Supplemental Online Content

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Supplement 1. Trial protocol

This supplemental material has been provided by the authors to give readers additional information about their work.

Inactivated SARS-CoV-2 Vaccines (Vero Cell)

Clinical Trial Protocol

Protocol name: Multicenter, Randomized, Double Blind, Parallel Placebo Controlled, Phase III Clinical Trial to Evaluate the Efficacy, Safety and Immunogenicity of Inactivated SARS-CoV-2 Vaccines in Healthy Population Aged 18 years old and above

Protocol number: CNBG2020003SQ

Version Date: Oct. 08, 2020

Version Number: 4.0

Amendment 3

Study Sponsor:

China National Biotec Group Company Limited

Wuhan Institute of Biological Products Co., Ltd.

Beijing Institute of Biological Products Co., Ltd.

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STATEMENT OF COMPLIANCE

This study will be performed in compliance with Good Clinical Practice (GCP), the Declaration of Helsinki (with amendments) and local legal and regulatory requirements

SIGNATURE PAGE

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 Good Clinical Practice (GCP), the Declaration of Helsinki (with amendments) and the laws and regulations of the countries in which the study takes place.

Protocol name	Multicenter, Randomized, Double Blind, Parallel Placebo Controlled, Phase III Clinical Trial to Evaluate the Efficacy, Safety and Immunogenicity of Inactivated SARS-CoV-2 Vaccines (Vero Cell) in Healthy Population Aged 18 Years Old and Above	
Protocol Number	CNBG2020003SQ	
Version Date	Oct. 08, 2020	
Version Number	Version 4.0	
Sponsor	China National Biotec Group Company Limited（CNBG） Wuhan Institute of Biological Products Co., Ltd. (WIBP) Beijing Institute of Biological Products Co., Ltd. (BIBP)	
Sponsor 1 project leader	Name: Duan Kai Company: Wuhan Institute of Biological Products Co., Ltd Address: No.1, Huangjin Industrial Park Road, Zhengdian, Jiangxia District, Wuhan City Zip Code: 430207	Signature: Date:
Sponsor 2 project leader	Name: Yang Yunkai Company: Beijing Institute of Biological Products Co., Ltd Address: No. 6&9, Bo'xing No. 2 Road, Economic-Technological Development Area, Beijing, 100176, China Zip Code:100176	Signature: Date:

INVESTIGATOR'S COMPLIANCE DECLARATION

I have read this protocol and agree to conduct the study as outlined herein, and as implemented by any future protocol amendment/update, according to the terms of the clinical trial contract, and in accordance with supplementary study: conduct procedures and/or guidance or documents provided by the study sponsor, complying with the obligations and requirements of clinical investigators and all other requirements listed in relevant national and international regulations including ICH GCP guidelines.
I assume responsibility for the compliance of the site personnel reporting to me or assisting me with the study.

I confirm that I am aware of my obligations towards relevant regulatory authorities as it concerns my participation in this trial as investigator.

I agree to disclose and provide information to the Sponsor on any potential conflict of interest I may have participating in this study as investigator.

I declare that I will co-operate with the Sponsor personnel and/or representatives, and vendors managing or supporting the study, including CRO, timely and adequately to ensure timely study conduct and compliance with study documents and relevant regulations.

I am fully familiar with the correct method of using the vaccine described in the protocol and other information provided by sponsor, including but not limited to the following contents: current investigator's brochure (IB) or equivalent documents and relevant supplements.

I am familiar with and will abide by the GCP, the Guiding Principles for Quality Management of Vaccine Clinical Trials (Tentative) and all existing regulatory requirements.

Protocol name	Multicenter, Randomized, Double Blind, Parallel Placebo Controlled, Phase III Clinical Trial to Evaluate the Efficacy, Safety and Immunogenicity of Inactivated SARS-CoV-2 Vaccines (Vero Cell) in Healthy Population Aged 18 Years Old and Above
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Investigator's signature: _____

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Investigator's Name (Please print)

Date: _____

List of Abbreviations

ACE2	Angiotensin converting enzyme 2
ADE	Antibody Dependency Enhancement
AE	Adverse Event
BP	Blood Pressure
CI	Confidence Interval
CDC	Center for Disease Control and Prevention
COA	Certificate of Analysis
CoV	Coronavirus
COVID-19	Coronavirus disease of 2019
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
eCRF	electronic Case Report Form
EAC	Endpoint Assessment or Adjudication Committee
EDC	Electronic Data Capture System
FAS	Full Analysis Set
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GMT	Geometric Mean Titer
GMI	Geometric Mean Increase
IB	Investigator's Brochure
ICF	Informed Consent Form
IEC	Independent Ethics Committee
MERS	Middle East Respiratory Syndrome
NMPA	National Medical Products Administration
PPS	Per-Protocol Set
RNA	Ribonucleic acid

SAE	Serious Adverse Events
SARS	Severe Acute Respiratory Syndrome
SOP	Standard Operating Procedure
SS	Safety Set
SUSAR	Suspected and Unexpected Serious Adverse Reactions
VED	Vaccine Enhanced Disease
WHO	World Health Organization

Amendment History

Amendment 1, Protocol v.2.0

The main purpose of this amendment is to address ICH-GCP content requirements and to incorporate changes and clarifications based on feedback received by investigators.

Amendment 2, Protocol v.3.0

The main purpose of this amendment is to incorporate changes and clarifications based on feedback received by investigators and IRB.

Amendment 3, Protocol v.4.0

The main purpose of this amendment is to revise the interim analysis section and refine the case monitoring workflow.

Synopsis

Title of study	Multicenter, Randomized, Double Blind, Parallel Placebo Controlled, Phase III Clinical Trial to Evaluate the Efficacy, Safety and Immunogenicity of Inactivated SARS-CoV-2 Vaccines in Healthy Population 18 years old and above
Protocol number	CNBG2020003SQ
Sponsor	China National Biotec Group Company Limited (CNBG) 16th Floor, Fortune tower B, Chaoyang, Beijing, China,100029
Phase of development	Phase III
Planned study duration	Up to 1.5 year. It is designed to be completed when last vaccinated subject is followed-up for a calendar year, unless stopped earlier or extended following recommendation of the DSMB.
Subject participation duration	Planned – up to 1 year.
Locations	The trial will be conducted at approximately 10 institutions in Middle East Area (MEA) and could be extended outside MEA.
Study population	Healthy subjects aged 18 years old and above
Planned number of subjects	Total sample size is 45,000 or more, which are randomly allocated into investigational vaccine 1, investigational vaccine 2 and placebo control group.
Study design	Multicenter, Randomized, Double Blind, Placebo Controlled, Parallel
Investigational Product characteristics	WIBP: The inactivated SARS-CoV-2 Vaccine (Vero cell) is prepared by inoculating Verda Reno cells (Vero cell) with SARS-CoV-2 WIV04 strain, culturing, harvesting, inactivating, clarifying, concentrating, second inactivating, purifying and adding aluminum hydroxide adjuvant. BIBP: The inactivated SARS-CoV-2 Vaccine (Vero cell) is prepared by inoculating Verda Reno cells (Vero cell) with SARS-CoV-2 HB02 strain, culturing, harvesting, inactivating, clarifying, concentrating, purifying and adding aluminum hydroxide adjuvant.
Indication	Prevent SARS-CoV-2 caused disease (COVID-19)
Objectives	**Primary objective** To evaluate the efficacy against COVID-19 of inactivated SARS-CoV-2 Vaccines (Vero Cell) after 14 days following 2 doses of immunization in healthy subjects aged 18 years old and above **Secondary objectives** To evaluate the safety of inactivated SARS-CoV-2 Vaccines (Vero Cell) in healthy subjects aged 18 years old and above To evaluate the immunogenicity of inactivated SARS-CoV-2 Vaccines (Vero Cell) in healthy subjects aged 18 years old and above

	To evaluate the vaccine efficacy against severe cases of COVID-19 and deaths accompanied by COVID-19 of inactivated SARS-CoV-2 Vaccines (Vero Cell) after 14 days following 2 doses of immunization. **Exploratory study objective** To explore the anti-SARS-CoV-2 neutralizing antibody protective level against COVID-19 (immunological surrogate endpoint). The occurrence of ADE/VED after immunization
Study design	This clinical trial is conducted in multicenter, randomized, double blind, placebo-controlled design. Immunization schedule: 2 doses of investigational vaccines or placebo are inoculated to the deltoid muscle of the upper arm according to the immunization schedule of D0 & D21 (+7 days). **Safety observation** After each dose of vaccination, the subject is observed for 30 minutes on site, and local and systemic adverse events are collected. Within D0 & D21 (+7 days), the local and systemic reactions of the subjects are actively followed up and recorded on the vaccination diary card. Serious adverse events (SAE) need to be monitored within 12 months after vaccination, and followed up, recorded, and reported as required. **Efficacy observation** After the subjects are enrolled in the group, the monitoring of SARS-CoV-2 infection cases will begin. Planned and active follow-up is carried out on the subjects, and a monitoring network is established in local medical and health institutions to monitor SARS-CoV-2 infection-like cases in the subjects. Those diagnosed as suspected cases by clinicians will be studied as epidemiological case, including nasopharyngeal swabs, sputum and/or other lower respiratory secretions, venous blood in acute and convalescent stages are collected. SARS-CoV-2 nucleic acid will be tested by PCR method, or SARS-CoV-2 specific antibody test is performed. Subjects with positive nucleic acid are confirmed cases of COVID-19. (refer to case monitoring flowchart). The incidence of confirmed SARS-CoV-2 disease in three groups of study samples is calculated and the epidemiological protection rate and confidence interval of SARS-CoV-2 inactivated vaccine against SARS-CoV-2 disease are analyzed. **Immunogenicity observation** Subjects will be enrolled into the immunogenicity subgroups to evaluate the antibody response of the subjects to the Inactivated SARS-CoV-2 Vaccines/placebo. Collect the serums of 900 or more subjects at each site where allocated sample size is greater than 900 in 28 days after 2 doses of immunization, to explore the anti-SARS-CoV-2 neutralizing antibody protective level against COVID-19. **Case Definition** **Suspected cases:** Comprehensive judgment based on epidemiological history and clinical symptoms:

	Have any of the epidemiological history, and have two or more A symptoms, or have one or more B symptoms; If there is no clear epidemiological history, they should have two or more A symptoms or one or more B symptoms and detectable SARS-CoV-2 specific IgM; or have two or more A symptoms and One or more B symptoms. **① Epidemiological history** A. Long-term residence or stay in the affected area for more than 7 days is deemed to have an epidemiological history; or B. History of travel or residence in the community where the case was reported within 14 days before the onset of illness; or C. In contact with SARS-CoV-2 infected or asymptomatic infected persons within 14 days before the onset; or D. Cluster cases (2 or more cases of fever and/or respiratory symptoms occurred in a small area such as home, office, school, etc. within 2 weeks). **② Clinical symptoms** Symptoms A (last for at least 2 days): fever (axillary temperature ≥37.5℃); chills; sore throat; fatigue; nasal congestion or runny nose; body pain, muscle pain; headache; nausea or vomiting; diarrhea. Symptoms B: Cough; new taste or smell disorders; shortness of breath or difficulty breathing; imaging features of COVID-19 **Confirmed cases**: On the basis of the clarification of the suspected case, the COVID-19 PCR diagnosis is positive. **Differential diagnosis**: Encourage any possible pathogenic differential diagnosis. **Confirmed mild COVID-19 cases:** The clinical symptoms were mild, and there was no sign of pneumonia on imaging. **Confirmed moderate COVID-19 cases:** Showing fever and respiratory symptoms with radiological findings of pneumonia. **Confirmed severe COVID-19 cases**: Confirmed COVID-19 case meeting any one of the following criteria: ● Respiratory distress (RR≥30 breaths/min); ● Oxygen saturation≤93% at rest; ● Arterial partial pressure of oxygen (PaO2)/ fraction of inspired oxygen (FiO2)≦

	300mmHg (1mmHg=0.133kPa); ● The clinical symptoms progressively worsened, and the chest imaging showed >50% obvious lesion progression within 24-48 hours. **Confirmed Critical COVID-19 cases**: Confirmed COVID-19 case meeting any one of the following criteria: ● Respiratory failure and requiring mechanical ventilation; ● Shock; ● With other organ failure that requires ICU care; ● Death
Inclusion criteria	1. Healthy subjects aged 18 years old and above 2. By asking for medical history and physical examination, the investigator judged that the health condition is well. 3. Female subjects of childbearing age are not nursing or pregnant at the time of enrolment (negative urine pregnancy test) and have no family planning within the first 3 months after enrolment. Effective contraceptive measures have been taken within 2 weeks before inclusion. 4. During the whole follow-up period of the study, be able and willing to complete the whole prescribed study plan. 5. With self-ability to understand the study procedures, the informed consent & voluntarily sign an informed consent form and be able to comply with the requirements of the clinical study protocol.
First dose exclusion criteria	1. Confirmed acute cases of SARS-CoV-2 infection; 2. With a medical history of SARS, MERS virus infection (self-report, on-site inquiry); 3. Fever (axillary temperature > 37.0 ℃), dry cough, fatigue, nasal obstruction, runny nose, pharyngeal pain, myalgia, diarrhea, shortness of breath and dyspnea within 14 days before vaccination（Tympanic temperature / Temporal artery temperature = Axillary temperature + (0.5 ℃); 4. Positive urine pregnancy test result; 5. Body temperature axillary > 37.0 ℃ before vaccination（Tympanic temperature / Temporal artery temperature = Axillary temperature + (0.5 ℃); 6. With previous severe allergic reactions (such as acute allergic reactions, urticaria, skin eczema, dyspnea, angioneurotic edema or abdominal pain) or allergy to known ingredients of the inactivated SARS-CoV-2 vaccine; 7. With a medical history or family history of convulsion, epilepsy, encephalopathy or mental illness; 8. With congenital malformation or developmental disorder, genetic defects, severe malnutrition, etc.; 9. With known or suspected diseases include acute respiratory diseases (e.g. influenza like illness, acute cough, sore throat), severe cardiovascular diseases, severe liver diseases, severe kidney diseases, uncontrollable hypertension (systolic

	blood pressure > 150 mmHg, diastolic blood pressure > 90 mmHg), diabetic complications, malignant tumors, various acute diseases, or acute attack period of chronic diseases. 10. Has been diagnosed with congenital or acquired immune deficiency, HIV infection, lymphoma, leukemia or other autoimmune diseases; 11. With a history of coagulation dysfunction (such as coagulation factor deficiency, coagulation disease); 12. Receiving anti-TB therapy; 13. Receiving immune enhancement or inhibitor therapy within 3 months (continuous oral or IV administration for more than 14 days); 14. Vaccinated live attenuated vaccine within 1 month before vaccination and other vaccines within 14 days before vaccination; 15. Received blood products within 3 months before vaccination; 16. Received other investigational drugs within 6 months before vaccination; 17. Other circumstances judged by investigators that were not suitable for participating in this clinical trial.
Exclusion criteria for the second dose of vaccination	1. Urine pregnancy test positive. 2. Patients with high fever (body temperature ≥ 39.0 ℃) lasting for 3 days after the previous dose of vaccine and severe allergic reaction. 3. Serious adverse reactions causally related to previous dose of vaccine. 4. Reach the endpoint of the clinical study. 5. Other reasons for exclusion according to investigator.
Trial endpoint	**Endpoint of vaccine efficacy** **Primary endpoint** Vaccine efficacy against COVID-19 after 14 days following 2 doses of vaccination in healthy subjects aged 18 years old and above. All confirmed cases are all confirmed by EAC blinded review. **Secondary endpoint** To evaluate the vaccine efficacy against severe cases of COVID-19 and deaths accompanied by COVID-19 after 14 days following 2 doses of immunization. **Exploratory endpoint** To explore the anti-SARS-CoV-2 neutralizing antibody protective level against COVID-19 The occurrence of ADE/VED after immunization. **Immunogenicity endpoint** The four-fold increase rate, GMT and GMI of anti-SARS-CoV-2 neutralizing antibody in 14 days after full course of immunization.

	The 4-fold increase rate, GMT and GMI of anti-SARS-CoV-2 neutralizing antibody in 28 days after 2 doses of immunization. The GMT of anti-SARS-CoV-2 neutralizing antibody in 3rd month, 6th month, 9th month, and 12th month after 2 doses of immunization. **Safety endpoints** • The incidence of any adverse reactions/events within 30 minutes after each dose of vaccine • The incidence of solicited adverse reactions/events within D0~7 and unsolicited adverse reactions/events within D8~21 days after first dose of vaccination. The incidence of solicited adverse reactions/events within D0 ~ 7 and unsolicited adverse reactions/events within D8~28 days after second dose of vaccination. • The incidence of serious adverse events (SAE) from the beginning of the first dose to 12 months after the whole course of immunization.
Statistical Methods	**(1) General considerations** Quantitative data will be described by mean, median, standard deviation, minimum and maximum. Frequency and percentage will be used to describe qualitative data and ordinal data. All analysis will be performed by using SAS 9.4 or later version. **(2) Subject disposition and demographics** The number of subjects randomized, discontinued and completed in each group will be summarized. The discontinued subjects will be listed, including the reason for discontinuation. The number of subjects in the analysis sets will be presented as well. The demographics of all subjects will be summarized by groups. **(3) Efficacy analysis** The number of cases of admission, dropout, elimination, blood collection, dropout reasons, combined medication and combined vaccines in the experimental and placebo groups shall be described. The percentage of dropout and concomitant medication in the experimental and placebo groups shall be compared with χ^2 test or Fishers exact test. **Protection efficacy (FAS, mFAS and PPS analysis):** The person-year incidence rate of COVID-19 after 14 days following two-dose of vaccination will be calculated in Vaccine-1, Vaccine-2 and placebo groups. Vaccine efficacy from person-year incidence rate of Vaccine-1 and Vaccine-2 with the corresponding 95% CIs will be estimated. The differences between Vaccine-1, Vaccine-2 and placebo will be compared by using Poisson regression model. The person-year incidence rate is calculated by (number of confirmed cases during the effective follow-up period/number of observation years of all vaccinated subjects during the effective follow-up period) $\times$ 100%. In the calculation of person years in exposure, the start date is after 14 days following the 2nd dose. The end date is the

	diagnosed date of COVID-19 case for ones who are confirmed as COVID-19 cases or last follow-up date for others. Vaccine efficacy (VE) = 1- (person-year incidence in vaccine group/ person-year incidence in placebo group). Vaccine efficacy after 14 days following two-dose vaccination will be evaluated based on mFAS and PPS. The VE from mFAS population is the primary result, and the efficacy from PPS population is a sensitivity analysis result. Furthermore, the same statistical methods will be employed to estimate the VE after one dose based on FAS population. Kaplan-Meier plot will be used to depict the incidence of COVID-19 from FAS population. The same statistical methods as above are used to evaluate VEs against severe cases of COVID-19 and deaths accompanied by COVID-19. **(4) Immunogenicity analysis (FAS and PPS analysis):** Statistical description: The antibody titer should be logarithmically transformed. Minimum value, maximum value, median and quartile spacing, GMT and 95% CI should be shown. Comparison of antibody levels before immunization: Logarithmic conversion was carried out on antibody titers, and two independent sample T tests (normal and homogeneous variance) or corrected T tests (normal but uneven variance) shall be used to compare the GMT of neutralizing antibodies against COVID-19 before immunization between the experimental and placebo groups with various ages. Comparison of antibody levels after immunization: ✓ calculate the antibody 4-fold increase rate and 95% CI of anti-SARS-CoV-2 antibody in the experimental and placebo groups with various ages after immunization, and make superiority comparison. If the lower limit of 95% CI of antibody 4-fold increase rate is $\geqslant$ 10%, the superiority hypothesis is valid; ✓ calculate 95% CI of GMT ratio of anti-SARS-CoV-2 antibody in the experimental and placebo group after immunization. If the lower limit of 95% CI ratio is $\geqslant$ 1.1, the superiority hypothesis is valid; ✓ calculate the GMI and 95% CI of anti-SARS-CoV-2 antibody in the experimental group after immunization. **(5) Safety analysis (SS analysis)** Describe the frequency and number and incidence of adverse reactions/events. If a subject manifest the same adverse reaction/events repeatedly, the description on this adverse reactions/evens should indicate the most severity, the closest relationship with vaccination and the earliest starting time. However, in the list of adverse reactions/events, all adverse reactions/events will be listed. Using χ^2 test or correct χ^2 test or Fishers exact test, the incidence of total adverse reactions, systemic adverse reactions, local adverse reactions and unexpected adverse

