerability and reactogenicity in each of the dose strengths, which is in compliance with the G.S.R. 227(E) of the drugs and cosmetics rules in force.

The sample size is arrived at based on the WHO Guidelines on clinical evaluation of vaccines: regulatory expectations, "The phase I clinical studies carry out initial testing of a vaccine in small numbers".

Phase-II study:

The sample size is calculated based on the difference of seroconversion rate between higher dose and lower dose groups using "SAS Proc" to detect a treatment difference of -20%, -20% & -30% respectively for each of the comparisons with highest dose group. Multiplicity adjustment was applied for each of the comparisons with an overall significance level of 0.05 maintained. Hence the total sample size needed at the phase-I seamlessly followed by phase-II study would be 320 subjects and with the addition of not less than 10% dropout rate, it then would be 360 subjects for enrolment.

5.2 Nature of Study Population

Only healthy adult volunteers of either gender between 18 to 55 years of age at phase-I and 18-65 years of age at phase-II will be the study population in this study. Pregnant and nursing women are excluded from the enrolment.

6 Subject Eligibility

Only those subjects who fulfil ALL the inclusion and exclusion criteria will be enrolled into the study.

6.1 Inclusion Criteria

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Each subject must satisfy ALL of the following criteria at study entry:

1. Ability and willingness to provide written or thumb printed informed consent prior to performing any study specific procedure.

2. Subject, in the opinion of the investigator, has ability to communicate and willingness to comply with the requirements of the protocol.

3. Participants of either gender between ≥18 to ≤55 years of age at phase-I and ≥18 to ≤65 years of age at phase-II at the time of 1st vaccination.

4. Participants virologically seronegative to SARS-CoV-2 infection by RT-PCR and anti-SARS-CoV-2 antibody prior to enrolment.

5. Participants seronegative to HIV 1 & 2, HBV and HCV infection prior to enrolment.

6. Participants considered of stable health as judged by the investigator, determined by medical history and physical examination with normal vital signs as defined in the protocol. *[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 <100.4ºF prior to enrolment].*

7. Female participants of child bearing potential negative to urine pregnancy test 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;

8. Agrees not to participate in another clinical trial at any time during the total study period.

9. Agrees to refrain from blood donation during the course of the study.

10. Agrees to remain in the town where the study centre is located, for the entire duration of the study.

11. Willing to allow storage and future use of collected biological samples for future research in an anonymised form.

6.2 Exclusion Criteria

The following criteria should be checked at the time of study entry. If ANY exclusion criterion applies, the subject must not be included in the study:

1. History of vaccination with any investigational vaccine against COVID-19 disease;

2. Seropositive to IgG antibodies against SARS CoV-2

3. Living in the same household of any COVID-19 positive person;

4. Pregnant women, nursing women or women of childbearing potential who are not actively avoiding pregnancy during clinical trials;

5. Seriously overweight (BMI ≥ 40 Kg/m2);

6. Use of any investigational or non-registered product other than the study vaccine during the trial period or 3 months prior to enrolment;

7. 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);

8. Current or planned participation in prophylactic drug trials for the duration of the study.

9. Any clinically significant abnormal haematology and biochemical laboratory parameters tested at screening as judged by the investigator;

10. Body temperature of ≥100.4°F (>38.0°C) or symptoms of an acute illness at the time of screening or prior to vaccination;

11. History of severe psychiatric conditions likely to affect participation in the study;

12. History of any bleeding disorder (e.g. factor deficiency, coagulopathy or platelet disorder);

13. History of allergic disease or reactions likely to be exacerbated by any component of the Biological E's four COVID-19 vaccine formulations;

14. Chronic respiratory diseases, including asthma;

15. Chronic cardiovascular disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder and neurological illness;

16. Any other serious chronic illness requiring hospital specialist supervision;

17. Suspected or known current alcohol abuse as defined by an alcohol intake of greater than 42 units every week for at least one year;

18. 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;

19. Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required);

20. Any medical condition that in the judgment of the investigator would make study participation unsafe.

21. Individuals who are part of the study team or close family members of individuals conducting the study.

7 Study Assessment

7.1 Assessment of Safety

7.1.1 Assessment of Reporting of Adverse events

The period of observation for adverse events starts from the time the subject receives the single vaccination dose. All study subjects will be observed at site for at least 120 minutes after vaccination for evidence of immediate reactions and in particular for symptoms of allergic phenomena (such as rashes or other allergic manifestations). Each subject/LAR will be instructed to complete a diary card for 7 consequent days (Day 0 to Day 6) following first dose of vaccination, to record local and systemic symptoms. The diary is handed over to the PI at visit 3. Another diary would be issued after 2nd dose of vaccination at Day 28 and the subject/LAR will be instructed to complete a diary card for 7 consequent days and for any other AE. 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, Institutional Ethics committee (EC) 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 Ethics committee (EC), 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 determination as to the severity of the event and whether or not 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 and the sponsor periodically and as per regulatory requirement, until follow up visit of last subject.

SAE reporting should be preferably done by fax or as requested by the BE. If a centre cannot send a fax, 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:

Fax.: 040 27675003

Email: pharmacovigilance@biologicale.com

Phone: +91 40 71216242 (Landline)

Mobile: +91 7893611762 (Drug Safety Physician – Dr. Vijay. Y)

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.

7.1.2 Definition of Adverse Events

7.1.2.1 Adverse Events (AEs)

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 general reactions will be recorded differently. They will be followed-up for total duration of the study starting immediately following vaccine administration until 28 days after the second 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 adverse events (AEs) will be recorded for the entire study duration.

7.1.3 Serious Adverse Events (SAEs)

A serious AE (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening

  (NOTE: The term "life-threatening" in the definition of "serious" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe),

- requires inpatient hospitalization or results in prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect?
- is a medically important event or reaction.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

7.1.3.1 Unexpected Adverse Drug Reactions/Events:

An ADR 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.

7.1.4 Laboratory Parameters

A. Routine Laboratory Tests:

- **Haematology (once at baseline & again at day 56)–**
  1. Haemoglobin level (Hb)
  2. Red blood cell count (Total RBC count)
  3. White blood cell count (WBC count)
  4. Differential count (viz., Neutrophils, Lymphocytes, Eosinophils, Basophils and Monocyte count)
  5. Haematocrit % (PCV)
  6. Platelet count (PC)
- **Biochemistry (once at baseline & again at day 56)–**
  1. **Liver Function Tests (LFT)**
     a. Alanine aminotransferase (ALT)
     b. Aspartate aminotransferase (AST)

c. Alkaline Phosphatase (AP)
d. Total bilirubin (TB)
e. Direct (conjugated) bilirubin (DB)
f. Total protein
g. Albumin Globulin Ratio

2. **Kidney Function Tests (KFT)**
a. Serum Creatinine levels (SC)
b. Blood Urea Nitrogen (BUN)

3. Urine Pregnancy test (once at Baseline and again before 2nd dose)
a) Only for women of child bearing potential (as judged by the PI)

- **HIV 1&2, HBV and HCV (only once at Baseline (prevac))**

B. Special Serological Tests

1. **Immune serology**

a) Real time RT-PCR nasopharyngeal Swab Test (Nasal) (for detection of SARS-CoV-2 specific RNA in clinical samples)
b) Anti-SARS-CoV-2 total IgG titres and also IgG antibody subclasses (IgG1 & IgG2 only).
c) Neutralizing antibody (NAb) assay against live and/or pseudo typed SARS-CoV-2 virus
d) Interferon-Gamma Cytokine Levels (INF-γ) – To assess the Th1 response pre and post vaccination time points.

8 Study Conduct

This is a phase-I (36 subjects) seamlessly followed by phase-II (324 subjects), open label, randomised trial to assess safety, tolerability, reactogenicity and immunogenicity of the Biological E's "four candidate Covid-19 vaccine formulations" against COVID-19 disease in healthy adult volunteers of either gender between 18-55 years of age at phase-I and 18-65 years of age at phase-II.

Covid-19 vaccine with Alum & CpG 1018 as adjuvants (Total N= 360):

1. Formulation-1 (BECOV2D); n=90 subjects (12 subjects in P-I & 78 subjects in P-II)

2. Formulation-2 (BECOV2B); n=90 subjects (6 subjects in P-I & 84 subjects in P-II).

3. Formulation-3 (BECOV2C); n=90 subjects (6 subjects in P-I & 84 subjects in P-II).

4. Formulation-4 (BECOV2A); n=90 subjects (12 subjects in P-I & 78 subjects in P-II).

The aim of this Phase-I seamlessly followed by Phase-II study is to identify a preferred vaccine formulation among the 4 candidate test vaccine formulations based on overall safety and immunogenicity considerations.

The study will be executed as follows.

Initially, 12 subjects will be enrolled in phase 1 part of the study from each of the dose strengths. 7 days' diary data after 1st dose at visit-3 (day 7) will be presented to Data Safety Monitoring Board (DSMB) review.

Based on the positive recommendation from each of the DSMB review, the study will seamlessly move into phase-II by continuing enrolling balance subjects from respective groups simultaneously. The phase-II part of the protocol will help to select the right candidate for further clinical evaluation into phase 3.

All subjects will be randomly allocated on first come basis to one of the treatment arm, either in to one of the four candidate vaccine groups. The study vaccine will be administered via an intramuscular injection into the deltoid muscle of the non-dominant upper arm in a 2-dose schedule with 28 days' interval between doses. In case of anatomical features and/or medical indication preventing vaccination in the required side (left/right), the vaccine could be administered in other side/arm.

Table-1: Schedule of Time & Events

SCHEDULE OF TIME AND EVENTS – PHASE-I								
Type of Contact	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**
Time Points	**Day -3 to -1**	**Day 0**	**Day 7 (+4)**	**Day 28 (+4)**	**Day 42 (+4)**	**Day 56 (+4)**	**Day 208 (+14)**	**Day 393 (+14)**
Sampling Time Points	**Screen baseline**	**Dose-1**	**Safety Data for DSMB**	**Dose-2**	**Follow-up**	**Follow-up**	**Follow-up**	**Follow-up**
Signed Informed consent	●							
Allocate subject screening number	●							
Check inclusion/exclusion criteria evaluation	●	●						
Allocate subject enrolment number		●						
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	●	●	●	●	●	●		
Blood sample collection	● (15 mL)			● (10 mL)	● (10 mL)	● (15 mL)	● (5 mL)	● (5 mL)
Real time RT-PCR by nasopharyngeal swab	●							
Anti-SARS-CoV-2 IgG antibody estimation	●			●	●	●	●	●
Anti-SARS-CoV-2 IgG subclasses IgG1 & IgG2 estimation	●					●		
SARS-CoV-2 virus Neutralising Antibody (NAb) estimation	●			●	●	●	●	●
INF-γ cytokine assay	●			●		●		
Haematology & Biochemistry parameters	●					●		
HIV 1&2, HBV and HCV	●							
Urine Pregnancy test prior to vaccination in females	●			●				
Vaccine administration (0.5mL IM; deltoid muscle)		●		●				
120 minutes post-vaccination observation		●		●				
Distribution of diary card		●		●				
Recording of solicited local and general AEs within 7 days post-vaccination after each dose		●		●				
DSMB review of Day 7 safety data after 1st dose in each of the groups			●					
Recording of non-serious (unsolicited) AEs till day 56 post 1st dose		●		●		●		
Return of diary card			●		●			
Diary card transcription by investigator or assignee			●		●			
Recording of unsolicited AEs		●	●	●		●		
Recording of SAEs		●	●	●		●		
Recording of SAEs and medically attended AEs		●	●	●		●	●	●
Interim Data review			●			●		
Phase-I clinical study report v1.0 based on aggregate data up to day 56						●		
DSMB review of aggregate						●		

data as on Day 56								
Safety follow up after Day 56 for any SAEs and medically attended AEs							•	•

SCHEDULE OF TIME AND EVENTS – PHASE-II									
Type of Contact	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Clinical Study Report**	**Visit 6**	**Visit 7**	**Clinical Study Report**
Time Points	**Day -3 to -1**	**Day 0**	**Day 28 (+4)**	**Day 42 (+4)**	**Day 56 (+4)**		**Day 208 (+14)**	**Day 393 (+14)**	
Sampling 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 screening number	●								
Check inclusion/exclusion criteria evaluation	●	●							
Allocate subject enrolment number		●							
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	●	●	●	●	●				
Blood sample collection	● (15 mL)		● (10 mL)	● (10 mL)	● (15 mL)		● (5 mL)	● (5 mL)	
Real time RT-PCR (nasopharyngeal swab)	●								
Anti-SARS-CoV-2 IgG antibody estimation	●		●	●	●		●	●	
Anti-SARS-CoV-2 IgG subclasses IgG1 & IgG2 estimation	●				●				
SARS-CoV-2 virus neutralising Antibody (NAb) estimation	●		●	●	●		●	●	
INF-γ cytokine assay	●		●		●				
Haematology & Biochemistry parameters	●				●				

Only baseline screening against HIV 1&2, HBV and HCV	•								
Urine Pregnancy test in females only	•		•						
Vaccine administration (0.5mL IM; deltoid muscle)		•	•						
120 minutes post-vaccination observation		•	•						
Distribution of diary card		•	•						
Recording of solicited local and general AEs within 7 days post-vaccination after each dose		•	•	•					
Recording of non-serious (unsolicited) AEs till day 56 post 1st dose		•	•	•	•				
Return of diary card			•	•					
Diary card transcription by investigator or assignee			•	•					
Recording of unsolicited AEs		•	•	•	•				
Recording of SAEs		•	•	•	•				
Recording of SAEs and medically attended AEs		•	•	•	•				
Aggregate Data review					•				
Phase-II study report based on aggregate data up to day 56 to qualify for phase-III					•				
Safety follow up after Day 56 for any SAEs and medically attended AEs for 12 months post 2nd dose							•	•	

8.1 Visit Procedures

- For all subjects, the study period is divided into 8 schedule visits at Phase-I: Day -3 to-1 (Visit 1), Day 0 (Visit 2), Day 7 (Visit 3), Day 28 (Visit 4), Day 42 (Visit 5), Day 56 (Visit 6), Day 208 (Visit 7), and Day 393 (Visit 8).

- For all subjects, the study period is divided into 7 schedule visits at Phase-II: Day -3 to-1 (Visit 1), Day 0 (Visit 2), Day 28 (Visit 3), Day 42 (Visit 4), Day 56 (Visit 5), Day 208 (Visit 6), and Day 393 (Visit 7).

8.1.1 DAY -3 to -1 Procedures

8.1.1.1 Subject Information, informed consent form

The Investigator will explain and discuss with the subjects or subject's legally acceptable representative, the nature of the study, its requirements and risks to obtain written informed consent.

It is the investigator's responsibility to obtain freely given written informed consent from the subject or subject's legally acceptable representative, after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study, and before the subject is exposed to any study-related procedures, including screening tests for eligibility. The subject or subject's legally acceptable representative will be given a copy of the informed consent form along with subject information sheet (SIS), in regional languages, where necessary. The subject or subject's legally acceptable representative will be given ample time to decide his/her acceptance to allow his/her to be a subject in the present study.

Table-2: Baseline procedures

Procedures on Day -3 to -1 – Baseline	
Subject Information (Both verbal and written) to facilitate decision making, either to participate or not	✓
Signed Informed Consent.	✓
A Copy of Informed Consent handed over to subject or subject's legally acceptable representative to take home after it is duly signed by concerned parties.	✓

8.1.2 Post Consent Procedures

8.1.2.1 Screening of Subjects

Each subject will be assigned a unique screening number having 5 digits starting with "S" where 'S' stands for screening, followed by unique single letter code for each centre (e.g.: 'A' for Site code; refer page No.2) along with three digits '001'. The subject screening number will look like this "SA001". 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 subject's legally acceptable representative prior to screening. Only those subjects who have given informed consent, as applicable, will be assigned a screening number.

If the subject 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.

Table-3: Post consent procedures:

Procedures on Day -3 to -1	
Subject Screening Number	✓
Review of Inclusion & Exclusion Criteria	✓
Demographic Data	✓
Vaccination History	✓
Medical History	✓
General Examination	✓
Physical Examination	✓
Body temperature (for all participants)	✓
Pulse rate, Blood pressure and Respiratory rate	✓
Measure/record height and weight	✓
concomitant medications/vaccinations	✓
Blood sample collection (15 mL)	✓
Real time RT-PCR by nasopharyngeal swab	✓
Anti-SARS-CoV-2 IgG antibody estimation through Elisa	✓
SARS-CoV-2 virus Neutralising Antibody (NAb) estimation	✓
INF-γ cytokine assay	✓
Haematology & Biochemistry parameters	✓
Only baseline screening against HIV 1&2, HBV and HCV	✓
Urine Pregnancy test prior to vaccination in females only	✓

Note: ✓ mark means to do

8.1.2.2 Inclusion / Exclusion Criteria

The inclusion/exclusion criteria will be evaluated on the baseline i.e Day -3 to -1.

8.1.2.3 Demographic Data

Subject Initials, date of birth, gender, nationality, body weight (kgs), height (cms), social history (optional), mailing address and other contact details etc will be recorded in the source document during the baseline (visit-1) after obtaining informed consent form.

8.1.2.4 Medical History

Subject record of vaccinations along with occupational history, family history etc will be recorded on the source document during the baseline after obtaining written informed consent. 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.

8.1.2.5 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.

8.1.2.6 Vital Signs

All vital signs like body temperature in ºF (Fahrenheit), pulse rate per minute (bpm), blood pressure (mm of Hg for adults) and respiratory rate per minute (bpm) will be recorded during at each of the protocol specified visits.

8.1.2.7 Concomitant Medication

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.

8.1.2.8 Blood Sample Collection

Sufficient quantity of blood (5 to 15 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 and time of events table into appropriate vacutainer for analysis of the parameters as defined.

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 test requisition form (TRF) should accompany each test sample as provided. Serum samples should be stored at below minus 20° C till transferred to the central laboratory.

The serum samples will be collected by the sponsor assigned courier agency or representatives of the central laboratory assigned with the task, with prior intimation to respective sites. Analysis of Anti-SARS-CoV-2 IgG/SNT antibody estimation 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.

8.1.2.9 Nasopharyngeal swab Collection

A nasopharyngeal swab from nose will be collected at Day-3 to -1 and again at Day 28 for reverse transcription polymerase chain reaction (RT-PCR) testing.

8.1.2.10 Laboratory Investigations

A. Routine Laboratory Tests:

- **Haematology (once at baseline & again at day 56)–**
  1. Haemoglobin level (Hb)
  2. Red blood cell count (Total RBC count)
  3. White blood cell count (WBC count)
  4. Differential count (viz., Neutrophils, Lymphocytes, Eosinophils, Basophils and Monocyte count)
  5. Haematocrit % (PCV)
  6. Platelet count (PC)
- **Biochemistry (once at baseline & again at day 56)–**
  1. **Liver Function Tests (LFT)**
     a. Alanine aminotransferase (ALT)
     b. Aspartate aminotransferase (AST)
     c. Alkaline Phosphatase (AP)
     d. Total bilirubin (TB)
     e. Direct (conjugated) bilirubin (DB)
     f. Total protein
     g. Albumin Globulin Ratio
  2. **Kidney Function Tests (KFT)**
     a. Serum Creatinine levels (SC)
     b. Blood Urea Nitrogen (BUN)

3. Urine Pregnancy test (only once at Baseline and again before 2nd dose)

a) Only for women of child bearing potential (as judged by the PI)

- **HIV 1&2, HBV and HCV (only once at Baseline (prevac))**

B. Special Serological Tests

1. **Immune serology**
   a) Real time RT-PCR nasopharyngeal Swab Test (Nasal) (for detection of SARS-CoV-2 specific RNA in clinical samples)
   b) Anti-SARS-CoV-2 total IgG titres and also IgG antibody subclasses (IgG1 & IgG2 only).
   c) Neutralizing antibody (NAb) assay against live and/or pseudo typed SARS-CoV-2 virus
   d) Interferon-Gamma Cytokine Levels (INF-γ) - To assess the Th1 response pre and post vaccination time points.

Treatment/Assessment Visits

There is a pre-vaccination screening visit to assess the eligibility criteria set, -3 to -1 days prior to the 1st dose of vaccination. Day of the 1st vaccination will be considered as day 0. All participants will be invited to follow-up visits at day 7 (only at Phase-I), 28, 42, 56, 208 (28+180) and day 393 (28+365) respectively. A time window of +4 days is allowed from visit-3 to visit-6, visit 3 to visit 5 for phase1 and phase II respectively. A time window of 14 days will be allowed for the visit-7 and visit-8, Visit 6 and visit 7 for phase 1 and phase II respectively to ensure participant compliance to the visits.

8.1.2.11 Blood Sample Handling and Analysis

Instructions for Handling

Wherever laboratory materials are provided by the Sponsor, 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.

8.1.3 DAY 0 Procedures

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.

8.1.3.1 Vital Signs

All vital signs like body temperature in ºF (Fahrenheit), pulse rate per minute (bpm), blood pressure (mm of Hg for adults) and respiratory rate per minute (bpm) will be recorded during at each of the protocol specified visits.

8.1.3.2 Concomitant Medication

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.

8.1.3.3 Subject Randomization

All subjects (Phase I: n=36 and Phase II: n=324) who comply with all the inclusion and exclusion criteria at this visit will be randomized into the study. During this visit prior to subject randomization physical examination, body temperature, vital signs, concomitant medications details captured.

The primary purpose of randomizing subjects into treatment arm/groups is to prevent researchers, clinicians, and subjects from predicting, and thus influencing, which subject will receive which treatment. This important source of bias can be eliminated by concealing the upcoming allocation sequence from investigators and participants. Although there are many approaches to randomization that are known to effectively conceal the randomization sequence, the use of Interactive Web Response System (IWRS) is more effective. Under no circumstances the investigator is allowed to jump the sequence of allocation.

The allotment of randomisation number is initiated by assigning first randomisation no. e.g.: EA001 for the first subject who fulfilled all the screening criteria. This Randomisation number is an unique code of identification wherein E stands for Enrolment, 'A' stands for the study site code and serial number '001' stands for first enrolled subject, which will continue in the same serial order till all the subjects are randomised into one of the 4 groups under their respective age subsets in equal ratio. Please note that the randomisation number is different from the screening number.

Table 4: Visit Procedures

Procedures on Day 0	
Review of Inclusion & Exclusion Criteria	✓
Enrolment Number	✓
Physical Examination	✓

Procedures on Day 0	
Check contraindications and warnings and precautions before vaccination	✓
Body temperature (for all participants)	✓
Pulse rate, Blood pressure and Respiratory rate	✓
concomitant medications/vaccinations	✓
Vaccine administration (0.5mL IM; deltoid muscle)	✓
120 minutes post-vaccination observation	✓
Distribution of diary card, Thermometer, Scale	✓
Recording of non-serious (unsolicited) AEs till day 56 post 1st dose	✓
Recording of unsolicited AEs	✓
Recording of SAEs	✓
Recording of SAEs and medically attended AEs	✓

Note: ✓ mark means to do

8.1.3.4 Drug Administration

There would be 4 candidate formulations. Biological E's Covid 19 vaccine for preventive protection against Covid-19 disease is manufactured using *Pichia pastoris* as a protein expression system. It is a recombinant protein containing receptor binding domain (RBD) of SARS-CoV-2 Virus "spike protein".

SARS-CoV-2 RBD subunit Vaccine with Alum & CpG 1018 as adjuvants (Total N= 360):

1. Formulation-1 (BECOV2D); n=90 subjects (n=12 at P-I and n=78 in P-II)

2. Formulation-2 (BECOV2B); n=90 subjects (n=6 at P-I and n=84 in P-II)

3. Formulation-3 (BECOV2C); n=90 subjects (n=6 at P-I and n=84 in P-II)

4. Formulation-4 (BECOV2A); n=90 subjects (n=12 at P-I and n=78 in P-II)

Each study subject will receive a 0.5 mL dose of the investigational vaccine intramuscularly as per the randomization allotment through IWRS. The preferred site for injection is the deltoid muscle of the upper arm.

8.1.3.5 Injection technique

Intramuscular Route :

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 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.

8.1.3.6 Follow-up (Immediate Adverse Events)

All the subjects will be followed up to 120 minutes' post vaccination for immediate adverse reactions, if any. Late adverse reactions/ events if any till completion of the study would also be documented and necessary remedial measures would be initiated.

At the conclusion of this visit, subject or subject's legally acceptable representative will be given a thermometer, scale and subject diary to take home and record the body temperature measured orally using the standard digital thermometer, any local and systemic reactions and/or adverse events (AEs) either known or unknown for 7 consecutive days following vaccination dose.

8.1.3.7 Administration of Study Medication

The visit at Day 0 constitutes the 'Study Vaccine Administration Day' for all subjects. All the four study vaccines are administered by intramuscular route (IM) only.

- **Covid19 Vaccine with Alum & CpG 1018 as adjuvants (Total N= 360):**

1. Formulation-1 (BECOV2D); n=90 subjects (n=12 at P-I and n=78 in P-II)
2. Formulation-2 (BECOV2B); n=90 subjects (n=6 at P-I and n=84 in P-II)
3. Formulation-3 (BECOV2C); n=90 subjects (n=6 at P-I and n=84 in P-II)
4. Formulation-4 (BECOV2A); n=90 subjects (n=12 at P-I and n=78 in P-II)

Investigational vaccine 0.5 mL per dose will be given intramuscularly in a two dose schedule (Day 0 & Day 28).

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.

8.1.3.8 Recording of Adverse Events

At the conclusion of 0 day (visit-2) vaccination visit, subject's or the subject's legally acceptable representative (LAR) will be trained on completion of subject diary and will be given a subject diary to take home and record the body temperature, any adverse events (AEs) either known or unknown for 7 days following each vaccination visit. The PI delegated site staff will record the information on the adverse event section of the source document and the same will be transcribed in to the CRF. Serious adverse events (SAEs) will be collected throughout the subject's study participation.

8.1.4 DAY 7 Procedures (For Phase – I only)

8.1.4.1 Physical Examination

A brief symptom-directed physical examination is performed; the injection site of the previous visit will be inspected and evaluated; adverse events and changes in concomitant medications are documented. Subject diaries will be collected and verified and the severity of the reported local reaction will be assessed by the investigator. The severity of the all systemic reactions will be reported as part of adverse events.

8.1.4.2 Vital Signs

All vital signs like body temperature in ºF (Fahrenheit), pulse rate per minute (bpm), Blood Pressure (mm of Hg for adults) and respiratory rate per minute (bpm) will be recorded during at each of the protocol specified visits.

8.1.4.3 Concomitant Medication

At each study visit the Investigator will question the subject's or his/her Legally Acceptable representative (LAR) about any medication taken. Concomitant medication (if any), starting from Day -3 to -1 until the end of the trial, will be recorded in the source document and eCRF including details of trade name and/ or generic name of the medication, medical indication, total daily dose, route of administration, start and end dates of treatment.

Table-5: Visit procedures

Procedures on Day 7	
Physical Examination	✓

Procedures on Day 7	
Body temperature (for all participants)	✓
Pulse rate, Blood pressure and Respiratory rate	✓
concomitant medications/vaccinations	✓
Recording of non-serious (unsolicited) AEs till day 56 post 1st dose	✓
Return of Diary Card	✓
Diary card transcription by investigator or assignee	✓
Recording of unsolicited AEs	✓
Recording of SAEs	✓
Recording of SAEs and medically attended AEs	✓

Note: ✓ mark means to do

A brief symptom-directed physical examination is performed; the injection site of the previous visit will be inspected and evaluated; adverse events and changes in concomitant medications are documented.

Subject diaries will be verified and the severity of the reported local reaction will be assessed by the investigator. The severity of the systemic reactions will be reported as part of adverse events.

8.1.4.4 Recording of Adverse Events

Subject or Subject's LAR will be requested to handover the subject diary in order to record systemic and/or local reactions occurring at the injection site on to the source document and later to be transcribed on to the case report form. This subject diary will be attached as a part of the source document on completion of the study.

8.1.5 DAY 28 Procedures

8.1.5.1 Physical Examination

A brief symptom-directed physical examination is performed; adverse events and changes in concomitant medications are documented.

8.1.5.2 Vital Signs

All vital signs like body temperature in ºF (Fahrenheit), pulse rate per minute (bpm), Blood Pressure (mm of Hg for adults) and respiratory rate per minute (bpm) will be recorded during at each of the protocol specified visits.

8.1.5.3 Concomitant Medication

At each study visit the Investigator will question the subject's or his/her Legally Acceptable representative (LAR) about any medication taken. Concomitant medication (if any), starting from Day -3 to -1 until the end of the trial, will be recorded in the source document and case report form including details of trade name and/ or generic name of the medication, medical indication, total daily dose, route of administration, start and end dates of treatment.

8.1.5.4 Blood Sample Collection

Sufficient quantity of blood will be collected intravenously by a qualified study nurse during this visit for immunogenicity assessment. The entire quantity of whole blood will be assigned for serum separation and Anti-SARS-CoV-2 IgG antibody estimation.

Serum will be separated by centrifugation at 3500 rpm for 10 to15 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.

Table-6: Visit procedures

Procedures on Day 28	
Physical Examination	✓
Check contraindications and warnings and precautions before vaccination	✓
Body temperature (for all participants)	✓
Pulse rate, Blood pressure and Respiratory rate	✓
concomitant medications/vaccinations	✓

Blood sample collection	✓
Vaccine administration (0.5mL IM; deltoid muscle)	✓
Anti-SARS-CoV-2 IgG antibody estimation	✓
SARS-CoV-2 virus Neutralising Antibody (NAb) estimation	✓
INF-γ cytokine assay	✓
Recording of non-serious (unsolicited) AEs	✓
Distribution of diary card, Thermometer, Scale	✓
Return of Diary cards (at Phase II)	✓
Recording of unsolicited AEs	✓
Recording of SAEs	✓
Recording of SAEs and medically attended AEs	✓

Note: ✓ mark means to do

8.1.5.5 Drug Administration

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 intramuscular route (IM) 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.

8.1.5.6 Follow-up (Immediate Adverse Events)

All the subjects will be followed up to 120 minutes' post vaccination for immediate adverse reactions, if any. Late adverse reactions/ events if any till completion of the study would also be documented and necessary remedial measures would be initiated.

At the conclusion of Day 28, subject or subject's legally acceptable representative will be given a subject diary to take home and record the body temperature measured using the standard digital thermometer, any local and systemic reactions and/or adverse events (AEs) either known or unknown for 7 consecutive days following vaccination dose.

8.1.6 DAY 42 Procedures

8.1.6.1 Physical Examination

A brief symptom-directed physical examination is performed; adverse events and changes in concomitant medications are documented.

8.1.6.2 Vital Signs

All vital signs like body temperature in ºF (Fahrenheit), pulse rate per minute (bpm), Blood Pressure (mm of Hg for adults) and respiratory rate per minute (bpm) will be recorded during at each of the protocol specified visits.

8.1.6.3 Concomitant Medication

At each study visit the Investigator will question the subject's or his/her Legally Acceptable representative (LAR) about any medication taken. Concomitant medication (if any), starting from Day -3 to -1 until the end of the trial, will be recorded in the source document and case report form including details of trade name and/ or generic name of the medication, medical indication, total daily dose, route of administration, start and end dates of treatment.

8.1.6.4 Blood Sample Collection

Sufficient quantity of blood will be collected intravenously by a qualified study nurse during this visit for immunogenicity assessment. The entire quantity of whole blood will be assigned for serum separation and Anti-SARS-CoV-2 IgG antibody estimation.

Serum will be separated by centrifugation at 3500 rpm for 10 to15 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.