	reactions in the experimental and placebo groups within 30 minutes, 0-7 days and 8-28 days after inoculation of each dose were compared χ^2 test or correct χ^2 test or Fishers exact is used to compare the difference of SAE incidence rate between the experimental and placebo groups within 360 days after the whole inoculation. The rank sum of two independent samples is used to compare the average grade of adverse reactions in the experimental and placebo groups. In the analysis of adverse events/reactions stratified by symptoms and SAE, MedDRA coding is used to carry out comparative analysis of SOC level and PT level respectively .
The interim analyses	Two interim analyses are planned in this trial when 1/3 and 2/3 of expected COVID-19 cases are observed. Early stopping for efficacy is considered in the interim analysis. Lan DeMets O'Brien-Fleming spending function is employed to control the family-wise type I error within 5% of two-sided. When the number of COVID-19 cases in any one vaccine (vaccine-1 or vaccine-2) and placebo groups achieves 50, the first interim analysis will be performed and the corresponding nominal significance level is α_1 =0.0001 (one-sided). When 100 COVID-19 cases in any one vaccine (vaccine-1 or vaccine-2) and placebo groups are observed, the second interim analysis will be conducted and the corresponding nominal significance level is α_2=0.0060 (one-sided). If the null hypothesis is not rejected in the two interim analyses, the nominal significance level of final analysis is α_3=0.0231 (one-sided). In the practical clinical trial, the nominal significance level will be calculated based on the number of COVID-19 cases observed at the interim analysis from pre-specified Lan DeMets O'Brien-Fleming spending function. The interim analyses will be performed by DSMB. Since CNBG's COVID-19 inactivated vaccine clinical trial project is following 1 (vaccine 1):1 (vaccine 2):1 (control) three-group settings, in order to ensure the integrity of the clinical trial, the research team cannot access to any information regarding the number of endpoint cases in either the vaccine group or the control group, therefore, the number of cases occurred in individual group can only be unblinded and monitored independently by the DSMB. When the total number of cases in one of the vaccine group (such as vaccine 1) and the control group reaches 50, the DSMB will conduct the first interim analysis, if the efficacy of the vaccine 1 reaches statistical criterion, i.e. the statistical test P value is less than 0.0001 (corresponding to the efficacy of point estimates of more than 76%), which could suggest that the vaccine 1 satisfies the basic regulatory requirement on the efficacy of a inactivated SARS-CoV-2 vaccine. When the total number of cases in the other vaccine group (such as vaccine 2) and the control group also reaches 50, at which time, the same statistical test will be carried out. If the statistical criteria are also met, it would also indicate that the efficacy of vaccine 2 has met with the basic requirements. If one vaccine group or both vaccine groups could not reach statistical criteria at the first interim analysis, the cases will be continuously monitored until 100 cases across one of the vaccine groups (such as vaccine 1) and the control group are monitored by the DSMB

	and the second interim analysis will be conducted, if the efficacy of the vaccine 1 reaches statistical criterion, i.e. the statistical test P value is less than 0.006 (corresponding to the efficacy of point estimates of more than 59%), which could suggest that the vaccine 1 satisfies the basic regulatory requirement on the efficacy of a inactivated SARS-CoV-2 vaccine. When the total number of cases in the other vaccine group (such as vaccine 2) and the control group also reaches 100, the same statistical analysis will be carried out. If the statistical criteria are also met, it would also indicate that the efficacy of vaccine 2 has met with the basic requirements. If one vaccine group or both vaccine groups could not reach statistical criteria at the second interim analysis, the cases will be continuously monitored until 150 cases across one of the vaccine groups (such as vaccine 1) and the control group are monitored by the DSMB and the final analysis will be conducted, if the efficacy of the vaccine 1 reaches statistical criterion, i.e. the statistical test P value is less than 0.023 (corresponding to the efficacy of point estimates of more than 50%), which could suggest that the vaccine 1 satisfies the basic regulatory requirement on the efficacy of an inactivated SARS-CoV-2 vaccine, otherwise, the efficacy of vaccine 1 will be considered as inconclusive. When the total number of cases in the other vaccine group (such as vaccine 2) and the control group also reaches 150, the same statistical analysis will be carried out. If the statistical criteria are also met, it would also indicate that the efficacy of vaccine 2 has met with the basic requirements, otherwise, the efficacy of vaccine 2 will be considered as inconclusive. If vaccine 1 (or vaccine 2) is conditionally approved for marketing authorization based on interim analysis data from a pivotal clinical efficacy trial, then the cases should be continuously monitored post-marketing authorization, until 150 cases are monitored across vaccine 1 (or vaccine 2) study group and control group in order to complete the clinical trial.

1. Introduction

The inactivated SARS-CoV-2 vaccine (Vero cell) developed by CNBG is used to prevent the disease caused by SARS-CoV-2, which has been approved for clinical trial by National Medical Products Administration (NMPA) in accordance with the Drug Administration Law of the People's Republic of China. The product qualified by National Institute for Food and Drug Control (NIFDC) , and permitted to use as investigational vaccine in clinical trials.

CNBG has obtained the clinical approval for Phase III, to further evaluate the vaccine efficacy, safety and immunogenicity against SARS-CoV-2 through multicenter randomized, double-blinded, placebo parallel control method in healthy subjects.

2. Background and Rationale

2.1 Disease Background

Coronavirus belongs to Coronavirus family and is a pathogen that can spread across races and is easy to cause respiratory diseases. Coronaviruses are divided into four genera, namely (a-coronaviruses, β-coronaviruses, γ-coronaviruses, and δ-coronaviruses. According to the gene sequence, β-coronaviruses are divided into four subgroups: A, B, C and D coronaviruses. In 2018, the World Health Organization (WHO) further divided β-coronavirus into five major subgroups: Embecovirus (formerly A), Sarbecovirus (formerly B), Merbecovirus (formerly C), Nobecovirus (formerly D) and Hibecovirus. Among them, the first two subgroups mainly infect mammals, and the coronaviruses that can infect human are HCoV-OC43, HCoV-229E, SARS-CoV, HCoV-NL63, HCoV-HKU1, MERS-CoV and 2019-nCoV, respectively. 2019-nCoV belongs to Sarbecovirus subgroup [1]. In 2003, Severe Acute Respiratory Syndrome (SARS) infected more than 8,000 people with a mortality rate of nearly 10%. In 2012, the Middle East Respiratory Syndrome (MERS) infected nearly 2,500 people and the mortality rate was as high as 37%. In December 2019, patients with pneumonia of unknown causes showed fever, cough, dyspnea, accompanied by medical imaging change of patchy diffuse infiltration of the lungs [2]. Through genome sequencing and analysis of lower respiratory tract alveolar lavage fluid samples from patients with pneumonia of unknown cause, a novel coronavirus different from any known virus was found. WHO named the virus SARS-CoV-2, and the disease caused by the virus was named COVID-19. WHO listed the epidemic as a public health emergency of international concern. At present, the source of infection of the disease is mainly patients infected with SARS-CoV-2. Asymptomatic infected people may also become the source of infection. Airway droplets and close contact transmission are the main transmission routes. There is a possibility of aerosol transmission under long-term exposure to high concentration aerosol in a relatively closed environment. Since SARS-CoV-2 can be isolated from feces and urine, attention should be paid to aerosol or contact transmission caused by feces and urine to environmental pollution. The population is generally susceptible, and the prognosis of the elderly and those with chronic diseases is poor. The symptoms of children's cases are relatively mild. As of June 26th, 2020, more than 9.6 million people have been confirmed and 486,000 people have died worldwide. The fatality rate is far lower than that of SARS and MERS. However, the number of infections and the

overall mortality rate are significantly higher than that of SARS and MERS. Therefore, the research and development of 2019-NCOV vaccine is urgent.

Preclinical research literature of SARS-CoV and MERS-CoV coronavirus vaccines shows that some candidate inactivated and recombinant coronavirus vaccines may have antibody dependence enhancement (ADE), which is a potential safety problem to be paid attention to and solved in this clinical research.

2.2. Pathogenic Background

SARS-CoV-2 belongs to the coronavirus family of the order Nidovirales, 80 ~ 120 nm in diameter, with about 30,000 bases of enveloped single strand positive strand RNA viruses. Its genetic material is the largest of all known RNA viruses. It has a methylation "cap" at that 5 'end of the RNA strand, and a polyA "tail" structure at 3 'end. This structure is very similar to eukaryotic mRNA, also an important structural basis for its genomic RNA itself to play the role of translation template. 2019-nCoV first uses viral RNA as a template to express RNA polymerase, then RNA polymerase completes transcription and synthesis of negative strand RNA, synthesis of various structural protein mRNA, and replication of viral genome RNA, and assembles and generates new coronavirus particles at endoplasmic reticulum, which are secreted out of cells through Golgi apparatus to form a cycle of virus replication. The homology between its genome and MERS virus is about 50%.

Coronavirus consists of nucleocapsid protein (N protein), spike protein (S protein), envelope protein (E protein), Membrane protein (M protein), Hemagglutinin-esterase (HE protein) and ribonucleic acid (RNA). The S protein makes the virus crown-like, playing a critical role in the recognition and binding of host cell surface receptors. The high similarity of amino acid sequences between the receptor-binding domain (RBD) domain of SARS-CoV-2 and SARS-CoV and the predicted protein structure indicate that SARS-CoV-2 can effectively use human angiotensin converting enzyme II (ACE2) as a receptor to enter cells, potentially promoting human-to-human transmission [3]. The experimental results show that the affinity between ACE2 protein and SARS-CoV-2 is about 20 times than that of SARS-CoV virus, resulting in high infectivity of SARS-CoV-2 [4]; M protein participates in the formation and germination of virus envelope and transports nutrients. HE protein is a short bulge forming the envelope, which may be related to the early adsorption of coronavirus. HE protein of some coronaviruses can cause agglutination of red blood cells and adsorption of red blood cells.

Based on current research and understanding, viruses are sensitive to ultraviolet rays and heat. At 56℃ for 30min, diethyl ether, 75% ethanol, chlorine-containing disinfectant, peracetic acid, nitrogen imitation and other lipid solvents can effectively inactivate the virus, while chlorhexidine cannot effectively inactivate the virus [5].

2.3. Vaccine Background

With the spread of the SARS-CoV-2 epidemic in the world, vaccines have become the best weapon for epidemic prevention and control. After the outbreak of the epidemic, many domestic and international enterprises and scientific research institutions began the research and development of the SARS-CoV-2 vaccine.

At present, no vaccine to prevent coronavirus disease (COVID-19) in 2019 has been approved for listing. According to public reports, since the rapid spread of the epidemic, as of Oct 2nd, more than 118 companies and scientific research institutions around the world are developing 193 SARS-CoV-2 vaccine projects. Vaccine products mainly include recombinant protein vaccine, inactivated vaccine, viral vector vaccine, DNA vaccine and mRNA vaccine, of which recombinant protein vaccine, DNA vaccine and mRNA vaccine have made rapid progress. Based on the experience accumulated in the research and development of coronavirus vaccines in the past, the target of vaccines is also mainly focused on S protein. Currently there are 42 candidate vaccines in clinical evaluation stage, including nucleic acid vaccines, vector vaccines and inactivated virus vaccines. Among them, China has approved 10 products for clinical research, 4 of which are inactivated virus vaccines and the rest are based on other technical platforms.