Table-7: Visit procedures

Procedures on Day 42	
Physical Examination	✓
Body temperature (for all participants)	✓
Pulse rate, Blood pressure and Respiratory rate	✓
concomitant medications/vaccinations	✓
Blood sample collection	✓
Anti-SARS-CoV-2 IgG antibody estimation	✓
SARS-CoV-2 virus Neutralising Antibody (NAb) estimation	✓

Procedures on Day 42	
Recording of non-serious (unsolicited) AEs	✓
Return of Diary Card	✓
Diary card transcription by investigator or assignee	✓
Recording of unsolicited AEs	✓
Recording of SAEs	✓
Recording of SAEs and medically attended AEs	✓

Note: ✓ mark means to do

A brief symptom-directed physical examination is performed; the injection site of the previous visit will be inspected and evaluated; adverse events and changes in concomitant medications are documented.

Subject diaries will be verified and the severity of the reported local reaction will be assessed by the investigator. The severity of the systemic symptoms will be reported as part of adverse events.

8.1.6.5 Recording of Adverse Events

Subject or Subject's LAR will be requested to handover the subject diary in order to record local reactions and systemic events occurring at the injection site on to the source document and later to be transcribed on to the case report form. This subject diary will be attached as a part of the source document on completion of the study.

8.1.7 DAY 56 Procedures

8.1.7.1 Physical Examination

A brief symptom-directed physical examination is performed; adverse events and changes in concomitant medications are documented.

8.1.7.2 Vital Signs

All vital signs like body temperature in ºF (Fahrenheit), pulse rate per minute (bpm), Blood Pressure (mm of Hg for adults) and respiratory rate per minute (bpm) will be recorded during at each of the protocol specified visits.

8.1.7.3 Concomitant Medication

At each study visit the Investigator will question the subject's or his/her Legally Acceptable representative (LAR) about any medication taken. Concomitant medication (if any), starting from Day -3 to -1 until the end of the trial, will be

recorded in the source document and case report form including details of trade name and or generic name of the medication, medical indication, total daily dose, route of administration, start and end dates of treatment.

8.1.7.4 Blood Sample Collection

Sufficient quantity of blood will be collected intravenously by a qualified study nurse during this visit for immunogenicity assessment, Haematology & Biochemistry Parameters. Serum will be separated by centrifugation at 3500 rpm for 10 to15 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.

Table-8: Visit procedures

Procedures on Day 56	
Physical Examination	✓
Body temperature (for all participants)	✓
Pulse rate, Blood pressure and Respiratory rate	✓
concomitant medications/vaccinations	✓
Blood sample collection	✓
Anti-SARS-CoV-2 IgG antibody estimation	✓
SARS-CoV-2 virus Neutralising Antibody (NAb) estimation	✓
INF-γ cytokine assay	✓
Haematology & Biochemistry parameters	✓
Recording of non-serious (unsolicited) AEs	✓
Recording of unsolicited AEs	✓
Recording of SAEs	✓
Recording of SAEs and medically attended AEs	✓
Aggregate Data review	✓

Note: ✓ mark means to do

8.1.7.5 Recording of Adverse Events

At the conclusion of this visit, subject's or the subject's legally acceptable representative (LAR) will be asked for any adverse events since last visit.

8.1.7.6 Aggregate Data review

Aggregate data will be summarised at 56 days' post 2nd dose for all subjects in the treatment groups. At the end of the phase-II, clinical study report will be presented to the regulators for their review and approval for a) an emergency use license (EUL) and/or b) to proceed to larger phase-III efficacy study.

8.1.8 DAY 208 Procedures (6 Months post 2nd Dose)

8.1.8.1 Physical Examination

A brief symptom-directed physical examination is performed; adverse events and changes in concomitant medications are documented.

8.1.8.2 Vital Signs

All vital signs like body temperature in ºF (Fahrenheit), pulse rate per minute (bpm), blood pressure (mm of Hg for adults) and respiratory rate per minute (bpm) will be recorded during at each of the protocol specified visits.

8.1.8.3 Concomitant Medication

At each study visit the Investigator will question the subject's or his/her Legally Acceptable representative (LAR) about any medication taken. Concomitant medication (if any), starting from Day -3 to -1 until the end of the trial, will be recorded in the source document and case report form including details of trade name and/ or generic name of the medication, medical indication, total daily dose, route of administration, start and end dates of treatment.

8.1.8.4 Blood Sample Collection

Sufficient quantity of blood will be collected intravenously by a qualified study nurse during this visit for immunogenicity assessment. The entire quantity of whole blood will be assigned for serum separation and Anti-SARS-CoV-2 IgG antibody estimation.

If necessary, serum will be separated by centrifugation at 3500 rpm for 10 to15 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.

Table-9: Visit procedures

Procedures on Day 208	
Physical Examination	✓

Procedures on Day 208	
Body temperature (for all participants)	✓
Pulse rate, Blood pressure and Respiratory rate	✓
Blood sample collection	✓
Anti-SARS-CoV-2 IgG antibody estimation	✓
SARS-CoV-2 virus Neutralising Antibody (NAb) estimation	✓
Recording of SAEs and medically attended AEs	✓
Safety follow up after Day 56 for any SAEs and medically attended AEs	✓

Note: ✓ mark means to do

8.1.8.5 Recording of Adverse Events

At the conclusion of this visit, subject's or the subject's legally acceptable representative (LAR) will be asked for any adverse events since last visit.

8.1.9 DAY 393 Procedures (12 Months post 2nd Dose)

8.1.9.1 Physical Examination

A brief symptom-directed physical examination is performed; adverse events and changes in concomitant medications are documented.

8.1.9.2 Vital Signs

All vital signs like oral body temperature in ºF (Fahrenheit), pulse rate per minute (bpm), blood pressure (mm of Hg for adults) and respiratory rate per minute (bpm) will be recorded during at each of the protocol specified visits.

8.1.9.3 Concomitant Medication

At each study visit the Investigator will question the subject's or his/her Legally Acceptable representative (LAR) about any medication taken. Concomitant medication (if any), starting from Day -3 to -1 until the end of the trial, will be recorded in the source document and case report form including details of trade name and or generic name of the medication, medical indication, total daily dose, route of administration, start and end dates of treatment.

8.1.9.4 Blood Sample Collection

Sufficient quantity of blood will be collected intravenously by a qualified study nurse during this visit for immunogenicity assessment. The entire quantity of

whole blood will be assigned for serum separation and Anti-SARS-CoV-2 IgG antibody estimation.

The serum will be separated by centrifugation at 3500 rpm for 10 to15 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.

Table-10: Visit procedures

Procedures on Day 393	
Physical Examination	✓
Body temperature (for all participants)	✓
Pulse rate, Blood pressure and Respiratory rate	✓
Blood sample collection	✓
Anti-SARS-CoV-2 IgG antibody estimation	✓
SARS-CoV-2 virus Neutralising Antibody (NAb) estimation	✓
Recording of SAEs and medically attended AEs	✓
Safety follow up after Day 56 for any SAEs and medically attended AEs	✓

Note: ✓ mark means to do

8.1.10 Early Termination Visit

Subjects, who are dropped out/withdrawn from the study prematurely, will undergo all investigations that are planned for final visit, if somehow possible. The reason for early termination must be clarified as detailed as possible and reported in the source data and in the eCRF. The reasons for drop-out of the subject from the study will be specified, where possible.

8.1.11 Amendment of Protocol

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 institutional ethics committee 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. 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 Institutional Ethics Committee, 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.

8.1.12 Premature Study Termination

The institutional 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's parent or legally acceptable representative, ii) will assure appropriate therapy and follow-up for the subjects, iii) inform the regulatory authorities and institutional 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 institutional ethics committee or by the sponsor is binding on the Investigator.

8.2 Deviations from The Protocol

8.2.1 Relevant 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 Institutional Ethics Committee (EC) will be informed of all major protocol changes by the investigator in accordance with the Institutional 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 participant, the sponsor and the reviewing IEC 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 must be submitted as a change/amendment in research. The IEC must approve the request before the proposed change is implemented. If a major, non-emergent deviation occurs without prior IEC approval the event is considered non-compliance. Non-compliance must be reported to the IEC 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 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 participant'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: 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 review as a "change in research" and approved by the IEC prior to instituting any planned deviations.

8.2.2 Premature Subject Withdrawal

- Subject/LAR will be informed that they are free to withdraw from the study at any time without stating the reason.
- 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 tachypnea.
- The investigator may withdraw a subject from the study if:
  - The subject suffers from significant illness or undergoes surgery during the course of the study.
  - The subject experiences serious adverse events and withdrawal would be in the best interest of the subject.
  - The subject or the LAR wishes to withdraw from study.

9 Study Treatment

9.1 Dosing Schedule

9.1.1 Rationale for dose selection

There would be 4 candidate vaccine formulations. Biological E's Covid-19 vaccine is manufactured using *Pichia pastoris* as a protein expression system. It is a recombinant protein containing receptor binding domain (RBD) of SARS-CoV-2 Virus "spike protein".

BioE's COVID19 vaccine belongs to protein sub-unit category. The Receptor Binding Domain from the Spike protein of SARS-CoV-2 virus is the antigenic component and aluminum hydroxide and CpG1018 are the adjuvants in the vaccine formulated in tris-saline buffer. These components were selected based on multiple rounds of comparative immunogenicity and safety studies in mice and rats and rabbits. Due to lack of direct correlation between safe and immunogenic doses in mice to humans, we had to use a matrix strategy to select the formulations that will be evaluated in Phase I/II clinical trials to finalize the optimum formulation for pivotal Phase III studies. The 7 microgram RBD dose yielded excellent immune response in mice and historically the human doses

tend to be approximately five times the effective dose in mice. In order to assess the dose response behavior; three RBD doses i.e. 15, 25 and 50 microgram were selected to bracket the expected human dose. Alhydroxide serves the purpose of adjuvant as well as an adsorber for the RBD antigen as well as the co-adjuvant CpG1018. The two doses of Alhydroxide (500 and 750 µg of Alhydroxide represented as Al+++) were selected to ensure sufficient binding capacity for adsorption as well as within the maximum allowable human dose limit of 1250 µg. CpG1018 content of 500 and 250 µg per dose were based on prior experience with another protein sub-unit vaccine against hookworm pathogen as well as to assess the dose response behavior. Tris-saline at neutral pH was chosen as the formulation buffer based on compatibility with all three components and to ensure stable adsorption of RBD and CpG1018 to Alhydroxide.

9.1.2 Concomitant Medication

No concomitant medication will be administered except for the management of any adverse event at the discretion of the principal investigator. In case any medication is administered during the course of the study, the decision to continue or discontinue the subject in the study would be taken by the investigator in consultation with sponsor based on whether the administered medication is known to interfere with the immune response.

9.1.3 Washout Period

No washout period is applicable for this study.

9.2 Study Drug Supplies and administration

9.2.1 Packaging of Clinical Supplies

This vaccine across all four formulations will be made available in single dose (0.5 mL) vials by Biological E. Ltd., to the study sites. The vaccines will be suitably coded to facilitate randomisation using 'IWRS' technique.

9.2.2 Storage, Stability and Dispensing Requirements

All the study vaccines will be stored at 2 to 8ºC at all times and temperature record will be maintained throughout the study period. All study medications will be stored and administered by the Investigator or his designated qualified medical personnel. Clinical study supplies will be received by a designated person at the study site, handled and stored properly. These will not be delivered/or administered until all required documentation is present at the study site file (Ethics Committee approval, signed contract and protocol, regulatory authority approval, where required).

All study vaccines 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/record to this effect has to be maintained. It is advisable to have a back-up refrigerator in case of power failure. Uninterruptible power supply (UPS) is recommended if no back-up refrigerator is available. If any discrepancy in the package arises, this must be communicated immediately to the sponsor / study site and vice-versa.

9.2.3 Dose Modification for Study Drug Toxicity

No change in the prescribed dosing schedule will be permitted at any time during the study period.

9.2.4 Possible Drug Interactions

No known drug interactions for these study vaccines.

9.2.5 Concomitant therapy

No concomitant medication will be administered except for the management of any adverse event at the discretion of the principal investigator. In case any medication is administered during the course of the study, the decision to continue or discontinue the subject in the study would be taken by the investigator in consultation with sponsor based on whether the administered medication is known to interfere with the immune response.

9.2.6 Blinding procedures

This is an open label study. However, the in-charge of the laboratory testing will remain blinded to the treatment, and codes will be used to link the subject and study (without any link to the treatment attributed to the subject) to each sample.

10 Adverse Events

10.1 Local and Systemic Tolerability

The following tables list the expected adverse events with the investigational candidate vaccine.

10.2 Solicited Adverse Events

- **Solicited AEs***

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 lifethreatening 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 lifethreatening 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.

- **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. Participants will be asked to contact the study team if they develop any symptoms suggestive of COVID-19 at any point during the trial. Symptomatic participants 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

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 diarrhea 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-threateningconsequences
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
Dyspnea (Shortness of	0	None

breath or difficulty in breathing)**	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.*

10.3 Un-solicited Adverse Events

Any other (unsolicited) adverse event reported at any time, until 28th day after the last dose. The intensity up to the maximum will be recorded according to the following guidelines:

Table-6: Severity Assessment

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.

10.4 Subject Diary

Diary Cards 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.

According to ICH-GCP E6 (R2) guidelines (1.52), subject’s diary card is a “Source Document”. It is an investigator responsibility to ensure that data on the

diary card correspond to the real health status of subject and to accurately transcribe data from the Diary Card 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 card. The diary assessments will occur 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 (for first dose: Day 7 in phase 1 and Day 28 in phase II, for second dose: at Day 42) and any missing information would be updated after proper interrogation. 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 card 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.

10.5 Adverse event evaluation

Serious AEFI:
1) 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.
Additional AEFIs that need systematic causality assessment are:

- Serious unexplained AEFI occurring within 7 days after 1st vaccination dose and 14 days after 2nd vaccination dose and which is not listed in product label;
- Events causing significant individual or community concern.

Categories for causality Assessment

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.

10.6 Classification

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.

10.7 Actions Taken

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.

Table-7: Action Taken

a) in general	**b) on the investigational product**
▪ None	▪ no action regarding study drug
▪ drug therapy started	▪ Study drug temporarily stopped
▪ test performed (e.g. 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.

10.8 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).

10.9 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.

10.9.1 Classification of action when an unexpected adverse event occurs

1. Investigational product discontinued / drug 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

10.10 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, Institutional Ethics committee (IEC) 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, with each call annotated with time and summary of the discussion.

The notification must be sent to the address or tele-fax number, 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 randomisation 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 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 (IND) 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.

10.11 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.

10.12 Criteria for Withdrawal of Subjects from The Study

1. 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.
2. 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.

3. Any subject who withdraws voluntarily or by legally acceptable representative from the study;
4. Failure of subject or legally acceptable representative for whatever reason to comply with requirements of the protocol;
5. Withdrawal from the treatment is considered by the Investigator to be in the subject's best interest.
6. The subject dies during the study period;
7. A subject who returns for the concluding visit foreseen in the protocol is considered to have completed the study.

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.

- **Close safety monitoring:** The Investigator's responsibility, in the Phase I study, is to closely monitor for any immediate and late local and systemic

tolerability and reactogenicity of the candidate Covid-19 vaccine during the post vaccination period in the study.

- Table below shows the minimum criteria (termed “holding rules”) which, if any occur in subjects vaccinated with the candidate Covid-19 vaccine during the course of the study will lead to holding of further vaccination of subjects until safety review of available study data has occurred.

Vaccination holding rules for serious adverse events

Table 1: Vaccination holding rules for serious and severe adverse events

Holding rule #	Event	Threshold criteria:
1a	Subjects experience life-threatening SAE or death	≥1 subject
1b	Subjects withdrawn from the study following a Grade 3 vaccine-related (S)AE	>1 subject
1c	Subjects with any vaccine-related local or general solicited symptoms leading to hospitalization, or vaccine-related fever 104°F (>40°C), or necrosis at the injection site	>1 subject

Any single event (solicited symptom, AE and SAE) listed in these holding must be reported to the Sponsor within 24h.
For holding rule #1a, each subject experiencing a life-threatening SAE or death will invoke an immediate suspension of the vaccination.
For holding rules #1b and 1c, “vaccine-related” implies that the observation is not to be attributed to another, non-vaccination-related cause (for example anaemia caused by major trauma with haemorrhage)
For holding rule #1c, fever is defined as temperature 104°F (>40°C),. The preferred route for recording temperature in this study will be using digital thermometer.