Inactivated Virus Vaccine Inactivates the virus obtained by culture by heating or chemical methods. The inactivated virus loses its pathogenicity and retains the main antigenic characteristics of the virus capsid, which can stimulate the specific immune response of human body. The research and development process of inactivated virus vaccine is simple and clear. Only by screening out appropriate virus strains and establishing appropriate virus inactivation and purification methods can the preparation of vaccine products be completed quickly.

With the development of COVID-19 epidemic, the SARS-CoV-2 vaccine is the only effective way to prevent the spread of 2019-nCoV in the long run.

3. Trial Objectives and Purpose

To evaluate the efficacy, safety and immunogenicity of the inactivated SARS-CoV-2 vaccines (Vero cell) developed by Wuhan/Beijing Institute of Biological Products Co., Ltd in healthy people aged 18 years old and above.

3.1. Primary Objective

To evaluate the efficacy against COVID-19 of inactivated SARS-CoV-2 Vaccines (Vero Cell) after 2 doses of immunization in healthy subjects aged 18 years old and above.

3.2. Secondary Objective

To evaluate the safety of inactivated SARS-CoV-2 vaccines in healthy subjects aged 18 years old and above;

To evaluate the immunogenicity of inactivated SARS-CoV-2 vaccines in healthy subjects aged 18 years old and above;

To evaluate the vaccine efficacy against severe COVID-19 and deaths associated with COVID-19 after 14 days following 2-dose immunization.

3.3. Exploratory Study

Explore the anti-SARS-CoV-2 neutralizing antibody protective level after 14 days following 2-dose immunization (immunological surrogate endpoint).

The occurrence of ADE/VED after immunization.

4. Trial Design and Description

4.1. Description of the Trial

This is a multicenter, randomized, double-blind, placebo-controlled, Phase 3 trial in 45,000 health subjects.

The study consists of the following 2 periods:

- A vaccination period of up to 6 weeks

After voluntary signed consent the subject will be assessed for general health condition and if eligible is confirmed immunization of 2-doses of investigational vaccine or placebo are inoculated to the deltoid muscle of the upper arm according to the D0, D21 (+7 Days) immunization schedule.

- A safety follow-up period of up to 12 months after vaccination.

After completion of both vaccination and immediate safety assessment (till visit 10), a period of safety follow-up begins with regular subject visits and phone contacts.

Subjects will be randomized in a 1:1:1 ratio to receive either SARS-CoV-2 WIV04 vaccine or SARS-CoV-2 HB02 vaccine or placebo two times for the period of maximum 28 days.

4.2. Procedures and Methodology

Sample size: Total of 45,000 or more healthy volunteers aged 18 years old and above will be enrolled, of whom 15,000 subjects will receive the investigational vaccine 1, 15,000 subjects will receive the Investigational vaccine 2 and 15,000 subjects will receive Placebo.

Immunization schedule: 2 doses of investigational vaccine or placebo will be injected into the deltoid muscle of upper arm according to the immunization schedule of D0, D21 (+7 Days).

Safety observation: After each dose of vaccination, subjects will remain in the clinical trial site for 30 minutes, the local and systemic adverse events will be assessed. With D0, D21 (+7 Days), the local and systemic solicited reactions will be actively followed up and recorded on the vaccination diary card/contact card. Serious adverse events (SAE) need to be monitored for 12 months after vaccination, and followed up, recorded, and reported as required.

Immunogenicity observation: 900 or more subjects at each site where allocated sample size is greater than 900 will be enrolled into immunogenicity subgroups, to evaluate the antibody response of subjects to inactivated SARS-CoV-2 vaccine/placebo.

Observation of vaccine efficacy:

The cases of COVID-19 will be monitored from the first dose vaccination. It is necessary to follow up visit on a planned and active basis and establish monitoring networks in local neighborhood committees (villages) and medical and health institutions and be able to know the subjects which have fever, dry cough, fatigue caused by unknown reasons. Nasopharyngeal swabs, sputum, other lower respiratory tract secretions and venous blood will be collected from patients suspected of SARS-CoV-2 infection with or without nasal obstruction, runny nose, pharyngeal pain, myalgia, or diarrhea. PT-PCR will be used to detect the nucleic acid of the SARS-CoV-2 and the specific antibody of the SARS-CoV-2 will also tested. The incidence rate of COVID-19 in two groups of study samples will be calculated and the epidemiological protection rate and confidence interval of inactivated SARS-CoV-2 vaccine against COVID-19 will be analyzed.

Case Definition:

Suspected cases:

Comprehensive judgment based on epidemiological history and clinical symptoms:

Have any of the epidemiological history, and have two or more A symptoms, or have one or more B symptoms;

If there is no clear epidemiological history, they should have two or more A symptoms or one or more B symptoms and detectable SARS-CoV-2 specific IgM; or have two or more A symptoms and One or more B symptoms.

① **Epidemiological history**

A. Long-term residence or stay in the affected area for more than 7 days is deemed to have an epidemiological history; or

B. History of travel or residence in the community where the case was reported within 14 days before the onset of illness; or

C. In contact with SARS-CoV-2 infected or asymptomatic infected persons within 14 days before the onset; or

D. Cluster cases (2 or more cases of fever and/or respiratory symptoms occurred in a small area such as home, office, school, etc. within 2 weeks).

② **Clinical symptoms**

Symptoms A (last for at least 2 days): fever (axillary temperature ≥37.5℃); chills; sore throat; fatigue; nasal congestion or runny nose; body pain, muscle pain; headache; nausea or vomiting; diarrhea.

Symptoms B: Cough; new taste or smell disorders; shortness of breath or difficulty breathing; imaging features of COVID-19

Confirmed cases:

On the basis of the clarification of the suspected case, the COVID-19 PCR diagnosis is positive.

Differential diagnosis:

Encourage any possible pathogenic differential diagnosis.

Confirmed mild COVID-19 cases:

The clinical symptoms were mild, and there was no sign of pneumonia on imaging.

Confirmed moderate COVID-19 cases:

Showing fever and respiratory symptoms with radiological findings of pneumonia.

Confirmed severe COVID-19 cases:

Confirmed COVID-19 case meeting any one of the following criteria:

- Respiratory distress (RR≥30 breaths/min);
- Oxygen saturation≤93% at rest;
- Arterial partial pressure of oxygen (PaO2)/ fraction of inspired oxygen (FiO2)≦300mmHg (1mmHg=0.133kPa);
- The clinical symptoms progressively worsened, and the chest imaging showed >50% obvious lesion progression within 24-48 hours.

Confirmed Critical COVID-19 cases:

Confirmed COVID-19 case meeting any one of the following criteria:

- Respiratory failure and requiring mechanical ventilation;
- Shock;
- With other organ failure that requires ICU care;
- Death

We will make an interim analysis of the change of incidence, according to which the protocol will be adjusted as necessary.

Please refer to Table 1. for the sample size and procedures of the clinical trial.

Table 1: Sample Size and Program of Phase III Clinical Trial

Age group	Vaccine	Immunization Schedule	Sample Size	Safety	Blood Collection timing
Subjects aged 18 years old and above	Investigational Vaccine-1	D0, D21 (+7 Days)	15,000	1. Collecting AE and SAE within D1-8 and D0, D21 (+7 Days) after each dose of immunization; 2. Collect SAE for 12 months of after immunization	Collect blood samples from all subjects before vaccination, D14 after 2-dose vaccination; Collect blood samples from 900 or more subjects on D28, 3rd, 6th ,9th,12th month after 2 doses immunization at each site where allocated sample size is greater than 900.
	Investigational Vaccine -2		15,000		
	Placebo		15,000		
Total			45,000		

Note: Vaccination window period +7 days. Blood collection window+10 days.

4.3. Consideration of control group

At present, there is no Inactivated SARS-CoV-2 vaccine on the market. In order to ensure the scientific evaluation of the vaccine, considering that the final product of this vaccine contains adjuvant, aluminum hydroxide adjuvant with the same dose is selected as placebo control.

4.4. Endpoints

4.4.1 Vaccine Efficacy Endpoint

Primary Endpoint

The efficacy against COVID-19 of the inactivated SARS-CoV-2 vaccine (Vero cell) after 14 days following 2 doses of immunization in healthy subjects aged 18 years old and above.

Secondary endpoint

The efficacy against severe cases of COVID-19 and deaths accompanied by COVID-19 of the inactivated SARS-CoV-2 vaccine (Vero cell) after 14 days following 2 doses of immunization.

Exploratory endpoint

The protective level of anti-SARS-CoV-2 neutralizing antibody after 14 days following 2 doses of immunization.

4.4.2. Immunogenicity Endpoint

Collect blood samples from all subjects in 14 days after 2 doses.

If a confirmed case is found, the antibody level of the confirmed case needs to be tested, and the patient's four-fold increase rate, GMT, and GMI of the anti-SARS-CoV-2 antibody in 14 days after 2 doses should be analyzed to explore the immunogenicity endpoint. The four-fold increase rate, GMT, and GMI of the anti-SARS-CoV-2 antibody 28 days after 2 doses of immunization;

The GMT of the anti-SARS-CoV-2 antibody in 3rd month, 6th month, 9th month, and 12th month after 2 doses of immunization;

4.4.3. Safety Endpoint

The incidence of adverse reactions/events within 30 minutes after each dose of vaccination.

The incidence of solicited and unsolicited adverse reactions/events within D0 ~ 7, and unsolicited events and SAEs within D8 ~ 21/28 after each dose of vaccination.

The incidence of serious adverse events (SAE) from the first dose of vaccination to 12 months after the last dose of vaccination.

4.5. Vaccine efficacy

Research Indicators

$$\text{Vaccine efficacy} = \left(1 - \frac{\text{incidence density of vaccine group}}{\text{incidence density of placebo group}}\right) \times 100\%.$$

Incidence density during the follow-up period = (number of confirmed cases during the effective follow-up period/number of observation years of all vaccinated subjects during the effective follow-up period) × 100%. In the calculation of the number of observation years, the termination of follow-up period is considered as follows: for COVID-19 cases in the subjects, once there are confirmed cases that meet the diagnostic criteria of the "Diagnosis and Treatment Protocol for COVID-19" (the latest version), relevant data will be collected to complete follow-up; For non-cases, the follow-up of vaccine efficacy will be continued until the day of withdrawal from the study.