Table 2: Vaccination holding rules for safety evaluations (solicited and unsolicited AEs)

Holding rule #	Event	Threshold criteria
2a	Subjects reporting any Grade 3 solicited local symptoms requiring medical advice, within the 7-days post-vaccination period	>3 subjects
2b	Subjects reporting any Grade 3 vaccine-related solicited general symptoms requiring medical advice, within 7-days post-vaccination period	>3 subjects
2c	Subjects reporting any Grade 3 vaccine-related unsolicited AE requiring medical advice, within 7-days post-vaccination period	>3 subjects
For combination of holding rules 2a, 2b and 2c		>3 subjects

Any single event (solicited symptom, AE and SAE) listed in these holding must be reported to the Sponsor within 24h.

For holding rules #2b and 2c, “vaccine-related” implies that the observation is not to be attributed to another, non-vaccination-related cause (for example anaemia caused by major trauma with haemorrhage)

10.13 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.

10.14 Criteria for Withdrawal of Subjects from The Study

1. 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.
2. The Investigator will evaluate any subject who demonstrates a significant deterioration in his/her clinical status. Evidence that would suggest such deterioration includes:

    c) Subjective increase in symptomatology

    d) Worsening laboratory parameters.

3. Any subject who withdraws voluntarily or by legally acceptable representative;
4. Failure of subjects or legally acceptable representative for whatever reason to comply with requirements of the protocol;
5. Withdrawal from the treatment is considered by the Investigator to be in the subject’s best interest.
6. The subject dies during the study period;

10.15 Procedure for Handling Dropouts

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 missing a visit. Dropouts will not be replaced. Investigators will make an attempt 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.

10.16 Reasons for Dropout

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)

10.17 Sponsor's Termination of Trial

The Sponsor may terminate the trial if it becomes aware of any medical reasons for doing so, or for administrative reasons that the Sponsor deems appropriate.

11 Ethical Consideration

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) & Indian Council of Medical Research (ICMR) Ethical Guidelines for Biomedical Research on Human Participants.

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 Institutional Ethics Committees 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).

The subject/LAR will receive a copy of any updates to the signed and dated written informed consent form or other pertinent written information.

11.1 Risk/benefit Assessment

11.1.1 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.

- Further Management - 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.

11.2 Ethical Committee Review and Communications

An Ethics Committee is an independent body that has collectively the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed study. It will be formed according to local law and comprises of at least 5 members, with at least one member whose primary area of interest is in a non-scientific area and one member who is independent of the institution/study site.

The Investigator or sponsor may request the institutional ethics committee to provide its written procedures and membership/voting lists. The Ethics Committee will maintain written records of its activities and minutes of its meetings. All relevant records pertaining to the study will be maintained for a period of at least 15 years or as per the local regulatory requirements after the completion of the study and will be available to regulatory authorities on request.

The Investigator will report promptly to the Ethics Committee when any of the following occurs:

1. Deviations from, or change of, the protocol to eliminate immediate hazards to the study subjects;

2. Changes increasing the risk to subjects and/or affecting significantly the conduct of the study;

3. All adverse drug reactions that are both serious and unexpected;

4. New information that may affect adversely the safety of the subject or the conduct of the study;

5. When the study has been completed.

11.3 Responsibilities of Investigator

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 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;

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. 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 BE Ltd before the new member of the team can perform critical and/or significant study-related activities.

11.4 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.

11.5 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.

11.6 Regulatory Affairs

This study will be carried out in compliance with regulations in force at the time of execution. Before initiating the study, the Investigator, if required by the applicable regulatory requirement(s) will submit any required application(s) to the appropriate authority(ies) for review, acceptance, and/or permission to begin the study. A copy of the submission and approval/acknowledgements from both Indian licensing authority and Institutional ethics committee will be held in the central files at BE LTD and also in the site master file.

11.7 Informed Consent Process

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 and regulatory/licensing authority(ies) will be granted direct 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, must be approved along with the protocol, and any other necessary documentation by the IEC 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 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 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.

11.7.1 Statement of Subject Confidentiality

11.7.2 Confidentiality of Study Data

Permission for direct 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 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 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, BE 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, and the regulatory authority(ies) will be granted direct 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.

11.7.3 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.

11.7.4 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.

12 Study Monitoring and Supervision

12.1 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
- 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 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 in the Monitor's check list 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 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.

12.2 Quality System

The Clinical Research team of BE Ltd is responsible for implementing and maintaining quality assurance and quality control systems with written Standard Operating Procedures (SOP) where needed. BE Ltd is also responsible for ensuring that all parties involved with the study agree to direct 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 will maintain a close liaison with the Investigator and staff to clarify problems that may arise during the study, and to insure 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.

12.3 Audit

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.

12.3.1 The Auditor will be especially interested in the following items

1. Log of visits from the Sponsor's representative;
2. IEC 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 and the Sponsor;
8. Record retention.

12.4 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.

12.5 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 and any other correspondence
3. A copy of the IEC membership list
4. Original signed and stamped IEC-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 Institutional ethics committee(s) 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 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.

12.6 Documentation of the Study Data

12.6.1 Case Report Form

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 on data clarification form (DCF). 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 randomisation/enrolment number shall begin as No. EA001 (where 'E' stands for enrolment, 'A' stands for centre/site code (refer page 2 of the protocol and 001 stands for first subject enrolled).

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 within 48-96 hours. This also applies to potential study participants 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 within 48 hours of them being brought to their attention. Any questions or comments related to the eCRF will be directed to the assigned Site Monitor.

12.6.1.1 Screening Evaluation / Randomisation

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 randomisation:

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 & Neutralizing antibodies)
11. Study vaccine administration
12. Dispensation of subject Diary card and its training to the Subject or LAR.
13. Concomitant medications if any

14. All Adverse events (both local & systemic)

15. Severity of symptoms as reported by the subject or LAR and the causality assessment of AEs as judged by the investigator

12.6.1.2 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).

12.7 Quality Assurance

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 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
- Adverse events
- Concomitant medication intake
- Early withdrawal date and withdrawal reason, if applicable

- Dosing dates
- Subject screening number and Enrolment 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.

12.8 Final Report

Biological E Ltd. 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.

12.9 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.

12.10 Publication(s)

Publication of any of the trial data for the study is only permitted in accordance with the details outlined in the study contract between the Investigators and the sponsor of the study. No study material should be published without a written permission from the sponsor and the sponsor retains the full rights not to permit publication of trial data at any point of time without assigning any reasons.

12.11 Contracts

Contracts will be prepared between the relevant parties setting out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters.

13 Investigational Product Management

13.1 Investigational Product Description (4-formulations)

13.1.1 Covid-19 Vaccine (Investigational Vaccine)

COMPOSITION:

Each dose of 0.5mL contains:

- **Investigational Candidate Vaccines**

Covid-19 vaccine with Alum & CpG 1018 as adjuvants (Total N= 360):

1. BECOV2A: RBD Antigen (50 µg) + Aluminium Hydroxide (750 µg) + CpG 1018 (500 µg) (n=12 subjects at Phase-I & n=78 subjects at Phase-II)

Each dose of 0.5 mL Contains

Component Details	Quantity per 0.5mL
RBD antigen of SARS CoV-2 (Covid-19)	50 µg
Aluminium Hydroxide gel as Al^{+++}	750 µg
CpG 1018	500 µg
Buffer (Tris and NaCl in WFI)	q.s to 0.5 mL

2. BECOV2B: RBD Antigen (25 µg) + Aluminium Hydroxide (750 µg) + CpG 1018 (500 µg) (n=6 subjects at Phase-I & n=84 subjects at Phase-II)

Each dose of 0.5 mL Contains

Component Details	Quantity per 0.5mL
RBD antigen of SARS CoV-2 (Covid-19)	25 µg
Aluminium Hydroxide gel as Al^{+++}	750 µg
CpG 1018	500 µg
Buffer (Tris and NaCl in WFI)	q.s to 0.5 mL

3. BECOV2C: RBD Antigen (25 µg) + Aluminium Hydroxide (500 µg) + CpG 1018 (250 µg) (n=6 subjects at Phase-I & n=84 subjects at Phase-II)

Each dose of 0.5 mL Contains

Component Details	Quantity per 0.5mL
RBD antigen of SARS CoV-2 (Covid-19)	25 µg
Aluminium Hydroxide gel as Al^{+++}	500 µg
CpG 1018	250 µg
Buffer (Tris and NaCl in WFI)	q.s to 0.5 mL

4. BECOV2D: RBD Antigen (15 µg) + Aluminium Hydroxide (750 µg) + CpG 1018 (500 µg) (n=12 subjects at Phase-I & n=78 subjects at Phase-II)

Each dose of 0.5 mL Contains

Component Details	Quantity per 0.5mL
RBD antigen of SARS CoV-2 (Covid-19)	15 µg
Aluminium Hydroxide gel as Al^{+++}	750 µg
CpG 1018	500 µg
Buffer (Tris and NaCl in WFI)	q.s to 0.5 mL

- Biological E's novel recombinant RBD subunit vaccine formulations:
  - » **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 of single human dose (SHD).
  - » **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.

13.2 Method of Packing, Labelling and blinding of Study Substances

13.2.1 Labelling

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

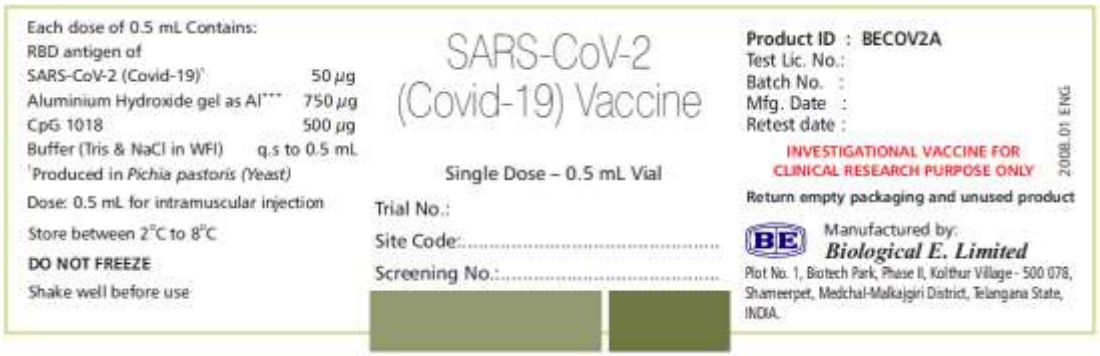
The vial label will contain reference to the study trial number the name of Investigational product with quantity, form and administration route, date of

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.

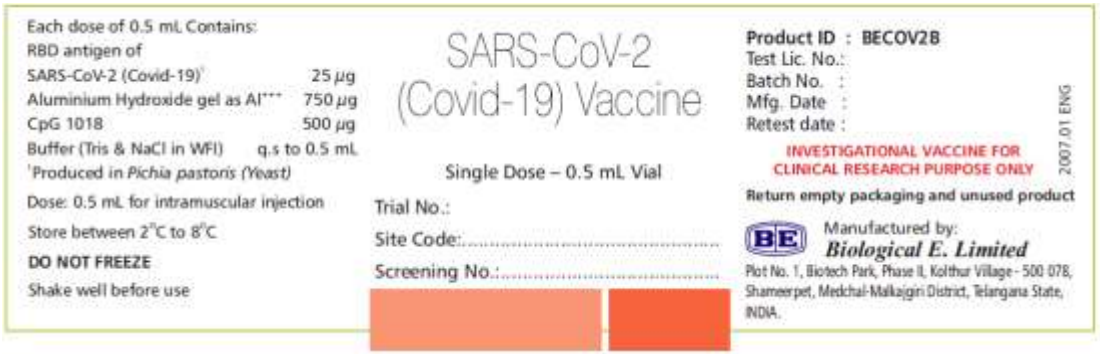
Specimen Labels – Investigational vaccine Vials:

The investigational vaccines will have the following four compositions:

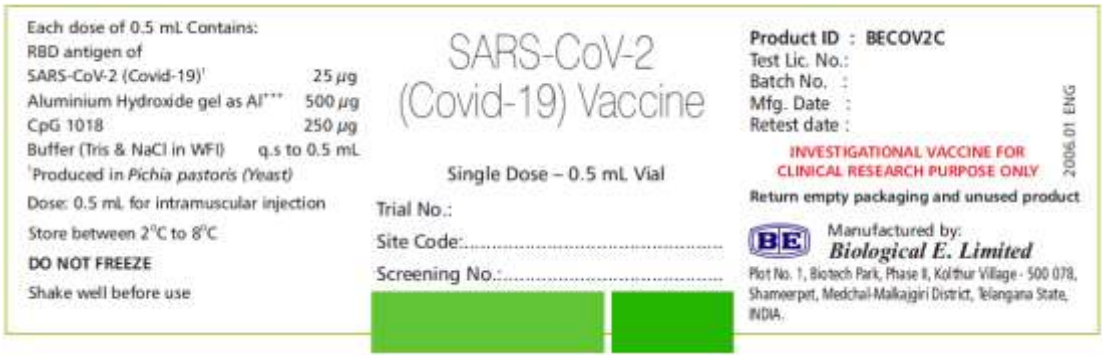
BECOV2A:



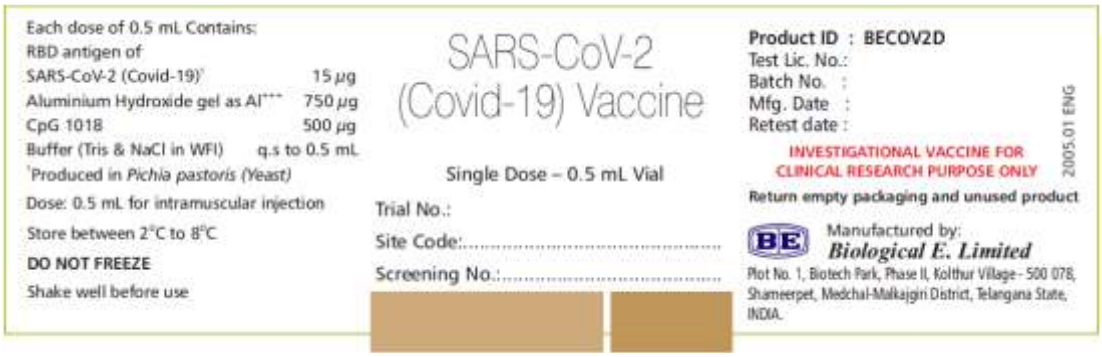
BECOV2B:



BECOV2C:



BECOV2D:



13.2.2 Packaging of Clinical Supplies

The investigational product BE's Covid-19 vaccine is made available in single dose (0.5 mL) vials as supplied by BE Ltd.

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 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 IMP 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.

13.2.3 Method of assigning treatments to subjects

Subjects meeting all of the inclusion and exclusion criteria and who have turned up for the 0 day will be randomised based on a pre-defined computer generated randomisation created using SAS or any other software through IWRS.

Allotment to four treatment groups will be accomplished by randomisation in a 1:1:1:1 ratio at this phase-I seamlessly followed by phase-II study.

Competitive recruitment strategy or compensating the enrolment deficit at one site with the other or involving additional study site would be opted to ensure timely completion of enrolment where required.

A copy of the computer generated randomisation list of subject numbers will be maintained by a member located at Biological E. Limited. The purpose of randomisation is to eliminate treatment selection bias and ensure balance of prognostic factors across treatment groups.

The study statistician will retain the right to change the randomisation process to facilitate competitive recruitment, if required. Randomization will be through IWRS system.

The total number of subjects to be randomized is 360, although a larger number will be screened. Subjects will be randomised into treatment groups in 1:1:1:1 ratio. Subjects will be withdrawn from further participation in the study if post dose they experience serious adverse events which deserve discontinuation.

The allotment of enrolment number is initiated by assigning first randomisation no. eg: EA001 for the first subject who fulfilled all the screening criteria. This Randomisation number is a unique code of identification wherein 'E' stands for Enrolment, 'A' stands for centre code and serial number '001' stands for first enrolled subject, which will continue in the same serial order till all the subjects are randomised into each of the groups. Please note that the randomisation number (EA001) is different from the screening number (SA001).