4.6. Evaluation of immunogenicity indicators

The 4-fold increase rate, GMT and GMI of anti-SARS-CoV-2 antibody.

The presence of four-fold growth rate in the anti-SARS-CoV-2 antibody: for anti-SARS-CoV-2 antibody, four-fold growth rate or more increase in antibody titers after vaccination.

GMT: geometric mean titer.

GMI: geometric mean titer increases multiple.

4.7. Safety observation parameters and classification standards

4.7.1. Safety observation parameters

Both solicited adverse events and unsolicited adverse events are collected within D0-7, as well as D8-21/28 after vaccination

Solicited injection site (local) adverse events: pain, induration, swelling, rash, flush, pruritus.

Solicited adverse events at non-vaccination sites (systemic): fever, diarrhea, constipation, dysphagia, anorexia, vomiting, nausea, muscle pain (non-vaccination sites), arthralgia, headache, cough, dyspnea, pruritus at non-vaccination sites (no skin damage), skin and mucosal abnormalities, acute allergic reactions, fatigue.

Other unsolicited adverse events: Any adverse events and medical events other than the above occurred during clinical trials, such as acute diseases, accidental injuries, etc.

4.7.2 Adverse Event Classification Standards

Based on No.102 Announcement (2019) issued and implemented by the National Medical Products Administration, "Guidelines for Classification Standards of Adverse Events in Clinical Trials of Prophylactic Vaccines", to determine the adverse events at vaccination sites, adverse events at non-vaccination sites, vital signs and laboratory test indicators after vaccination are determined.

Table 2. Classification of Adverse Events at Injection Site (Local)

Symptoms/ signs	Grade 1	Grade 2	Grade 3	Grade 4
Pain	Does not affect or slightly affects limb movement	Affect physical activity	Affect daily life	Loss of basic self-care ability or hospitalization
Induration *, swelling * * #	2.5-< 5 cm in diameter or 6.25-< 25 cm^2 in area without or slightly affecting daily life	5 ~ < 10 cm in diameter or 25 ~ < 100 cm^2 in area or affecting daily life	Diameter ≥ 10 cm or area ≥ 100 cm^2 or ulceration or secondary infection or phlebitis or aseptic abscess or wound drainage or serious impact on daily life	Abscess, exfoliative dermatitis, necrosis of dermis or deep tissue
Rash *, redness* * #	2.5-< 5 cm in diameter or 6.25-< 25 cm^2 in area without or slightly affecting daily life	5 ~ < 10 cm in diameter or 25 ~ < 100 cm2 in area or affecting daily life	Diameter ≥ 10 cm or area ≥ 100 cm^2 or ulceration or secondary infection or phlebitis or aseptic abscess or wound drainage or serious impact on daily life	Abscess, exfoliative dermatitis, necrosis of dermis or deep tissue
Pruritus	Itching at the inoculation site was relieved by itself or within 48 hours after treatment.	The pruritus at the inoculation site was not relieved within 48 hours after treatment.	Affect daily life	NA

Note: * In addition to directly measuring the diameter for grading evaluation, the progress and changes of measurement results shall also be recorded.

** The maximum measured diameter or area shall be used.

The evaluation and classification of induration and swelling, rash and redness should be based on the functional grade and actual measurement results, and the index with higher grade should be selected.

Table 3. Classification of Adverse Events at Non-injection Site (Systemic)

Symptoms/ signs	Grade 1	Grade 2	Grade 3	Grade 4
Fever * (axillary temperature℃)	37.3 ~ < 38.0	38.0 ~ < 38.5	38.5 ~ < 39.5	≥ 39.5 for more than 3 days
Diarrhea	Slight or transient, 3-4 times/day, abnormal fecal characteristics, or slight diarrhea lasting less than 1 week	Moderate or persistent, 5 ~ 7 times/day, abnormal fecal characteristics, or diarrhea > 1 week	> 7 times/day, abnormal fecal characteristics, or hemorrhagic diarrhea, orthostatic hypotension, electrolyte imbalance, intravenous infusion > 2L	Hypotensive shock, requiring Hospitalization
Constipation *	Need fecal softener and dietary adjustment	Need laxative drugs	Stubborn constipation requires manual dredging or enema.	Toxic Hirschsprung's disease or intestinal obstruction
Dysphagia	Mild discomfort when swallowing	Restricted diet	Diet and conversation are very limited. Do not eat solid food	Do not eat liquid food; Need intravenous nutrition
Anorexia	Loss of appetite but no reduction in food intake	Decreased appetite and food intake, but no significant weight loss	Loss of appetite and significant weight loss	Need measures to intervene (e.g. Gastric tube feeding, parenteral nutrition)
Vomiting	1 ~ 2 times/24 hours without affecting the activity	3 ~ 5 times/24 hours or limited activity	> 6 times within 24 hours or intravenous fluid infusion is required.	Hospitalization or other nutrition is required due to hypotensive shock.
Nausea	Transient (< 24 hours) or intermittent and food intake is basically normal.	Persistent nausea leads to reduced food intake (24-48 hours)	Persistent nausea results in almost no food intake (> 48 hours) or the need for intravenous fluid infusion.	Life-threatening (e.g. Hypotensive shock)
Myalgia (non-vaccination site)	Does not affect daily activities	Slightly affecting daily activities	Severe muscle pain, seriously affecting daily activities	Emergency or hospitalization
Arthralgia	Mild pain, no obstruction of function	Moderate pain; The need for analgesics and/or pain impairs function but does not affect daily activities.	Severe pain; Need for analgesics and/or pain affects daily activities	Disabling pain

Headache	Do not affect daily activities and do not need treatment.	Transient, slightly affecting daily activities, may require treatment or intervention	Seriously affecting daily activities and requiring treatment or intervention	Refractory, requiring emergency or hospitalization
Cough	Transient without treatment	Persistent cough, effective treatment	Paroxysmal cough, uncontrollable treatment	Emergency or hospitalization
Dyspnea	Dyspnea during exercise	Normal activity dyspnea	Difficulty in breathing during rest	Dyspnea, need oxygen therapy, hospitalization or assisted breathing
Non-injection site pruritus (No skin damage)	Mild itching does not affect or slightly affects daily life.	Pruritus Affects Daily Life	Itching makes it impossible to carry out daily life.	NA
Abnormal skin and mucosa	Erythema/itching/color Change	Diffuse rash/maculopapule/dryness/desquamation	Blisters/exudations/desquamation/ulcers	Exfoliative dermatitis involves mucosa, or erythema polymorpha, or suspected Stevens-Johnsons syndrome
Acute allergic reaction**	Local urticaria (blisters) without treatment	Local urticaria, requiring treatment or mild angioedema, without treatment	Extensive urticaria or angioedema requiring treatment or mild bronchospasm	Anaphylactic shock or life-threatening bronchospasm or laryngeal edema
Fatigue	Does not affect daily activities	Affect normal daily activities	Seriously affecting daily activities and unable to work	Emergency or hospitalization

Note: * Axillary temperature is usually used in China, which is converted into tympanic temperature, oral temperature and anal temperature when necessary. Usually, tympanic temperature/temporal artery temperature = axillary temperature +0.5 ℃. When persistent high fever occurs, the cause of high fever should be determined as soon as possible.

* For constipation, attention should be paid to the changes before and after vaccination.

For clinical abnormalities not covered in the above classification Table 3, the intensity classification evaluation of adverse reactions shall be carried out according to the following standards:

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild: short-term (< 48h) or slight discomfort, does not affect activities, does not need treatment	Moderate: Mild or moderate movement restriction, may require medical treatment, no or only mild treatment is required.	Severe: obvious activity Restricted, need to see a doctor and receive treatment, may need to be hospitalized.	Critical: May threaten life, severely restricted activities, requiring monitoring and treatment	Death

4.7.3. Relationship between Adverse Events and Investigational Vaccines

Impossible: Adverse events occur due to other factors, and there is sufficient evidence to prove that adverse reactions/events are caused by other reasons and have nothing to do with vaccination.

Unlikely: The occurrence of adverse events may be caused by other factors, such as the clinical status of the subject, other treatments or accompanying drugs, which are inconsistent with the known adverse reactions of vaccination.

Possible: Adverse events are consistent with known investigational vaccine information, have a reasonable temporal sequence with vaccination, and/or have occurred for vaccination. There is also a causal relationship with the investigational vaccine, but it may also be related to other factors.

Likely: Adverse events are consistent with the known investigational vaccine information and have causal relationship with the investigational vaccine, and cannot be explained by other factors, such as the clinical condition of the subject, other treatments or concomitant medication.

Definite: Adverse events are consistent with the known investigational vaccine information and have a causal relationship with the investigational vaccine, and this relationship cannot be explained by other factors, such as the clinical status of the subject, other treatments or accompanying drugs. In addition, adverse events occurred repeatedly when the subjects used the investigational vaccine again.

5. Selection and Withdrawal of Subjects

The subjects must fulfill all eligibility criteria to be involved in this study. No exemptions from any in-/exclusion criteria will be allowed. If any deviation from eligibility is retrospectively detected for an already randomized subject, the investigator and sponsor must decide immediately whether it is safe to treat this subject further within the study.

5.1. Study Population

5.1.1. Inclusion criteria

1. Healthy subjects aged 18 years old and above;
2. By asking for medical history and physical examination, the investigator judged that the health condition is well.
3. Female subjects of childbearing age were not pregnant at the time of enrolment (negative urine pregnancy test), were not nursing and had no family planning within the first 3 months after enrollment. Effective contraceptive measures have been taken within 2 weeks before enrolment;
4. During the whole follow-up period of the study, be able and willing to complete the whole prescribed research plan;
5. With self-ability to understand the study procedures, the informed consent & voluntarily

sign an informed consent form and be able to comply with the requirements of the protocol.