13.2.4 Subject identification code numbering system

Each subject will be assigned a unique screening number having 5 digits starting with “S” stands for screening followed by unique single letter centre code for each centre (e.g.: ‘A’ for Centre code) along with two digits ‘001’. The subject screening number will look like this “SA001”. 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.

13.2.5 Storage, Dispensing and Return of Study Drug

All study medications 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 has 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.

13.2.6 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.

13.2.7 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.

14 Data Analysis

The primary objective of the study is to assess the safety, tolerability and reactogenicity of two intramuscular doses of the BE's Covid-19 vaccine, administered with a 28-day interval between doses, in 18-55 years old at phase-I and 18-65 years old at phase-II in healthy adult volunteers of either gender.

Biological E's analysis of data from this clinical trial will follow a statistical analysis plan (SAP) that will be agreed on in advance with all concerned. The statistical analysis plan includes analyses of data from all the groups, including demographic data.

Furthermore, potential utility of the BE's investigational vaccine will be evaluated based on the full range of observations including primary and secondary endpoints.

14.1 Analysis of Populations

14.1.1 Total Vaccinated Cohort (TVC)

All the demographic and primary safety analyses will be based on this population, defined as subjects who entered into the study and have received at least one single intramuscular dose of study vaccination. All analysis based on this TVC population will be carried out using the actual treatment received and will be the primary analysis population. This population will be used for all demographics, baseline characteristics, safety and reactogenicity assessments in each of the vaccination groups.

14.1.2 According to protocol (ATP)

ATP population is defined as population in which data from subjects, who have results available at all protocol specified timepoints for Interferon-Gamma, anti SARS-CoV-2 IgG and anti-SARS-CoV-2 NAb antibodies. This will be the secondary analysis population for immunogenicity assessment.

14.2 Safety Analysis at both Phase-I & Phase-II

a) Safety:

To evaluate the safety and reactogenicity of Biological E's four novel "protein subunit SARS-CoV-2 vaccine formulations" in 18-55 years old at phase-I and 18-65 years old at phase-II in healthy adults. All subjects entered into the study and who received at least one dose of study vaccine will be included in the safety analysis.

Safety Variables:

- Local injection site adverse reactions
- Systemic adverse events (both solicited and unsolicited)
- Clinically significant abnormal haematology and biochemistry parameters.
- Clinically significant abnormal body temperature, pulse rate, respiratory rate and blood pressure findings as judged by the principal investigator.
- Clinically significant local & systemic examination findings as judged by the principal investigator.

End point(s) - Safety:

» Proportion of subjects with solicited adverse reactions during first 120 minutes of post-vaccination observation period and for 7 consecutive days (Day 0-6) thereafter, captured through subject diary after each dose.

» Proportion of subjects with unsolicited local and systemic adverse events (AEs) during the post-vaccination follow up period of 28 days after each of the two doses. (time frame: until 28 days after 2nd dose)

» Serious adverse events (SAEs) if any, during the total study duration (time frame: until 28 days after 2nd dose).

» Any clinically significant abnormal laboratory parameters in comparison with baseline values (time frame: until 28 days after 2nd dose).

» Any clinically significant abnormal vital signs at each of the protocol specified visits (time frame: until 12 months post 2nd dose).

Safety will be assessed by monitoring AEs, local and systemic tolerability, and the safety laboratory parameters including abnormal vital signs of clinical significance as judged by the principal Investigator of the respective study site.

The number and percentage of subjects with adverse events (AE) and serious AEs will be presented overall by system organ class & by preferred term.

The percentage of subjects with at least one local adverse event (solicited and unsolicited), with at least one systemic adverse event (solicited and unsolicited) and with any adverse event during the solicited follow-up period will be tabulated

with exact 95% CI. The same calculations will be performed for symptoms rated as Grade 3 and above.

Systemic and local tolerability, recorded in subject diaries, will be summarized in a frequency table with percentages based on the number of observed values. Based on the positive recommendation from each of the DSMB reviews, the study will seamlessly move into phase-II by continuing enrolling balance subjects from respective groups simultaneously.

The percentage of subjects reporting each individual solicited local and general adverse event during the solicited follow-up period will be tabulated with exact 95% CI.

A. The following local (injection-site) adverse events will be solicited:

Pain &/or Tenderness at the injection site
Redness at the Injection site
Swelling &/or Induration at the injection site

B. The following general AEs will be solicited:

Fever
Headache
Chills
Myalgia
Fatigue or Malaise
Urticaria
Nausea
Arthralgia

Note: Temperature will be recorded at the same time in a day by digital thermometer. Should additional temperature measurements be performed at other times of day, the highest temperature, regardless of route, will be recorded in the eCRF.

Occurrence of fever will be reported at all protocol specified time points, as well as the occurrence of temperature >104°F (>40°C) with causal relationship to vaccination. Duration and prevalence of fever will be presented.

C. The following COVID-19 disease symptoms will also be solicited:

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

Fever
Chills
Cough
Fatigue or Malaise
Shortness of breath or difficulty in breathing
Expectoration
Myalgia
Rhinorrhoea (congestion or runny nose)
Sore throat
Nausea
Vomiting
Diarrhoea
Loss of smell (anosmia)
Loss of taste (ageusia)
Abdominal Discomfort

For all solicited symptoms, the same tabulation will be performed for Grade 3 adverse events and for adverse events with relationship to vaccination.

The verbatim reports of unsolicited symptoms will be reviewed by a physician and the signs and symptoms will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology. The percentage of subjects with at least one report of unsolicited adverse event classified by the MedDRA and reported up to 28 days after each vaccination will be tabulated with exact 95% CI. The same tabulation will be performed for Grade 3 unsolicited adverse events and for unsolicited adverse events with a relationship to vaccination.

Serious adverse events and withdrawal due to adverse event(s), if any, will be described in detail. The percentage of subjects reporting AEs resulting in a medically attended visit will also be tabulated.

Holding rules and safety monitoring at both Phase-I & Phase-II

The goal is to proceed cautiously with the administration of all the four candidate formulations. This helps to ascertain the safety profile of each of the four investigational formulations in healthy adults before proceeding to further phases of the study with the preferred formulation as an outcome. This study will be closely monitored by a data and safety monitoring board (DSMB) by reviewing the safety data at protocol specified intervals.

Safety monitoring for this study will be performed by a data & safety monitoring board (DSMB), a multidisciplinary independent safety review body. The DSMB will perform a review of aggregate data in accordance to the enrolment guidelines as well as in the event of any holding rule.

The below tables list minimum criteria (termed "*holding rules*") which, if any occur in subjects vaccinated under any one of the study groups during the course of the study will lead to suspension of further vaccination doses, not only for that subject but also in all sites until formal safety review of available study safety data (both subject data and aggregate data) by DSMB will have occurred.

Table 1: Vaccination holding rules for serious and severe adverse events

Holding rule #	**Event**	**Threshold criteria:**
1a	Subjects experience life-threatening SAE or death	≥1 subject
1b	Subjects withdrawn from the study following a Grade 3 vaccine-related (S)AE	>1 subject
1c	Subjects with any vaccine-related local or general solicited symptoms leading to hospitalization, or vaccine-related fever 104°F (>40°C), or necrosis at the injection site	>1 subject

Any single event (solicited symptom, AE and SAE) listed in these holding must be reported to the Sponsor within 24h.

For holding rule #1a, each subject experiencing a life-threatening SAE or death will invoke an immediate suspension of the vaccination.

For holding rules #1b and 1c, "vaccine-related" implies that the observation is not to be attributed to another, non-vaccination-related cause (for example anaemia caused by major trauma with haemorrhage)

For holding rule #1c, fever is defined as temperature 104°F (>40°C). The preferred route for recording temperature in this study will be using digital thermometer.

Table 2: Vaccination holding rules for safety evaluations (solicited and unsolicited AEs)

Holding rule #	**Event**	**Threshold criteria**
2a	Subjects reporting any Grade 3 solicited local symptoms requiring medical advice, within the 7-days post-vaccination period	>3 subjects
2b	Subjects reporting any Grade 3 vaccine-related solicited general symptoms requiring medical advice, within 7-days post-vaccination period	>3 subjects
2c	Subjects reporting any Grade 3 vaccine-related unsolicited AE requiring medical advice, within 7-days post-vaccination period	>3 subjects
For combination of holding rules 2a, 2b and 2c		>3 subjects

Any single event (solicited symptom, AE and SAE) listed in these holding must be reported to the Sponsor within 24h.

For holding rules #2b and 2c, "vaccine-related" implies that the observation is not to be attributed to another, non-vaccination-related cause (for example anaemia caused by major trauma with haemorrhage)

Interpretation of analyses: This prospective study consists of 4 treatment groups, in which all subjects receive vaccination as per their group assignment and the outcomes will be assessed over 28-day period after each dose. All subjects will be followed up for safety until 12 months post 2nd dose. Hence all safety analysis would be descriptive in nature.

Conduct of analyses: Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the final study report.

Sequence of analyses: All analyses will be conducted on data as clean as possible. Analysis will be performed when all data up to 28 days after each vaccine dose will be available. This analysis will include analysis of safety, tolerability, reactogenicity and immunogenicity. A long term follow-up of safety and immunogenicity data will be presented in the final clinical study report.

14.3 Immunogenicity Analysis at both Phase-I & Phase-II

- Immunogenicity data (both IgG titres, INF-γ cytokine levels and NAb titres) shall be assessed by according to protocol population (ATP).
- Serum anti-SARS-CoV-2 IgG antibody titres will be determined by a validated assay and also by using the neutralizing antibody (NAb) assay against live and/or pseudo typed SARS-CoV-2 virus once at baseline, Day 28, Day 42, Day 56 and again at 6 months & 12 months post 2nd dose.
- Proportion of subjects achieving seroconversion (viz., ≥4-fold rise from baseline) at day 28 will be calculated.
    - Seroconversion is defined as the appearance of antibodies (i.e. titre greater than or equal to 4-fold rise) in the serum of subjects seronegative before vaccination.
    - Vaccine response rate is defined as an initially seronegative subject at pre-vaccination, showing rise in antibody concentration ≥4-fold the pre-vaccination antibody concentration.
    - Seronegative is defined as a person with no detectable levels of antibodies against vaccine specific antigen.
- Geometric mean titres will be calculated at baseline, day 28, day 42 and day 56 in all study groups. The geometric mean titres (GMT) calculation will be performed by taking the anti-log of the mean of the log concentration transformations. Antibody titres below the lower limit of quantitation (LLOQ) of the assay will be given an arbitrary value of half the cut-off of LLOQ for the purpose of GMT calculation.
- In addition, the geometric mean fold rise (GMFR) in anti-SARS-CoV IgG antibody titres and NAb titres at day 28 post 2nd dose, from baseline, along with their corresponding 2-sided 95% CIs, will be presented.

14.4 Statistical Analysis

For the purposes of analysis, two subsets of recruited subjects shall be identified in each of the vaccine groups: Total vaccinated cohort (TVC) and the According to Protocol (ATP) cohort.

Total Vaccinated Cohort (TVC): All the demographic and primary safety analyses will be based on this population, defined as subjects who entered into the study and have received at least one single intramuscular dose of study vaccination. All analysis based on this TVC population will be carried out using the actual treatment received and will be the primary analysis population. This population will be used for all demographics, baseline characteristics, safety and reactogenicity assessments in each of the vaccination groups.

According to Protocol (ATP): ATP population is defined as population in which data from subjects, who have results available at all protocol specified timepoints for Interferon-Gamma, anti SARS-CoV-2 IgG and anti-SARS-CoV-2 NAb antibodies. This will be the secondary analysis population for immunogenicity assessment.

The ATP cohort for analysis will include:

- All evaluable subjects who meet all eligibility criteria.
- All evaluable subjects who have received at least a one dose of study vaccine according to the protocol.
- All evaluable subjects for whom administration site of study vaccine(s) is known.
- All evaluable subjects who comply with the procedures and visit intervals defined in the protocol.
- All evaluable subjects who did not present with a medical condition leading to elimination from an ATP analysis.

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16 Appendices

16.1 Study Synopsis

PHASE – I & II

CLINICAL STUDY PROTOCOL SYNOPSIS

A Novel Covid-19 vaccine containing Receptor Binding Domain of SARS-CoV-2

* * *

Sponsor: Biological E. Limited, Hyderabad, India

Study/Trial Title:
A prospective open label randomised phase-I seamlessly followed by phase-II study to assess the safety, reactogenicity and immunogenicity of Biological E's novel Covid-19 vaccine containing Receptor Binding Domain of SARS-CoV-2 for protection against Covid-19 disease when administered intramuscularly in a two dose schedule (0, 28D) to healthy volunteers

Study Code: BECT062

Trial No.: BECT/Covid-19-phase-I&II/062

Protocol No.: BECT062/Covid-19-phase-I&II/CTP-01

Version No. & Date: 1.1 dated 07.10.2020

Clinical Phase of Development: Phase-I seamlessly followed by phase-2 study.

Investigational New Drug: Biological E's novel Covid-19 vaccine

Target Indication: For active immunization of at-risk individuals to prevent COVID-19

Sponsor Registered Office:
Biological E. Limited
18/1&3, Azamabad
Hyderabad – 500 020, Telangana, India

***Biological E. Limited*,**
18/1&3, Azamabad
Hyderabad – 500 020, Telangana, India

Background and Rationale

Background

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.

The first case of COVID-19 in India, which originated from China, was reported on 30 January 2020. As of 21 September 2020, the Ministry of Health and Family Welfare (MoH&FW) has confirmed a total of 55,62,663 cases, out of which 9,76,420 active cases, 44,97,867 recoveries and 88,965 deaths in the country [9]. India currently has the largest number of confirmed cases in Asia, [10] and has the second highest number of confirmed cases in the world [10].

About SARS-CoV-2 Virus

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].

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 ventilatory 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.

To date, there is no vaccine and no specific antiviral medicine to prevent or treat COVID-19. 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.

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.

Developing an effective and safe vaccine is urgently needed to prevent infection by severe acute respiratory syndrome (SARS)–associated coronavirus (SARS-CoV2). 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 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 and proposes a phase-I seamlessly followed by phase-II clinical trial in India to assess 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.

Trial Objectives at Phase-I Study:

» **Primary Objective**

» Primary objective at each of the dose strengths, starting from lower to higher, is to assess the safety, tolerability and reactogenicity of single intramuscular dose of the Covid-19 vaccine administered to 18-55 year-old healthy adult volunteers of either gender.

- A DSMB review of “post 7-days safety data” for 12 subjects from each of the dose strengths before seamlessly proceeding to phase-II.
- However, all 12 subjects in each of the dose strengths will receive their second dose 28 days after first dose and continue to be followed up for safety and immunogenicity at day 56 and later till 12 months post 2nd dose.

» **Secondary Objective**

» To assess the immunogenicity of two intramuscular doses of the adsorbed 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 volunteers.

End Points

» **Primary End-point(s):**

» Safety and reactogenicity after each dose of Covid-19 vaccine in terms of:

- any adverse reactions within 2 hours of immediate post vaccination period;
- any solicited symptoms within 7 consecutive days after each dose captured through subject diary;
- any unsolicited adverse events during 28 days after each dose of study vaccination;
- Serious and other medically attended adverse events in all study participants at 6 months and 12 months post 2nd dose.

» **Secondary End-points(s):**

» Immune response after each dose of Covid-19 vaccine in terms of:

➢ IgG antibodies against SARS-CoV-2 RBD antigen at baseline, 28, 42, 56 days and again at 6 months and 12 months post 2nd dose.

- Seroconversion rates in terms of proportion of subjects with ≥4-fold increase in IgG antibodies from baseline.
- Geometric mean titres and Geometric mean fold rise in IgG titres from baseline.
- IgG antibody subclasses (IgG1 & IgG2) against SARS-CoV-2 RBD at baseline and again at Day 56 will be presented.

➢ Virus neutralizing antibody (NAb) assay against SARS-CoV-2 virus at baseline, 28, 42, 56 days and again at 6 months and 12 months post 2nd dose.

- Seroconversion rates in terms of proportion of subjects with ≥4-fold increase in neutralizing antibodies from baseline.
- Geometric mean titres and Geometric mean fold rise in neutralizing antibodies from baseline.

➢ Interferon-gamma cytokine levels at baseline, Day 28 and again at Day 56.

Independent DSMB Review:

An independent data safety monitoring board (DSMB) setup for this purpose will review 7 days' diary data after 1st dose at visit-3 (Day 7), in first 12 subjects from each of the three dose strengths.

1. First DSMB: In first 12 subjects from BECOV2D (15 µg/dose)

2. Second DSMB: In first 12 subjects from BECOV2B & BECOV2C (25 µg/dose)
3. Third DSMB: In first 12 subjects from BECOV2A (50 µg/dose)

Based on the positive recommendation from DSMB after 7-day safety review of respective dose strengths, the study will move seamlessly into phase-II by continuing enrolling balance subjects in the respective groups.

A fourth DSMB review occurs 28 days' post 2nd dose for all the subjects at the end of phase II.

The phase-I seamlessly followed by phase-II of the protocol will help to select the right candidate for further clinical evaluation into next phase.

Trial Objectives at Phase-II Study:

» **Primary Objective(s):**

» To assess the immunogenicity of two intramuscular doses of Covid-19 vaccine, administered with a 28-day interval between two doses, in 18-65 year-old healthy adult volunteers of either gender.

» **Primary End-points(s):**

» Immunogenicity in all the groups in terms of:

➢ Virus neutralizing antibody (NAb) assay against SARS-CoV-2 virus at baseline, 28, 42, 56 days and again at 6 months and 12 months post 2nd dose.

- Seroconversion rates in terms of proportion of subjects with ≥4-fold increase in neutralizing antibodies from baseline.
- Geometric mean titres and Geometric mean fold rise in neutralizing antibodies from baseline.

» **Secondary Objective(s):**

» To assess the safety and reactogenicity of two intramuscular doses of Covid-19 vaccine, administered with a 28-day interval between doses, in 18-65 year-old healthy adult volunteers of either gender.

» **Secondary Safety End-point(s):**

» Safety and reactogenicity after each dose of Covid-19 vaccine in terms of:

- any adverse reactions within 2 hours (first 120 min) of immediate post vaccination period;
- any solicited symptoms within 7 consecutive days after each dose captured through subject diary;
- any unsolicited adverse events during 28 days after each dose of study vaccination;
- Serious and other medically attended adverse events in all study participants at 6 months and 12 months post 2nd dose.

» **Secondary Immunogenicity End-point(s):**

- IgG antibodies against SARS-CoV-2 RBD antigen at baseline, 28, 42, 56 days and again at 6 months and 12 months post 2nd dose.
  - Seroconversion rates in terms of proportion of subjects with ≥4-fold increase in IgG antibodies from baseline.
  - Geometric mean titres and Geometric mean fold rise in IgG titres from baseline.
  - IgG antibody subclasses (IgG1 & IgG2) against SARS-CoV-2 RBD at baseline and again at Day 56 will be presented.
- Interferon-gamma cytokine levels at baseline, Day 28 and again at Day 56.

Study Design and Duration

This is a phase-I seamlessly followed by phase-II, open label, randomized trial to assess safety, tolerability, reactogenicity and immunogenicity of the Biological E's 4 candidate vaccine formulations for preventive protection against COVID-19 disease in adult volunteers of either gender between 18-55 years of age in Phase-I and 18-65 years of age in phase-II.

The aim of this phase-I seamlessly followed by phase-II is to select a preferred vaccine formulation among the 4 candidate formulations based on overall safety and immunogenicity considerations.

A total of 12 subjects from each of the dose strengths would be enrolled at phase-I for safety assessment. An independent DSMB will review the 7 days' safety data post 1st dose of vaccination from 12 subjects enrolled in each of the dose strengths at this phase I. Based on favourable outcome from DSMB, the study will seamlessly proceed to phase-II. Meanwhile, these 12 subjects from each dose strength will also receive their second dose and will be followed up till 12 months for any SAEs and medically attended AEs.

The sample size at these phases is given below:

A) Phase-I study (n=36 [12 subjects from each of the dose strengths])

B) Phase-II study (n=324)

At each of these phases, a 0.5mL dose of the candidate Covid-19 vaccine will be administered as per their group assignment, via an intramuscular injection into the deltoid muscle of the non-dominant arm in a 2-dose schedule with 28 days' interval between doses. In case of anatomical features and/or medical indication preventing vaccination in the required side (left/right), the vaccine could be administered in other side/arm.

Volunteers will initially be invited for a screening visit (Day -3). 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 volunteer decides to take part, they

will be asked to sign a consent form. The attending physician will then check whether the volunteer is eligible to take part. This will involve taking a medical history and performing a physical examination as deemed necessary, collecting blood sample for estimation of haematology, biochemistry, anti-SARS-CoV-2 RBD IgG and serum neutralising antibodies, serological tests to rule out HIV, HBV and HCV infections (only once at screening), urinary pregnancy test negativity for women (before 1st dose and again before 2nd dose) along with measuring of vital signs viz., respiratory rate, pulse rate, blood pressure and body temperature.

A) Phase-I Study Procedures (N=36):

A total of 12 healthy RT-PCR and anti-SARS-CoV-2 antibodies negative volunteers will be screened and enrolled into each of the dose strengths, as per eligibility criteria set in the trial.

Covid-19 Vaccine with Alum & CpG 1018 as adjuvants (Total n= 36):

4. Dose Strength-1 with 15µg/dose (BECOV2D); n=12
5. Dose Strength-2 with 25µg/dose (BECOV2B & BECOV2C); n=12
6. Dose Strength-3 with 50µg/dose (BECOV2A); n=12

An independent DSMB would review the safety, tolerability and reactogenicity data seven days after first dose of vaccination. Based on favourable outcome, the study would seamlessly progress into phase-II. All the participants at this phase will continue to receive their second dose (Day 28) after DSMB clearance and will be followed up parallel for 6 months and 12 months after 2nd dose of vaccine administration.

There would be a total of 8 visits for each participant during the study. There is a pre-vaccination screening visit (day -3 to -1) to assess the eligibility criteria set, day -3 to -1 prior to the 1st dose of vaccination. Day of the 1st vaccination will be considered as day 0. All participants will be invited to follow-up visits at day 7, 28, 42, 56 and again at 6 months (28+180) and 12 months (28+365) post second dose. A time window of +4 days is allowed from visit-3 to visit-6 and a time window of 14 days will be allowed for the visit-7 and visit-8 respectively to ensure participant compliance to the visits. A whole blood sample of 5-15 mL will be collected intravenously at each of the protocol specified time points, as specified in the schedule of time and event table, by a trained nurse or a phlebotomist.

Participants will be asked to contact the study team if they develop any symptoms suggestive of COVID-19 at any point during the trial. Symptomatic participants will be asked to present for a 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.

Safety monitoring: The seamless phase-I part of the study will be overseen by an DSMB. A data & safety monitoring board (DSMB) with independent group of experts will be constituted before initiation of any study related procedures at

phase-I. The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. The primary responsibilities of the DSMB are to 1) review and evaluate the accumulated study data for participant safety, study conduct and progress, and 2) to make recommendations to sponsor concerning the continuation, modification, or termination of the trial as per the protocol defined time points. The DSMB will consider study-specific data as well as relevant background knowledge about the disease, test agent, or study population under study.

The first DSMB safety review will be at visit-3 (day 7) after the 7 days' diary data post 1st dose is gathered and tabulated, in all the dose strengths. Based on the positive recommendation at each of the dose strengths, the study will seamlessly move to phase-II for further screening and enrolment. The fourth DSMB review occurs 28 days' post 2nd dose for all the subjects enrolled at the end of phase-II. There will be a further follow-up at 6 months and 12 months post 2nd dose with a scheduled out-patient visit in the trial.

Safety surveillance:

- Each subject will be observed for at least 120 minutes following the administration of the study vaccine with appropriate medical treatment readily available in case of anaphylaxis or any other adverse reaction.

- All AEs and SAEs will be recorded and reported until the end of the phase-1 study. During the vaccination visits at day 0 and day 28, a diary card will be provided to the subject or the Legally Acceptable Representative to record any local and systemic symptoms experienced after each vaccination.

- Solicited local and general AEs will be collected during seven consecutive post-vaccination days (Day 0 – Day 6) and unsolicited AEs, if any, until day 56 and for any serious AEs until the end of the phase-I study (12 months post 2nd dose).

- Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures, are essential and required for study conduct.
- Holding rules have been predefined to guide the evaluation of safety during the study.
- Any single event (solicited symptom, AE and SAE) that are relevant for the holding rules described must be reported to the Sponsor within 24 hours.
- If the investigator becomes aware of a holding rule being met, he/she will suspend vaccination at his/her site and will inform the Sponsor Biological E. immediately who would then suspend vaccination at the other sites and inform the DSMB immediately.

- If the Sponsor becomes aware of a holding rule being met, the Sponsor will suspend further vaccination in all sites and will inform the DSMB immediately. All safety information available up to the time of suspension will be shared with the DSMB for their review and recommendation whether to stop, modify or continue the conduct of the study.
- Participants will be asked to contact the study team if they develop any symptoms suggestive of COVID-19 at any point during the trial. Symptomatic participants will be asked to present for a visit to test for SARS-CoV-2 by RT-PCR method.
- The 7-day safety results for the first 12 subjects in each of the dose strengths will be submitted to DSMB.
- The GO criteria to move into phase II will be conditional on the favorable outcome of a safety evaluation based on safety data from all the 12 vaccinated subjects in each of the dose strengths, collected up to the day 7 post first dose in Phase I. Until the outcome of the DSMB safety evaluation is reported in writing, further vaccinations and enrolments will be effectively on hold.
- The recommendation of the DSMB will be notified to the investigator(s), and to the Institutional Ethics Committee (IEC) before proceeding seamlessly into phase-II

The final responsibility to decide whether or not the trial should be stopped permanently rests with the Sponsor, after having considered all the safety information available and the recommendation of DSMB. If the trial is stopped, a letter indicating the reasons for stopping the study will be sent to the IEC via the investigator, and to the National Regulatory Authority (DCGI) via the Sponsor.

The study will be conducted in accordance with the WMA's Declaration of Helsinki, International Conference on Harmonization, Good Clinical Practice, Belmont Principles, and other applicable regulatory and clinical requirements. The study protocol and its associated documents will be reviewed and approved by the Institutional ethics committees of the respective study sites.

B) Phase-II Study Procedures (N=324):

A total of 324 healthy RT-PCR and anti-SARS-CoV-2 antibodies negative participants will be enrolled, as per eligibility criteria set in the phase II trial, with subjects randomised into one of the 4 groups. All participants having an average actual study duration of 56 days (until visit-5) and will be followed up further for 6 months (visit-6) and 12 months (visit-7) after the second dose as a scheduled out-patient visit.

Covid-19 Vaccine with Alum & CpG 1018 as adjuvants (Total N=324):
1. Formulation-1 (BECOV2D); n=78 subjects
2. Formulation-2 (BECOV2B); n=84 subjects

3. Formulation-3 (BECOV2C); n=84 subjects
4. Formulation-4 (BECOV2A); n=78 subjects

There would be a total of 7 visits for each participant during the study at this phase II. There is a pre-vaccination screening visit (day -3 to -1 day) to assess the eligibility criteria set, 3 days prior to the 1st dose of vaccination. Day of the 1st vaccination will be considered as day 0.

All participants will be invited to follow-up visits at day 28, 42, 56, 208 (28+180) and day 393 (28+365) respectively. A time window of +4 days is allowed from visit-3 to visit-5 and a time window of 14 days will be allowed for the visit-6 and visit-7 respectively to ensure participant compliance to the visits.

The enrolled study participants will be asked to contact the study team if they develop any symptoms suggestive of COVID-19 at any point during the trial. Symptomatic participants will be asked to present for a visit to test for SARS-CoV-2 by RT-PCR by a trained nurse or a phlebotomist. 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.

Total Number of Sites

A total of 360 subjects (36 at phase-I and 324 at phase-II) will be enrolled across five study sites within India.

List of Investigators

GCP trained, qualified and experienced Investigators will conduct the study at each of the study site.

Sample Size

Phase-I study:

This open label randomised phase-I study is primarily designed to descriptively assess the safety, tolerability, reactogenicity and immunogenicity of Biological E's Covid-19 vaccine in 18-55 year-old healthy adult volunteers of either gender. The sample size for the study is not based on power computations, as this is a first-in-human study primarily to assess the safety, tolerability and reactogenicity in each of the dose strengths, which is in compliance with the G.S.R. 227(E) of the drugs and cosmetics rules in force.

The sample size is arrived at based on the WHO Guidelines on clinical evaluation of vaccines: regulatory expectations, "The phase I clinical studies carry out initial testing of a vaccine in small numbers".

Phase-II study:

The sample size is calculated based on the difference of seroconversion rate between higher dose and lower dose groups using "SAS Proc" to detect a treatment difference of -20%, -20% & -30% respectively for each of the comparisons with highest dose group. Multiplicity adjustment was applied for each of the comparisons with an overall significance level of 0.05 maintained. Hence the total sample size needed at the phase-I seamlessly followed by

phase-II study would be 320 and with the addition of not less than 10% dropout rate, it then would be 360 subjects for enrolment.

Study Population

At phase-II (N=324) study: 18-65 year-old adult volunteers of either gender based on recruitment criteria set in the protocol.

For the purposes of analysis, two subsets of recruited subjects shall be identified: Total vaccinated cohort (TVC) for safety assessment and the According to Protocol (ATP) cohort for immunogenicity assessment.

Inclusion Criteria at Phase-I and Phase-II respectively:

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Each subject must satisfy ALL of the following criteria at study entry:

1. Ability and willingness to provide written or thumb printed informed consent prior to performing any study specific procedure.

2. Subject, in the opinion of the investigator, has ability to communicate and willingness to comply with the requirements of the protocol.

3. Participants of either gender between ≥18 to ≤55 years of age at phase-I and ≥18 to ≤65 years of age at phase-II at the time of 1st vaccination.

4. Participants virologically seronegative to SARS-CoV-2 infection by RT-PCR and anti-SARS-CoV-2 antibody prior to enrolment.

5. Participants seronegative to HIV 1 & 2, HBV and HCV infection prior to enrolment.

6. Participants considered of stable health as judged by the investigator, determined by medical history and physical examination with normal vital signs as defined in the protocol. *[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 <100.4ºF prior to enrolment].*

7. Female participants of child bearing potential negative to urine pregnancy test 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;

8. Agrees not to participate in another clinical trial at any time during the total study period.

9. Agrees to refrain from blood donation during the course of the study.

10. Agrees to remain in the town where the study centre is located, for the entire duration of the study.

11. Willing to allow storage and future use of collected biological samples for future research in an anonymised form.

Exclusion Criteria

The following criteria should be checked at the time of study entry. If ANY exclusion criterion applies, the subject must not be included in the study:

1. History of vaccination with any investigational vaccine against COVID-19 disease;

2. Seropositive to IgG antibodies against SARS CoV-2

3. Living in the same household of any COVID-19 positive person;

4. Pregnant women, nursing women or women of childbearing potential who are not actively avoiding pregnancy during clinical trials;

5. Seriously overweight (BMI ≥ 40 Kg/m2);

6. Use of any investigational or non-registered product other than the study vaccine during the trial period or 3 months prior to enrolment;

7. 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);

8. Current or planned participation in prophylactic drug trials for the duration of the study.

9. Any clinically significant abnormal haematology and biochemical laboratory parameters tested at screening as judged by the investigator;

10. Body temperature of ≥100.4°F (>38.0°C) or symptoms of an acute illness at the time of screening or prior to vaccination;

11. History of severe psychiatric conditions likely to affect participation in the study;

12. History of any bleeding disorder (e.g. factor deficiency, coagulopathy or platelet disorder);

13. History of allergic disease or reactions likely to be exacerbated by any component of the Biological E's four COVID-19 vaccine formulations;

14. Chronic respiratory diseases, including asthma;

15. Chronic cardiovascular disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder and neurological illness;

16. Any other serious chronic illness requiring hospital specialist supervision;

17. Suspected or known current alcohol abuse as defined by an alcohol intake of greater than 42 units every week for at least one year;

18. 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;

19. Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required);

20. Any medical condition that in the judgment of the investigator would make study participation unsafe.

21. Individuals who are part of the study team or close family members of individuals conducting the study.

Drug Formulations

At Phase-I:

All the 36 enrolled subjects (12 subjects from each one of the dose strengths) will receive respective Biological E's candidate Covid-19 vaccine based on randomization.