5.1.2. Exclusion Criteria for the first dose

1. Confirmed acute cases of SARS-CoV-2 infection;
2. With a medical history of SARS, MERS virus infection (self-report, on-site inquiry);
3. Fever (axillary temperature > 37.0 ℃，,tympanic temperature/temporal artery temperature> 37.5 ℃), dry cough, fatigue, nasal obstruction, runny nose, pharyngeal pain, myalgia, diarrhea, shortness of breath and dyspnea within 14 days before vaccination;
4. Positive urine pregnancy test result;
5. Axillary temperature > 37.0 ℃ before vaccination（tympanic temperature/temporal artery temperature> 37.5 ℃）;
6. With previous severe allergic reactions (such as acute allergic reactions, urticaria, skin eczema, dyspnea, angioneurotic edema or abdominal pain) or allergy to known ingredients of the inactivated SARS-CoV-2 vaccine;
7. With a medical history or family history of convulsion, epilepsy, encephalopathy or mental illness;
8. With congenital malformation or developmental disorder, genetic defects, severe malnutrition, etc.;
9. With known or suspected diseases include acute respiratory diseases (e.g. influenza like illness, acute cough, sore throat), severe cardiovascular diseases, severe liver diseases, severe kidney diseases, uncontrollable hypertension (systolic blood pressure > 150 mmHg, diastolic blood pressure > 90 mmHg), diabetic complications, malignant tumors, various acute diseases, or acute attack period of chronic diseases.
10. Has been diagnosed with congenital or acquired immune deficiency, HIV infection, lymphoma, leukemia or other autoimmune diseases;
11. With a history of coagulation dysfunction (such as coagulation factor deficiency, coagulation disease);
12. Receiving anti-TB therapy;
13. Receiving immune enhancement or inhibitor therapy within 3 months (continuous oral or IV administration for more than 14 days);
14. Vaccinated live attenuated vaccine within 1 month before vaccination and other vaccines within 14 days before vaccination;
15. Received blood products within 3 months before vaccination;

16. Received other investigational drugs within 6 months before vaccination;
17. Other circumstances judged by investigators that were not suitable for participating in this clinical trial.

5.1.3. Exclusion criteria for the second dose of vaccine

1. Patients with high fever (axillary temperature ≥ 39.0 ℃) lasting for 3 days after the previous dose of vaccine and severe allergic reaction;
2. Serious adverse reactions with causal relationship with the previous dose of vaccine;
3. Reach the endpoint of the study;
4. Urine pregnancy test positive;
5. for the subjects newly identified or with newly occurred symptoms which does not meet the inclusion criteria for the first dose or meets the exclusion criteria for the first dose after the previous dose of vaccine is vaccinated, the investigator shall determine whether they should continue to participate in the trial;
6. Other reasons for exclusion that investigator believes.

If any of the following occurs during the trial, the relevant subjects are not required to stop the trial:

- Non-specific immunoglobulins were used during the study;
- Continuous oral or IV administration of steroid hormones for 14 days.

5.1.4. Criteria for early withdrawal of subjects from trial

Subjects will be withdrawn from the trial in advance when any of the following conditions occur:

1. The subject or the subject's guardian requests to withdraw from the clinical trial;
2. Intolerable adverse events, whether related to test drugs;
3. The health status of the subjects does not allow them to continue to participate in this trial.
4. The subjects were vaccinated with other investigational vaccines during the study period.
5. Reach the endpoint of clinical trials;
6. Any other reason that the investigator believes.

5.1.5 Criteria for clinical trial suspension or termination

When the incidence of grade 3 and above adverse reactions reaches 15% or above or a case of suspected and unexpected serious adverse reactions (SUSAR) occurs, the sponsor,

investigator, and ethics committee shall discuss whether there is a need to suspend or terminate the clinical trial.

6. Study Treatments

At present, there is no Inactivated SARS-CoV-2 vaccine on the market. In order to ensure the scientific evaluation of the vaccine, considering that the final product of this vaccine contains adjuvant, aluminum hydroxide adjuvant with the same dose is selected as placebo control.

6.1. Study Products Description and Characteristics

The inactivated SARS-CoV-2 vaccines (Vero cell) are prepared by inoculating African green monkey kidney cells (Vero cell) with the SARS-CoV-2 WIV04/HB02 strain, culturing, harvesting, inactivating, clarifying, concentrating, purifying and adding aluminum hydroxide adjuvant. After inoculating the vaccine, the recipients can produce immune response against diseases caused by SARS-CoV-2.

6.1.1. Investigational vaccine-1

Name: Inactivated SARS-CoV-2 vaccine (Vero cell)

Manufacturer: Wuhan Institute of Biological Products Co., Ltd.

Wuhan Institute of Virology, Chinese Academy of Sciences

Specification: 200 WU/dose for each person, 0.5 mL for each dose

Storage conditions: 2-8 ℃

Batch Number of Vaccine: 202006009/202006011

See "Specification Report" of National Institute for Food and Drug Control

6.1.2. Investigational Vaccine-2

Name: Inactivated SARS-CoV-2 vaccine (Vero cell)

Manufacturer: Beijing Institute of Biological Products Co., Ltd.

Specification: 0.5 ml/dose per person, containing 4μg of viral protein

Storage conditions: 2-8 ℃

Batch Number of Vaccine:202005003

See "Specification Report" of National Institute for Food and Drug Control

6.1.3. Placebo control

Name: Inactivated SARS-CoV-2 Vaccine (Vero Cell) Aluminum Adjuvant

Manufacturer: Wuhan Institute of Biological Products Co., Ltd.

Storage conditions: 2-8 ℃

Specification: 0.5 mL for human use every time, without SARS-CoV-2 antigen.

Batch Number and Validity Period: 202006002

See the Specification Report by National Institute for Food and Drug Control.

6.1.4. Production Technology

The preparation of this SARS-CoV-2 vaccine is done by inoculating the isolated and qualified SARS-CoV-2 strain on Vero cells. After culturing the cells, harvesting the virus solution, concentrating, inactivating with β-propiolactone, purifying, and adsorbing with aluminum hydroxide adjuvant, the vaccine is fully prepared. The vaccine production process adopts culture technology to obtain high titer virus harvest solution. After ultrafiltration concentration and column chromatography purification, the virus purified solution with a purity of more than 95% was obtained. After virus inactivation, the monovalent stock solution was prepared, and after adjuvant adsorption, the product was packaged into a finished product. All quality parameters fully met the requirements of "Regulations for Manufacturing and Vero Cell of SARS-CoV-2 Inactivated Vaccine".

- ✓ The whole batch inactivation method is adopted to ensure the inactivation effect, uniformity and immunogenicity of the virus.
- ✓ Chromatography purification process is adopted to improve the purity and safety of the product. Large volume chromatography column is adopted to ensure the uniformity of product quality.

6.2. Non-investigational Medicinal Products

There are no non-investigational medicinal products in this study.

6.3. Blinding Procedures

6.3.1. Methods of blinding and Randomization

Statistical staff for allocation of concealment would write the programs for random grouping and make the blind codes. Blind codes are divided into primary blind codes and secondary blind codes. ,

Blind codes will be stored in a restricted location with access granted only to the unblinded statistical staff. The primary blind codes are the group codes, and each vaccine number is the investigational vaccine or control vaccine corresponding to the research number, which is represented by different letters. The secondary blind codes will uncover the final blind codes, i.e. the vaccine name represented by letters, and the low-dose, medium-dose and high-dose investigational vaccine or control vaccine. The random grouping allocate in concealment program and blind codes are put into envelopes in duplicate, signed and sealed, and kept in one copy for the investigator and one copy for the sponsor respectively. Staff for allocation of concealment are not allowed to participate in clinical trials, nor are they allowed to disclose any content regarding the allocation of concealment to any staff participating in clinical trials.

The sponsor shall provide the qualified investigational vaccines and control vaccines, and the third-party statistical unit shall organize the allocation of concealment. Stata 12.0 software shall be used to generate random codes by randomization method, and the investigational vaccines and control vaccines shall be randomly allocated with serial numbers (each vaccine has a unique serial number).

6.3.2. Code breaking during the study

(1) Unblinding

When the immunogenicity results for 14 days after the whole course of immunization are obtained, adequate confirmed cases of COVID-19 are collected, the database is locked and unblinded after ensuring that the data are correct, and the safety, immunogenicity and protection effect will be evaluated after unblinding.

(2) Emergency Unblinding

If there is an emergency (such as serious adverse events) in the field work, inform the Ethics Committee and carry out emergency unblinding if necessary.

An online electronic system will be used for emergency unblinding. An investigator will be authorized in the research site, usually the person in charge of the site. When an emergency unblinding occurs in the research site, such as SAEs potentially associated with vaccines, quick knowledge of vaccine groupings is needed, in order to carry out emergency treatment. On-site investigators can log in to their personal authorized account number on the system to initiate an emergency unblinding application. The system will send the emergency unblinding application to the sponsor, PI and monitor simultaneously for approval. After all authorized personnel log in to the system and approved, the online system will inform the on-site person the blind codes of the research number. In case of clustered adverse events or interruption of the trial for any reason, the sponsor and the investigator shall jointly approve for unblinding in advance.

6.4. Vaccine packaging and labelling

All investigational vaccines are packaged in different doses in boxes with the same appearance and only marked by the random number of vaccines. The random number of vaccines is the research number. Different vaccine doses under the same research number are distinguished by the suffix of the random number. The numbering rules are as follows: XXXXX-1 represents the first dose of vaccine for XXXXX subjects, XXXXX-2 represents the second dose of vaccine for XXXXX subjects,

6.4.1. Vaccine labeling

(1) Each vaccine 0.5 ml dose shall be packaged separately in a single dose syringe, and the vaccine number shall be sticked.

(2) After the vaccine is put into use, the initials of the subject and the vaccination date shall be filled in the outer package respectively, and the active tag shall be sticked onto the original record form. The vaccination staff shall verify before conducting vaccination. During the trial process, the outer package of all used vaccines shall be kept for future reference.

Vaccines, small boxes are distinguished by different vaccine doses under the same research number, i.e. Random number and suffix.

Phase III Clinical Trial Label Illustration

(1) Outer packing box label:

SARS-CoV-2 Vaccine (Vero Cell), Inactivated

Only used for clinical trial

Vaccine number: XXXXXX

Initials: Immunization date: MM DD YY

Store at 2-8 ℃, 0.5 mL/dose

Batch Number: 202005003/202006009/202006002

Valid until: May 8，2022

(2) Vaccine syringe:

SARS-CoV-2 Vaccine (Vero Cell), Inactivated

(**Only for Clinical Trial)**

Vaccine Number: **XXXXXX**

Batch Number:
202005003/202006009/202006002

SARS-CoV-2 Vaccine (Vero Cell), Inactivated

Only used for clinical trial

Vaccine number: XXXXXX

Initials: Immunization date: MM DD YY

Store at 2-8 ℃, 0.5 mL/dose

Batch Number: 202005003/202006009/202006002

Valid until: May 8，2022

(3) Movable Label:

Vaccine No.: XXXXXX **Initials:**

Vaccine No.: XXXXXX **Initials:**

6.4.2. Backup vaccine

In case of vaccine damage (including package damage), unstable sediment, abnormal turbidity, etc. cannot be used (determined according to dosage form), backup vaccines must be put into use and 2% backup vaccines must be prepared for each dose. Using an online electronic system to obtain the number of the backup vaccine, once the vaccination staff or vaccine administrators on the research site identify an abnormal situation of the vaccine, vaccination should be suspended immediately, and an application for access to backup vaccines should be initiated through the online system. After the approval by the person in charge on site, the vaccine administrator and vaccination staff should pick the backup vaccines with relevant numbers from the stock for vaccination. The access to backup vaccines would be sent to the sponsor, PI and monitor by the system at the same time. When the backup vaccine is put into use, its label and the original vaccine label should be stuck onto the original record at the same time.