A. Investigational Vaccine at Phase-I:

There would be three dose strengths (4 groups) evaluated sequentially by ascending dose at phase-I. Biological E's Covid-19 vaccine for preventive protection against Covid-19 disease is manufactured using *Pichia pastoris* as an protein expression system. It is a recombinant protein containing Receptor Binding Domain of SARS-CoV-2 Virus "spike protein".

- **Investigational Candidate Vaccine**

- Biological E's Covid-19 vaccine
  - » 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**:** 0.5 mL by Intra-muscular injection.

- » Dosage Regimen: Each subject will receive a 0.5 mL dose of investigational vaccine intramuscularly in 2-dose schedule.
- » Preferred Site: The preferred site for injection is the deltoid muscle of the upper arm.
- » Presentation**:** This would be a glass vial containing 0.5mL of single human dose (SHD).
- » Storage**:** The vaccine should be stored at a temperature between +2°C and +8°C. DO NOT FREEZE.
- » Do not use beyond the “Retest date” specified on the label.
- » 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.

B. Investigational Vaccine at Phase-II:

➢ **Investigational Candidate Vaccine**

- Biological E’s Covid-19 vaccine
  - » 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**:** 0.5 mL by Intra-muscular injection.
  - » Dosage Regimen: Each subject will receive a 0.5 mL dose of investigational vaccine intramuscularly.
  - » Preferred Site: The preferred site for injection the deltoid muscle of the upper arm.
  - » Presentation**:** This would be a transparent glass vial containing 0.5mL of single human dose (SHD).
  - » Storage**:** The vaccine should be stored at a temperature between +2°C and +8°C. DO NOT FREEZE.
  - » Do not use beyond the “Retest date” specified on the label.
  - » 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.

Pre-study Screening and Baseline Evaluation

After obtaining the informed consent from the subject/LAR, followed by preliminary screening (day -3 to -1) as per inclusion and exclusion criteria, a total of 360 healthy adult volunteers of either gender will be enrolled in 18-55 years old at phase-I (n=36) and 18-65 year old at phase-II (n=324).

SCHEDULE OF TIME AND EVENTS – PHASE-I								
Type of Contact	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**
Time Points	**Day -3 to -1**	**Day 0**	**Day 7 (+4)**	**Day 28 (+4)**	**Day 42 (+4)**	**Day 56 (+4)**	**Day 208 (+14)**	**Day 393 (+14)**
Sampling Time Points	**Screen baseline**	**Dose-1**	**Safety Data for DSMB**	**Dose-2**	**Follow-up**	**Follow-up**	**Follow-up**	**Follow-up**
Signed Informed consent	●							
Allocate subject screening number	●							
Check inclusion/exclusion criteria evaluation	●	●						
Allocate subject enrolment number		●						
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	●	●	●	●	●	●		
Blood sample collection	● (15 mL)			● (10 mL)	● (10 mL)	● (15 mL)	● (5 mL)	● (5 mL)
Real time RT-PCR by nasopharyngeal swab	●							
Anti-SARS-CoV-2 IgG antibody estimation	●			●	●	●	●	●
Anti-SARS-CoV-2 IgG subclasses IgG1 & IgG2 estimation	●					●		
SARS-CoV-2 virus Neutralising Antibody (NAb) estimation	●			●	●	●	●	●
INF-γ cytokine assay	●			●		●		
Haematology & Biochemistry parameters	●					●		
HIV 1&2, HBV and HCV	●							
Urine Pregnancy test prior to vaccination in females	●			●				

Vaccine administration (0.5mL IM; deltoid muscle)		●		●				
120 minutes post-vaccination observation		●		●				
Distribution of diary card		●		●				
Recording of solicited local and general AEs within 7 days post-vaccination after each dose		●		●				
DSMB review of Day 7 safety data after 1st dose in each of the groups			●					
Recording of non-serious (unsolicited) AEs till day 56 post 1st dose		●		●		●		
Return of diary card			●		●			
Diary card transcription by investigator or assignee			●		●			
Recording of unsolicited AEs		●	●	●		●		
Recording of SAEs		●	●	●		●		
Recording of SAEs and medically attended AEs		●	●	●		●	●	●
Interim Data review			●			●		
Phase-I clinical study report v1.0 based on aggregate data up to day 56						●		
DSMB review of aggregate data as on Day 56						●		
Safety follow up after Day 56 for any SAEs and medically attended AEs							●	●

SCHEDULE OF TIME AND EVENTS – PHASE-II									
Type of Contact	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Clinical Study Report**	**Visit 6**	**Visit 7**	**Clinical Study Report**
Time Points	**Day -3 to -1**	**Day 0**	**Day 28 (+4)**	**Day 42 (+4)**	**Day 56 (+4)**		**Day 208 (+14)**	**Day 393 (+14)**	
Sampling 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 screening number	●								
Check inclusion/exclusion criteria evaluation	●	●							
Allocate subject enrolment number		●							
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	●	●	●	●	●				
Blood sample collection	● (15 mL)		● (10 mL)	● (10 mL)	● (15 mL)		● (5 mL)	● (5 mL)	
Real time RT-PCR (nasopharyngeal swab)	●								
Anti-SARS-CoV-2 IgG antibody estimation	●		●	●	●		●	●	
Anti-SARS-CoV-2 IgG subclasses IgG1 & IgG2 estimation	●				●				
SARS-CoV-2 virus neutralising Antibody (NAb) estimation	●		●	●	●		●	●	
INF-γ cytokine assay	●		●		●				
Haematology & Biochemistry parameters	●				●				

Only baseline screening against HIV 1&2, HBV and HCV	•								
Urine Pregnancy test in females only	•		•						
Vaccine administration (0.5mL IM; deltoid muscle)		•	•						
120 minutes post-vaccination observation		•	•						
Distribution of diary card		•	•						
Recording of solicited local and general AEs within 7 days post-vaccination after each dose		•	•	•					
Recording of non-serious (unsolicited) AEs till day 56 post 1st dose		•	•	•	•				
Return of diary card			•	•					
Diary card transcription by investigator or assignee			•	•					
Recording of unsolicited AEs		•	•	•	•				
Recording of SAEs		•	•	•	•				
Recording of SAEs and medically attended AEs		•	•	•	•				
Interim Data review					•				
Phase-II interim study report based on aggregate data up to day 56 to qualify for phase-III					•				
Safety follow up after Day 56 for any SAEs and medically attended AEs for 12 months post 2nd dose							•	•	

Laboratory Tests at Phase-I and Phase-II:

B. Routine Laboratory Tests:

- **Haematology (once at baseline & again at day 56)–**
  1. Haemoglobin level (Hb)
  2. Red blood cell count (Total RBC count)
  3. White blood cell count (WBC count)
  4. Differential count (viz., Neutrophils, Lymphocytes, Eosinophil, Basophils and Monocyte count)
  5. Haematocrit % (PCV)
  6. Platelet count (PC)

- **Biochemistry (once at baseline & again at day 56)–**
  1. **Liver Function Tests (LFT)**
     a. Alanine aminotransferase (ALT)
     b. Aspartate aminotransferase (AST)
     c. Alkaline Phosphatase (AP)
     d. Total bilirubin (TB)
     e. Direct (conjugated) bilirubin (DB)
     f. Total protein
     g. Albumin Globulin Ratio

  2. **Kidney Function Tests (KFT)**
     a. Serum Creatinine levels (SC)
     b. Blood Urea Nitrogen (BUN)

  3. Urine Pregnancy test (twice)
     a) Only for women of child bearing potential (as judged by the PI)

- **HIV 1&2, HBV and HCV (only once at Baseline (prevac))**

B. Special Serological Tests

Immune serology

e) Real time RT-PCR naso or oropharyngeal Swab Test (Nasal) (for detection of SARS-CoV-2 specific RNA in clinical samples)
f) Anti-SARS-CoV-2 total IgG titres and also IgG antibody subclasses (IgG1 & IgG2 only).
g) Neutralizing antibody (NAb) assay against live and/or pseudo typed SARS-CoV-2 virus
h) Interferon-Gamma Cytokine Levels (INF-γ) – To assess the Th1 response pre and post vaccination time points.

Concomitant Medication

No concomitant medication will be administered except for the management of any adverse event at the discretion of the principal investigator. In case any medication is administered during the course of the study, the decision to continue or discontinue the subject in the study would be taken by the investigator in consultation with sponsor based on whether the administered medication is known to interfere with the immune response.

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 &/or tenderness, redness and swelling &/or induration are expected to occur. Commonly expected systemic adverse events may include Fever, headache, chills, myalgia,

fatigue or malaise, urticarial, 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.

- Further Management - 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.

Premature Withdrawal/Discontinuation Criteria

- Subject/LAR will be informed that they are free to withdraw from the study at any time without stating the reason.
- If the subject develops signs and symptoms of covid-19, the same needs to be confirmed by RT-PCR test. 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 body temperature and tachypnea.
- The investigator may withdraw a subject from the study if:
    - The subject suffers from significant illness or undergoes surgery during the course of the study.
    - The subject experiences serious adverse events and withdrawal would be in the best interest of the subject.
    - The subject or the LAR wishes to withdraw from study.

Statistical Methods

1. Analysis of Population:

For the purposes of analysis, two subsets of recruited subjects shall be identified in each of the vaccine groups: Total vaccinated cohort (TVC) and the According to Protocol (ATP) cohort.

Total Vaccinated Cohort (TVC): All the demographic and primary safety analyses will be based on this population, defined as subjects who entered into the study and have received at least one single intramuscular dose of study vaccination. All analysis based on this TVC population will be carried out using the actual treatment received and will be the primary analysis population. This population will be used for all demographics, baseline characteristics, safety and reactogenicity assessments in each of the vaccination groups.

According to Protocol (ATP): ATP population is defined as population in which data from subjects, who have results available at all protocol specified timepoints for Interferon-Gamma, anti SARS-CoV-2 IgG and anti-SARS-CoV-2 NAb antibodies. This will be the secondary analysis population for immunogenicity assessment.

The ATP cohort for analysis will include:

- All evaluable subjects who meet all eligibility criteria.
- All evaluable subjects who have received at least a one dose of study vaccine according to the protocol.
- All evaluable subjects for whom administration site of study vaccine(s) is known.
- All evaluable subjects who comply with the procedures and visit intervals defined in the protocol.
- All evaluable subjects who did not present with a medical condition leading to elimination from an ATP analysis.

2. Variables and their Analysis:

a) Safety – Primary:

The primary objective of this study is to evaluate the safety and reactogenicity of Biological E's four novel "protein subunit SARS-CoV-2 vaccine formulations" in 18-55 years old at phase-I and 18-65 years old at phase-II in healthy human adults. Only descriptive analysis will be presented in this study. All subjects entered into the study and who received at least one dose of study vaccine will be included in the safety analysis.

Safety Variables:

- Local injection site adverse reactions

- Systemic adverse events (both solicited and unsolicited)
- Clinically significant abnormal haematology and biochemistry parameters.
- Clinically significant abnormal body temperature, pulse rate, respiratory rate and blood pressure findings as judged by the principal investigator.
- Clinically significant local & systemic examination findings as judged by the principal investigator.

Primary End point(s) - Safety:

» Proportion of subjects with solicited adverse reactions during first 120 minutes of post-vaccination observation period and for 7 consecutive days (Day 0-6) thereafter, captured through subject diary after each dose.

» Proportion of subjects with unsolicited local and systemic adverse events (AEs) during the post-vaccination follow up period of 28 days after each of the two doses. (time frame: until 28 days after 2nd dose)

» Serious adverse events (SAEs) if any, during the total study duration (time frame: until 28 days after 2nd dose).

» Any clinically significant abnormal laboratory parameters in comparison with baseline values (time frame: until 28 days after 2nd dose).

» Any clinically significant abnormal vital signs at each of the protocol specified visits (time frame: until 12 months post 2nd dose).

Safety will be assessed by monitoring AEs, local and systemic tolerability, and the safety laboratory parameters including abnormal vital signs of clinical significance as judged by the principal Investigator of the respective study site.

The number and percentage of subjects with adverse events (AE) and serious AEs will be presented overall by system organ class & by preferred term.

The percentage of subjects with at least one local adverse event (solicited and unsolicited), with at least one systemic adverse event (solicited and unsolicited) and with any adverse event during the solicited follow-up period will be tabulated with exact 95% CI. The same calculations will be performed for symptoms rated as Grade 3 and above.

Systemic and local tolerability, recorded in subject diaries, will be summarized in a frequency table with percentages based on the number of observed values. DSMB reviews the safety data once after 7 days' safety for the initially 12 subjects enrolled under each of the ascending dose strengths and again after 28 days' post 2nd dose for all subjects.

The percentage of subjects reporting each individual solicited local and general adverse event during the solicited follow-up period will be tabulated with exact 95% CI.

A. The following local (injection-site) adverse events will be solicited:

Pain (&/or Tenderness) at the injection site
Redness at the Injection site
Swelling (&/or Induration) at the injection site

B. The following systemic AEs will be solicited:

Fever
Headache
Chills
Myalgia
Fatigue or Malaise
Urticaria
Nausea
Arthralgia

Note: Temperature will be recorded at the same time in a day by digital thermometer. Should additional temperature measurements be performed at other times of day, the highest temperature, regardless of route, will be recorded in the eCRF.

Occurrence of fever will be reported at all protocol specified time points, as well as the occurrence of temperature >104°F (>40°C) with causal relationship to vaccination. Duration and prevalence of fever will be presented.

C. The following COVID-19 disease symptoms will also be solicited:

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

Fever
Chills
Cough
Fatigue or Malaise
Shortness of breath or difficulty in breathing
Expectoration
Myalgia
Rhinorrhoea (congestion or runny nose)
Sore throat

Nausea
Vomiting
Diarrhoea
Loss of smell (anosmia)
Loss of taste (ageusia)
Abdominal Discomfort

For all solicited symptoms, the same tabulation will be performed for Grade 3 adverse events and for adverse events with relationship to vaccination.

The verbatim reports of unsolicited symptoms will be reviewed by a physician and the signs and symptoms will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology. The percentage of subjects with at least one report of unsolicited adverse event classified by the MedDRA and reported up to 28 days after each vaccination will be tabulated with exact 95% CI. The same tabulation will be performed for Grade 3 unsolicited adverse events and for unsolicited adverse events with a relationship to vaccination.

Serious adverse events and withdrawal due to adverse event(s), if any, will be described in detail. The percentage of subjects reporting AEs resulting in a medically attended visit will also be tabulated.

Holding rules and safety monitoring at both Phase-I & Phase-II

The goal is to proceed cautiously with the administration of all the four candidate formulations. This helps to ascertain the safety profile of each of the four investigational formulations in healthy adults before proceeding to further phases of the study with the preferred formulation as an outcome. This study will be closely monitored by a data and safety monitoring board (DSMB) by reviewing the safety data at protocol specified intervals.

Safety monitoring for this study will be performed by a data & safety monitoring board (DSMB), an independent safety review body. The DSMB will perform a review of aggregate data in accordance to the enrolment guidelines as well as in the event of any holding rule.

The below tables list minimum criteria (termed "*holding rules*") which, if any occur in subjects vaccinated under any one of the study groups during the course of the study will lead to suspension of further vaccination doses, not only for that subject but also in all sites until formal safety review of available study safety data (both subject data and aggregate data) by DSMB will have occurred.