6.5. Products Storage and Stability Procedures

Vaccines should be stored and transported at 2 ~ 8 ℃ away from light to prevent freezing. The temperature during vaccine transportation and storage shall be dynamically monitored and recorded. If the storage and transportation temperature conditions exceed the specified range, the on-site investigators should immediately contact the personnel of the responsible clinical institutions and the sponsors to decide whether the vaccine can be used.

The responsible institution for vaccine clinical trials shall guide the site to formulate a management system for the investigational vaccine, and the management of receiving, keeping, preparing, recovering, returning/destroying of the investigational vaccine shall conform to the requirements of relevant laws and regulations. The responsible institution for vaccine clinical trials and the site shall designate personnel who have received GCP and relevant training to be responsible for the management of vaccines for trials.

6.5.1. Vaccine transportation

The whole process of vaccine management should meet the requirements of the cold chain, and there should be vaccine transportation and storage conditions that meet the requirements of the protocol. During the transportation of vaccines, there should be a transportation sheet and temperature monitoring. Upon arrival, the packaging condition and unpacking temperature should

be recorded. After the receiver receives the vaccines, the transportation sheet should be signed, faxed or copied to the consignor. Both parties should properly keep the transportation sheet.

6.5.2. Vaccine storage, distribution and use

Vaccines for testing should be kept in a separate area, locked in dedicated closet and managed by dedicated personnel. Vaccine receiver must verify and record the batch number, expiration period and delivery status of vaccines, establish work forms for vaccine handover, registration, use and recovery, fill in them as required, and keep them in the work records.

Investigational vaccine shall not be used for those are not clinical trial subjects.

6.5.3. Vaccine records

The sponsor will provide investigational vaccine, control vaccine (placebo) and vaccine handover sheet, and investigator will verify the name, batch number and quantity of the vaccine while receiving the vaccine.

Vaccine registration and use records: investigator shall establish vaccine registration and use records and distribute investigational vaccine and control vaccines according to the number of observation groups.

Record of vaccine recovery: The abandoned, expired and the remaining vaccines in this trial are returned to sponsor. Sponsor receives vaccines and verifies the batch number and quantity of vaccines, fills in the vaccine handover form, and makes relevant records, which are signed by vaccine manager and sponsor representatives.

6.6. Administration Route and Immunization Procedure

Administration route: lateral deltoid muscle of upper arm, intramuscular injection.

Immunization procedure: The subjects will complete 2 doses of vaccine on D0, D21(+7) days.

7. Study Schedule of Events and Visit Descriptions

7.1. Schedule of Events

Study assessments and procedures are presented by study period and visit in Table 4.

For all visits after the randomization visit, if the visit 2 is changed, then the next visit should take place according to the original study schedule.

7.2. Study Visit Descriptions

7.2.1. Procedures Performed at the Screening/Baseline Visit(s) D0

The following procedures/ assessments should be performed at Visit 1. In case of the investigator discretion the activities could be speared between visit 1 and visit 2 following the Table 4. Schedule of event

- ✓ Obtaining the informed consent:

The patient will receive verbal information concerning the aims and methods of the study, its constraints and risks, and the study duration. Written information will be provided to the subjects. Written informed consent must be signed by the patient and Investigator or delegate prior to any investigations

Written informed consent must be obtained prior to any additional corresponding sample collections/ assessments for the optional pharmacogenetic, antibody and other research samples;

- ✓ Assessment of all inclusion/exclusion criteria;
- ✓ Collection of demographic data (age, gender, race, and ethnicity; as allowed per local regulations);
- ✓ Collection of contact information (address, email, home, and cell phone number) for patient, patient's family, if applicable;
- ✓ Complete medical history will be obtained by interview of subjects prior to the first study vaccination to assure eligibility;
- ✓ For WOCBP, contraceptive measures will be reviewed;
- ✓ Measurement of body height and weight;
- ✓ Vital signs, including body temperature and pulse, will be obtained prior to the first study vaccination. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking body temperature.
- ✓ Standard physical examination (PE) will be performed on day 0 prior to the first study vaccination. If subject's medical history is known based on medical records (but not if there are no medical records available at all), a limited, targeted physical examination may be performed instead of standard scope PE prior to the first study vaccination by a study clinician, however in any case neurologic component of PE and physical examination of head/upper respiratory tract must be performed. Except for neurologic, head, and upper respiratory tract physical examination, for other body systems only findings relevant from the study perspective and not obvious from medical history need to recorded in the eCRF;
- ✓ EDC to be completed (for allocation of patient ID, registration of Screening);
- ✓ All concomitant medications taken before signing the ICF (at minimum those taken within 3 months prior to it, if applicable) will be recorded on the appropriate data collection form prior to the first study vaccination;
- ✓ The following laboratory testing: Urine pregnancy testing for WOCBP;
- ✓ Pre-administration reactogenicity assessments will be performed prior to the first study vaccination to establish baseline. Subjects will then receive a single dose of study vaccine via IM injection in the deltoid muscle of the non-dominant arm. The site of injection (right or left arm) and time of administration will be recorded on the appropriate data collection form. Subjects will be observed in the clinic for at least 30 minutes after the first study vaccination. The study

vaccination site will be examined, and observed reactions, AEs, SAEs (as applicable) will be assessed and recorded on the appropriate data collection form prior to discharge from the clinic.

- ✓ Subjects will be provided with a memory aid (paper diaries) and other study-related materials to record daily body temperature, solicited injection site and systemic reactions, any unsolicited AEs, and concomitant medications. Subjects will be encouraged to take their temperature on the vaccination day in the evening and then at selected approximately the same time each day for next 21/28 days after the vaccination day. Subjects will be instructed on how to complete the contact card in 0-21/28 days, prior to discharge from the clinic. Subjects will be instructed to notify the study center if they develop any reactions after the first study vaccination. PI or appropriate SI will assess the reaction and will give the subject further instructions on the proper course of action, including request for return to the clinic for immediate evaluation. The subjects will be instructed to return the completed contact card in 21/28 days.

7.2.2. Procedures Performed at the Safety Visit – on site

The following procedures/ assessments will be performed:

- ✓ Study personnel will review the memory aid information with subjects and assess and record all solicited events / unsolicited reactions, AEs, SAEs and concomitant medications on the appropriate data collection form;
- ✓ Vital signs (as applicable), including body temperature and pulse, will be obtained prior to the first study vaccination. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking body temperature;
- ✓ A targeted physical examination and/or vital signs collection may be performed by a study clinician if assessed as needed based on review of recent medical history;
- ✓ Counsel women of childbearing potential on contraception and avoidance of pregnancy.
- ✓ Study personnel will review interim medical history (other than reactogenicity events) with subjects and assess and record all unsolicited AE/SAEs and concomitant medications on the appropriate data collection form.

7.2.3. Procedures Performed at the Safety Visit – phone call

The following procedures/ assessments will be performed:

- ✓ Call subject on days 3, 7, 14, 24, 28, 42, 81, 141, 171, 231, 261, 351 and verbally confirm compliance with daily completion with study dairy (till Visit 5).
- ✓ Review any changes in the subject's concomitant medications and treatment information;
- ✓ Assess need for contraception and adherence to applicable lifestyle requirements. Establish willingness and ability to comply with lifestyle requirements going forward in the study;
- ✓ Assess and record any Adverse Events since the last visit.

7.2.4. Procedures Performed at the Second Vaccination Visit

- ✓ Study personnel will review the memory aid information with subjects and assess and record all solicited, reported reactions, AEs, SAEs (as applicable) and concomitant medications on the appropriate data collection form.
- ✓ Counsel women of childbearing potential on contraception and avoidance of pregnancy.
- ✓ Vital signs, including oral temperature and pulse, will be obtained prior to the first study vaccination. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature.
- ✓ A targeted physical examination should be performed by a study physician if assessed as needed based on medical interview concerning period between Visit 1 and Visit 5.
- ✓ Examine the vaccination site for Dose 1.
- ✓ Eligibility criteria will be reviewed with subjects prior to the second study vaccination to assure continued eligibility.
- ✓ Obtain interim medical history by interview of subjects prior to the second study vaccination and note any changes since the previous visit.
- ✓ All concomitant medications will be recorded on the appropriate data collection form prior to the second study vaccination.
- ✓ All unsolicited AEs/ SAEs will be assessed and recorded on the appropriate data collection form prior to the second study vaccination.
- ✓ A urine pregnancy test will be performed within 24 hours prior to the second study vaccination on all female subjects of childbearing potential. Results must be negative and known prior to the second study vaccination;
- ✓ Pre-administration reactogenicity assessments will be performed prior to the first study vaccination to establish baseline. Subjects will then receive a single dose of study vaccine via IM injection in the deltoid muscle of the non-dominant arm. The site of injection (right or left arm) and time of administration will be recorded on the appropriate data collection form. Subjects will be observed in the clinic for at least 30 minutes after the first study vaccination. The study vaccination site will be examined, and observed reactions, AEs, SAEs (as applicable) will be assessed and recorded on the appropriate data collection form prior to discharge from the clinic.
- ✓ Subjects will be provided with a memory aid (paper diaries) and other study-related materials to record daily temperature, solicited injection site and systemic reactions, any unsolicited AEs, and concomitant medications. Subjects will be encouraged to take their temperature on the vaccination day in the evening and then at selected approximately the same time each day for next 21/28 days after the vaccination day. Subjects will be instructed on how to complete the dairy, prior to discharge from the clinic. Subjects will be instructed to notify the study center if they develop any reactions after the first study vaccination. PI or appropriate SI will assess the

reaction and will give the subject further instructions on the proper course of action, including request for return to the clinic for immediate evaluation. The subjects will be instructed to return the completed diary, covering period between Visit 1 and Visit 2.

7.3. Unscheduled Visits

All attempts should be made to keep patients on the study schedule.