Table 1: Vaccination holding rules for serious and severe adverse events

Holding rule #	Event	Threshold criteria:
1a	Subjects experience life-threatening SAE or death	≥1 subject
1b	Subjects withdrawn from the study following a Grade 3 vaccine-related (S)AE	>1 subject
1c	Subjects with any vaccine-related local or general solicited symptoms leading to hospitalization, or vaccine-related fever 104°F (>40°C), or necrosis at the injection site	>1 subject

Any single event (solicited symptom, AE and SAE) listed in these holding must be reported to the Sponsor within 24h.
For holding rule #1a, each subject experiencing a life-threatening SAE or death will invoke an immediate suspension of the vaccination.
For holding rules #1b and 1c, "vaccine-related" implies that the observation is not to be attributed to another, non-vaccination-related cause (for example anaemia caused by major trauma with haemorrhage)
For holding rule #1c, fever is defined as temperature 104°F (>40°C). The preferred route for recording temperature in this study will be using digital thermometer.

Table 2: Vaccination holding rules for safety evaluations (solicited and unsolicited AEs)

Holding rule #	Event	Threshold criteria
2a	Subjects reporting any Grade 3 solicited local symptoms requiring medical advice, within the 7-days post-vaccination period	>3 subjects
2b	Subjects reporting any Grade 3 vaccine-related solicited general symptoms requiring medical advice, within 7-days post-vaccination period	>3 subjects
2c	Subjects reporting any Grade 3 vaccine-related unsolicited AE requiring medical advice, within 7-days post-vaccination period	>3 subjects
For combination of holding rules 2a, 2b and 2c		>3 subjects

Any single event (solicited symptom, AE and SAE) listed in these holding must be reported to the Sponsor within 24h.
For holding rules #2b and 2c, "vaccine-related" implies that the observation is not to be attributed to another, non-vaccination-related cause (for example anaemia caused by major trauma with haemorrhage)

Interpretation of analyses: This prospective study consists of three dose strengths at phase-I, in which 12 subjects from each dose strength receive vaccination and the outcomes will be assessed over 28-day period after each dose. All subjects will be followed up for safety until 12 months post 2nd dose. Seven days' post first dose safety data for each of the ascending dose strengths

will be reviewed by the DSMB and its favourable recommendation enables to proceed to phase-II. All safety analysis would be descriptive in nature.

Conduct of analyses: Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the final study report.

Sequence of analyses: All analyses will be conducted on data as clean as possible. Interim analysis will be performed when all data up to day 7 after first vaccination for each of the ascending dose strengths at phase-I will be analysed. This analysis will include analysis of safety, tolerability and reactogenicity only. Cumulative safety data after DSMB review till day 7 will be analysed for subjects in phase-I and again at 28 days post second dose in phase-II.

Immunogenicity Variables and Analysis (Secondary)

- Immunogenicity data (both IgG titres, INF-γ cytokine levels and NAb titres) shall be assessed by according to protocol population (ATP).
- Serum anti-SARS-CoV-2 IgG antibody titres will be determined by a validated assay and also by using the neutralizing antibody (NAb) assay against live and/or pseudo typed SARS-CoV-2 virus once at baseline, Day 28, Day 42, Day 56 and again at 6 months & 12 months post 2nd dose.
- Proportion of subjects achieving seroconversion (viz., ≥4-fold rise from baseline) at day 28 will be calculated.
    - Seroconversion is defined as the appearance of antibodies (i.e. titre greater than or equal to 4-fold rise) in the serum of subjects seronegative before vaccination.
    - Vaccine response rate is defined as an initially seronegative subject at pre-vaccination, showing rise in antibody concentration ≥4-fold the pre-vaccination antibody concentration.
    - Seronegative is defined as a person with no detectable levels of antibodies against vaccine specific antigen.
- Geometric mean titres will be calculated at baseline, day 28, day 42 and day 56 in all study groups. The geometric mean titres (GMT) calculation will be performed by taking the anti-log of the mean of the log concentration transformations. Antibody titres below the lower limit of quantitation (LLOQ) of the assay will be given an arbitrary value of half the cut-off of LLOQ for the purpose of GMT calculation.
- In addition, the geometric mean fold rise (GMFR) in anti-SARS-CoV IgG antibody titres and NAb titres at day 28 post 2nd dose, from baseline, along with their corresponding 2-sided 95% CIs, will be presented.

Statistical Methods at Phase-II

Analysis of Population:

The primary objective at phase-II is Immunogenicity and the secondary objective is safety of the investigational vaccine.

For the purposes of analysis, two subsets of recruited subjects shall be identified in each of the vaccine groups:

a) According to Protocol (ATP) cohort, and the

b) Total vaccinated cohort (TVC).

a) According to Protocol (ATP): ATP population is defined as population in which data from subjects, who have results available at all protocol specified visits for Interferon-Gamma, anti SARS-CoV-2 IgG and anti-SARS-CoV-2 virus neutralising antibodies (NAb). This will be the secondary analysis population for immunogenicity assessment.

The ATP cohort for analysis will include:

- All evaluable subjects who meet all eligibility criteria.
- All evaluable subjects who have received at least a one dose of study vaccine according to the protocol.
- All evaluable subjects for whom administration site of study vaccine(s) is known.
- All evaluable subjects who comply with the procedures and visit intervals defined in the protocol.
- All evaluable subjects who did not present with a medical condition leading to elimination from an ATP analysis.

b) Total Vaccinated Cohort (TVC): All the demographic and secondary safety analyses will be based on this population, defined as subjects who entered into the study and have received at least one single intramuscular dose of study vaccination. All analysis based on this TVC population will be carried out using the actual treatment received and will be the secondary analysis population. This population will be used for all demographics, baseline characteristics, safety and reactogenicity assessments in each of the vaccination groups.

a) Immunogenicity Variables and Analysis (Primary) at Phase-II:

- Immunogenicity data (both IgG titres, INF-γ cytokine levels and NAb titres) shall be assessed by according to protocol population (ATP).
- Serum anti-SARS-CoV-2 IgG antibody titres will be determined by a validated assay and also by using the neutralizing antibody (NAb) assay against live and/or pseudo typed SARS-CoV-2 virus once at baseline, Day 28, Day 42, Day 56 and again at 6 months & 12 months post 2nd dose.
- Proportion of subjects achieving seroconversion (viz., ≥4-fold rise from baseline) at day 28 will be calculated.

- Seroconversion is defined as the appearance of antibodies (i.e. titre greater than or equal to 4-fold rise) in the serum of subjects seronegative before vaccination.
- Vaccine response rate is defined as an initially seronegative subject at pre-vaccination, showing rise in antibody concentration ≥4-fold the pre-vaccination antibody concentration.
- Seronegative is defined as a person with no detectable levels of antibodies against vaccine specific antigen.

- Geometric mean titres will be calculated at baseline, day 28, day 42 and day 56 in all study groups. The geometric mean titres (GMT) calculation will be performed by taking the anti-log of the mean of the log concentration transformations. Antibody titres below the lower limit of quantitation (LLOQ) of the assay will be given an arbitrary value of half the cut-off of LLOQ for the purpose of GMT calculation.

- In addition, the geometric mean fold rise (GMFR) in anti-SARS-CoV IgG antibody titres and NAb titres at day 28 post 2nd dose, from baseline, along with their corresponding 2-sided 95% CIs, will be presented.

b) Safety Variables and analysis (Secondary) at Phase-II:

The secondary objective of this study is to evaluate the safety and reactogenicity of Biological E's Covid-19 vaccine in 18-65 years old healthy adults. Only descriptive analysis of safety (secondary) will be presented at this phase. All subjects entered into the study and who received at least one dose of study vaccine will be included in the safety analysis.

Safety Variables:

- Local injection site adverse reactions
- Systemic adverse events (both solicited and unsolicited)
- Clinically significant abnormal haematology and biochemistry parameters.
- Clinically significant abnormal oral body temperature, pulse rate, respiratory rate and blood pressure findings as clinically judged by the principal investigator.
- Clinically significant local & systemic examination findings as judged by the principal investigator.

Primary End point(s) - Safety:

» Proportion of subjects with solicited adverse reactions during first 120 minutes of post-vaccination observation period and for 7 consecutive days (Day 0-6) thereafter, captured through subject diary after each dose.

» Proportion of subjects with unsolicited local and systemic adverse events (AEs) during the post-vaccination follow up period of 28 days after each of the two doses. (time frame: until 28 days after 2nd dose)

» Any clinically significant abnormal vital signs at each of the protocol specified visits (time frame: until 28 days after 2nd dose).

» Serious and other medically attended adverse events in all study participants (time frame: until 28 days after 2nd dose).

Aggregate data will be summarised at 56 days' post 2nd dose for all subjects in all the treatment groups. At the end of the phase-II, clinical study report will be presented to the regulators for their review and approval for a) an emergency use license (EUL) and b) also to proceed to larger phase-III study.

The safety and immunogenicity for all the subjects enrolled in phase-I seamlessly followed by phase-II up to Day 56 will be presented in the clinical study report v1.0. This clinical study report will be updated with safety and immunogenicity data gathered during one-year follow-up period.

Safety will be assessed by monitoring AEs, local and systemic tolerability, and the safety laboratory parameters including abnormal vital signs of clinical significance as judged by the principal Investigator of the respective study site.

The number and percentage of subjects with adverse events (AE) and serious AEs will be presented overall by system organ class & by preferred term.

The percentage of subjects with at least one local adverse event (solicited and unsolicited), with at least one general adverse event (solicited and unsolicited) and with any adverse event during the solicited follow-up period will be tabulated with exact 95% CI. The same calculations will be performed for symptoms rated as Grade 3 and above.

Systemic and local tolerability, recorded in subject diaries, will be summarized in a frequency table with percentages based on the number of observed values.

The percentage of subjects reporting each individual solicited local and general adverse event during the solicited follow-up period will be tabulated with exact 95% CI.

A. The following local (injection-site) adverse events will be solicited:

Pain (&/or Tenderness) at the injection site
Redness at the Injection site
Swelling (&/or Induration) at the injection site

B. The following general AEs will be solicited:

Fever
Headache

Chills
Myalgia
Fatigue or Malaise
Urticaria
Nausea
Arthralgia

Note: Temperature will be recorded at the same time in a day by oral route. Should additional temperature measurements be performed at other times of day, the highest temperature, regardless of route, will be recorded in the eCRF.

Occurrence of fever will be reported per 0.5°C cumulative increments as well as the occurrence of temperature >104°F (>40°C) with causal relationship to vaccination. Duration and prevalence of fever will be presented.

C. The following COVID-19 disease symptoms will also be solicited:

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

Fever
Cough
Fatigue or Malaise
Shortness of breath
Expectoration
Myalgia
Rhinorrhoea
Sore throat
Vomiting
Diarrhoea
Loss of smell (anosmia)
Loss of taste (ageusia)
Abdominal Discomfort

For all solicited symptoms, the same tabulation will be performed for Grade 3 adverse events and for adverse events with relationship to vaccination.

The verbatim reports of unsolicited symptoms will be reviewed by a physician and the signs and symptoms will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology. The percentage of subjects with at least one report of unsolicited adverse event classified by the MedDRA and reported up to

28 days after each vaccination will be tabulated with exact 95% CI. The same tabulation will be performed for Grade 3 unsolicited adverse events and for unsolicited adverse events with a relationship to vaccination.

Serious adverse events and withdrawal due to adverse event(s), if any, will be described in detail. The percentage of subjects reporting AEs resulting in a medically attended visit will also be tabulated.

16.2 Informed Consent Form

Informed Consent Form

[To Participate in a Clinical Trial as per the third schedule of New drugs and clinical trials rules 2019]

Study Title:

A prospective open label randomised phase-I seamlessly followed by phase-II study to assess the safety, reactogenicity and immunogenicity of Biological E's novel Covid-19 vaccine containing Receptor Binding Domain of SARS-CoV-2 for protection against Covid-19 disease when administered intramuscularly in a two dose schedule (0, 28D) to healthy volunteers

Study Number: BECT062 **Scr. No.** | | | | | |

Trial No.: BECT/Covid-19-phase-I&II/062

Protocol No.: BECT062/Covid-19-phase-I&II/CTP-01

Protocol Version & Date: 1.1 dated 07.10.2020

Amendment No. & Date: 1.0 dated 07.10.2020

Informed Consent Version No.: 1.1 dated 07.10.2020

Subject's Initials: ……Subject's Name: ……

Date of Birth …….. Age: …….. Gender: ……

Investigator's Name: …….

Name of the Hospital: …….

Address of the subject: …….

…….

Qualification of Subject: ……

Occupation of Subject: ……

Annual Income of Subject: ……

Name and address of the nominee (s) and his/her relation to the subject for the purpose of compensation in case of trial related death:

Name:…….

Address:……

……

Relationship:……

		Subject initials / Thumb Impression (Only)
1.	I confirm that I have read/ had it read (check the appropriate) the subject information sheet (SIS) dated _____ before signing this consent form and I am in agreement with the content. I am now aware of the nature, risks and consequences of my participation in the above mentioned study. I have been offered ample opportunity to ask questions and have received answers that fully satisfy those questions.	[ ]
2.	I understand that my participation in the study is voluntary and that I am free to withdraw myself at any time, without giving any reason, without medical care or legal rights being affected.	[ ]
3.	I understand my responsibilities during the research study and agree to fulfil them.	[ ]
4.	I understand that I may receive any one out of the four study vaccine formulations based on the randomization.	[ ]
5.	I understand that no records shall be sent outside the Research Institute/Hospital; however, data of individual subjects can be disclosed only in a court of law under the Orders of the Presiding Judge or in some cases as may be required to communicate to Drug regulatory/Health Authority.	[ ]
6.	I understand and agree that personal health information about me will be collected, processed and disclosed as described in the attached subject information sheet. I understand that I will not be able to participate in the study if I do not consent to the collection, processing and disclosure of this information. I understand that my identity will not be published.	[ ]
7.	I understand and agree that blood samples will be taken from me and processed and transferred as described in the attached subject information sheet. I understand that I will not be able to participate in the research study if I do not consent to the collection, processing and disclosure of these blood samples.	[ ]
8.	I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw myself from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.	[ ]

9.	I understand that I have right to access personal information about me with the study doctor and the right to correct such information with the study doctor.	[ ]
10.	I agree not to restrict the use of any data or results that arise from this study, provided such a use is only for scientific purpose(s)	[ ]
11.	All the above has been explained to me in the language I know and I understand. I will be receiving a copy of the Informed Consent Form.	[ ]
12.	I give permission for the left over (blood or serum) samples to be stored indefinitely and may be used with de-identified information in future research and development.	[ ]
13.	I consent my voluntary participation as a subject in the above research study.	[ ]
14.	I am aware that in case of study related injury or death, Sponsor i.e. Biological E. Limited will provide complete medical care as well as compensation for the injury to the individual and in case of death to his/her legal heirs.	[ ]

Subject's Signature □ / Thumb impression □

_____ Date: _____/_____/_____ (dd/mm/yy)

Subject Name: _____

LAR's Signature □/ Thumb impression* □

_____ Date: _____/_____/_____ (dd/mm/yy)

LAR Name: _____

*Tick☑ whichever is applicable in the box specified

If Subject & LAR are Illiterate:

Signature of the Impartial Witness: _____ Date: ___/___/___
(dd/mm/yy)

Name of the Impartial Witness: _____

Physician's Confirmation

I confirm that I have fully informed the subject or subject's legally acceptable representative of the nature, risks, and consequences of the present study as well as the management of his/her medical data. The subject or legally acceptable representative has been given a copy of the Subject Information Sheet and will be given a copy of this informed consent form after it is signed and dated by the concerned parties.

A signed and dated copy of informed consent form along with subject information sheet was provided to the participant.

Signature of the Investigator: _____

Date: _____/_____/_____

(dd/mm/yy)

Study Investigator's Name: _____

I have received the copy of the signed and dated Informed consent form along with subject information sheet.

_____

(Signature / Thumb impression of the subject or LAR)

_____

(Name of the subject or subject's parent or LAR)

16.3 World Medical Association -Declaration Of Helsinki

Ethical Principles for Medical Research Involving Human Subjects

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.

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional

affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a

research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of

research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

- END -