Unscheduled visits may occur at any time during the study. Any of the following activities may be performed:

- ✓ Review memory aid (till Visit 10)
- ✓ Review and record all concomitant medications (if within 22 days after the last study vaccination day, inclusive of the vaccination day).
- ✓ All reactions recorded in diary/-ies, AEs, SAEs will be recorded on the appropriate data collection form. Recording of AEs in the EDC will be limited to SAEs if after 21 days after the last study vaccination day.
- ✓ Obtain interim medical history by interview of subjects and note any changes since the previous visit (if indicated).
- ✓ If deemed as relevant and/or needed, perform physical examination and/or obtain vital signs including oral temperature. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature.
- ✓ Examine study vaccination site and perform post- administration reactogenicity assessment (if within 14 days after the last study vaccination, inclusive of vaccination day)

7.4. Study Procedures

7.4.1. Vital signs

Vital signs (sitting blood pressure, pulse rate, respiratory rate and temperature) will be measured after 5 minutes of rest as indicated in the Table 4. Schedule of Events.

Blood pressure and heart rate will be measured using a standard calibrated blood pressure measuring device. A BP device that uses multiple cuff sizes based on the arm circumference is the required type of device. The appropriate cuff size for the subject must be used to ensure accurate measurement. The same device should be used throughout the study. Subject should be seated in a chair, back supported, and arms bared (free of restrictions such as rolled-up sleeves, etc.) and supported at heart level. Measurements should be taken on the same arm at each visit (preferably non-dominant).

Note: in case of high blood pressure values at screening, the investigator is responsible for the optimization of the patient's treatment to achieve blood pressure targets as defined by local

guidelines or the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (Chobanian 2003).

Heart rate should be measured at approximately the same time as BP for a minimum of 30 seconds. When the timing of BP and pulse (heart) rate measurements coincides with a blood collection or other study procedure, BP and pulse (heart) rate should be obtained first.

Measurement of body temperature will be collecting using the tympanic methods and the same method should be used consistently throughout the study.

7.4.2. Physical Examination

Standard physical examination should be performed prior to the first study vaccination, but if subject's medical history is known based on medical records, a limited, targeted physical examination may be performed instead of standard scope PE prior to the first study vaccination by a study clinician, however in any case neurologic component of PE and physical examination of head/upper respiratory tract must be performed. On visits other than 1 limited, targeted physical examination may be performed if assessed by investigator as needed.

Additional physical exams will be performed at other time points according to Table 4. Schedule of Events. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

7.4.3. Body Weight and Height

Body weight should be obtained at time points according to Table 4. Schedule of Events, with the patient wearing undergarments or very light clothing and no shoes, and with an empty bladder. The same scale should be used throughout the study.

The use of calibrated balance scales is recommended. Self-reported weights are not acceptable; patients must not read the scales themselves.

Height should be measured at screening; self-reported heights are not acceptable.

7.4.4. Reactogenicity Assessments

This will include an assessment of solicited events occurring from the time of each study vaccination through 7 days after the study vaccination (inclusive of vaccination day), which includes an assessment of systemic reactions (Fever; Decreased blood pressure and/or dizziness; Chills and/or sweating; Joint and/or muscle pain; Headache; Nasal congestion, runny nose, phlegm production, rhinitis; Problems with breathing (difficulty breathing, wheezing); General malaise, fatigue, loss of appetite; Itching on body/ pruritus; Swelling/ tender lymph nodes; Irritability; Rash; Cough; Sore throat; Stomach problems (abdominal pain, diarrhea, nausea, vomiting)) and local – injection site reactions (Blue spot/ bruising; Induration / Swelling; Redness / Warmth; Itching), Pain/ tenderness.

7.4.5. Medical History

Will be obtained by interview of the subjects. Subjects will be queried regarding a history of significant – clinically or from the study protocol perspective - medical disorders of the head, eyes,

ears, nose, throat, mouth, cardiovascular system, lungs, gastrointestinal tract, liver, pancreas, kidney, nervous system, blood, lymph glands, endocrine system, musculoskeletal system, skin, and genital/reproductive tract. A history of any allergies, cancer, immunodeficiency, psychiatric illness, and substance abuse will be solicited. The collection of medical history information will include a review of vaccine history and plans for vaccinations. Other vaccines history should include at least 30 days before the study and any other study-relevant vaccination received in the past.

7.4.6. Memory Aids

All subjects will complete a subject memory aid (paper diary) from the time of each study vaccination after the study vaccination Subject memory aids will be reviewed with the subject for AEs at the site visit following the first study injection, and over the phone (unless the subject comes to the site for scheduled or unscheduled visit). If a subject noted ongoing injection site or systemic reactogenicity on the 21/28 day following the study injection day, the memory aid will continue to be completed and reviewed until resolved. Subjects will be requested to deliver memory aids filled in after the second vaccination when completed to the site.

7.4.7. Laboratory Testing

All laboratory samples (including Antibody and research samples) will be collected after assessments are performed and before a vaccine is administered at visits that correspond with a dosing day.

Samples for laboratory testing will be collected at time points according to Table 4. Schedule of Events and analyzed by a central and/or local laboratory during the study. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites.
Collect the urines of all women at child-bearing age for pregnancy test, the testing results will be used for enrollment screening. Collect the nasopharyngeal swabs of all the volunteers for RT-PCR testing at the same time of the recruitment, the testing results will be used for subsequent analysis.

Pre-immunization blood collection Day 0

After enrollment, about 12.5ml of venous blood will be collected from all subject before the first dose of vaccine, the serum will be separated within 24 hours and divided into minimum of multiple tubes (each tube was not less than 0.5ml), and stored at -20 ℃ and below for antibody testing.

Blood collection from the subjects (all suspected or confirmed cases）

After the subjects developed typical COVID-19 symptoms, 12.5 ml venous blood will be collected for antibody testing, serum will be separated within 1-3 days and divided into multiple tubes (each tube was not less than 0.5 ml). Serum is stored at -20℃ and below (subjects of confirmed cases and suspected cases are tested for antibodies).

Sample collection after immunization

After enrollment, about 12.5ml venous blood of all the subjects will be collected 14 days after the 2nd dose of immunization. Serum is separated within 24 hours and divided into multiple tubes (each

tube is not less than 0.5 ml), and stored at -20℃ and below for immunogenicity antibody testing. The serums from all subjects 14 days after the 2nd dose of immunization will be matched to the serums from the monitored cases for testing of the exploratory immunological protective endpoint.

Otherwise, blood samples of 900 or more subjects at each site where allocated sample size is greater than 900 are collected 28 days, 3rd month, 6th month, 9th month, 12th month after 2 doses of immunization, serum is separated within 24 hours and divided into multiple tubes (each tube is not less than 0.5 ml), and stored at -20℃ and below for immunogenicity antibody testing.

Testing items for moderate, severe and critical symptomatic cases:

1. SARS-CoV-2 PCR swabs
2. Complete blood count and differential (WBC, lymphocytes...)
3. Blood chemistry (Liver function including liver enzymes, Renal function, Electrolytes, LDH, CRP, Ferritin, Glucose)
4. Coagulation profile (D-dimer)
5. Cellular immunity, cell count: CD3+, CD4+, CD8+, NK (CD56+), B (CD19+)
6. Cytokines: IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IFN-γ, TNF-α, Th-1, Th-2, etc.
7. IgM, IgG, neutralizing antibody in acute and convalescent phase (3-4 weeks after confirmed diagnosis)
8. Chest CT scan

For trial sites where conditions permit, etiological testing for the other respiratory pathogens are required for the symptomatic cases. Items marked "*" will be also subject to site conditions.

Blood Sample Numbering Rules

Before the first dose immunization: Study No. -0

14 days after 2 doses of immunization (D35+10 days): Study No. -1

28 days after full course immunization (D49+10 days): Study No. -2

3 months after full course immunization (D111+20 days): Study No. -3

6 months after full course immunization (D201+20 days): Study No. -4

9 months after full course immunization (D291+20 days): Study No. -5

12 months after full course immunization (D381+20 days): Study No. -6

Suspected or confirmed cases: Study No. -P1, P2, P3……

7.4.8 Case Monitoring

This clinical trial adopts a monitoring modality with passive monitoring as the main approach and active monitoring as a supplement. After the subjects received the first dose of vaccine, the monitoring of COVID-19 cases will be initiated until the end of the study, and relevant information will be collected.

Passive Monitoring

Passive monitoring has two situations where subjects spontaneously report and when symptoms occur, they actively go to the hospital for treatment.

1) After the subjects develop symptoms, they actively report to the investigator through the hotline or email;

2) When the subjects visit hospital after developed symptoms, the subjects are monitored through hospital system;

- When the subject has fever and/or respiratory symptoms that meet the definition of a suspected case, the subject should inform the investigator and go to the designated place for PCR testing;
- If the subject visits the hospital for treatment, the investigator should arrange to collect nasopharyngeal swabs for PCR testing every 2-3 days; determine the clinical classification based on the severity and duration of symptoms, and isolate the mild and moderate cases; arrange hospitalization for severe and critical cases;
- For non-hospitalized patients, the subjects will be followed up by remote teleconsultation and re-tested for PCR every 3 days to monitor and document the progress of the illness, medication status, symptom severity and other related information. If the subject's condition deteriorates, he needs to be sent to the hospital for timely treatment;
- For hospitalized patients, continue to pay attention to the development of the disease, and conduct testing and examination like blood routine, blood chemistry, imaging examinations as well as other medical treatment. Closely monitor and collect evidence related to the subject's diagnosis and treatment, and record the progress of the disease, medication, and the severity of symptoms until the outcome;
- Collect the PCR result, defined a confirmed case based on the positive result;
- The subject is in the convalescent phase which is 3-4 weeks after the first positive PCR result. During the convalescent period, the subject’s nasopharyngeal swab is collected for PCR retest

and neutralizing antibody test; if the PCR test result is positive, repeated PCR testing needs to be done once a week until the PCR result is negative.

2. Active monitoring

1）Weekly teleconsultation to collect information；

2）Regularly monitor and collect information；

The subsequent procedures for suspected cases identified through the above two monitoring process approaches is the same as passive monitoring procedures.

Endpoint assessment or adjudication of the cases

Establish an independent case Endpoint Assessment or Adjudication Committee (EAC) composed of 3 or more local medical experts to make a final diagnosis for each case. When a case meets the etiological indicators, the diagnosis and treatment progress document, case investigation document, serology, cytokines and other lab reports will be submitted to EAC, the case can be determined as a confirmed case of COVID-19 (clinical endpoint) after a blinded review of the EAC experts. Refer to the EAC charter (Appendix 1) for details.

Case Monitoring Flowchart

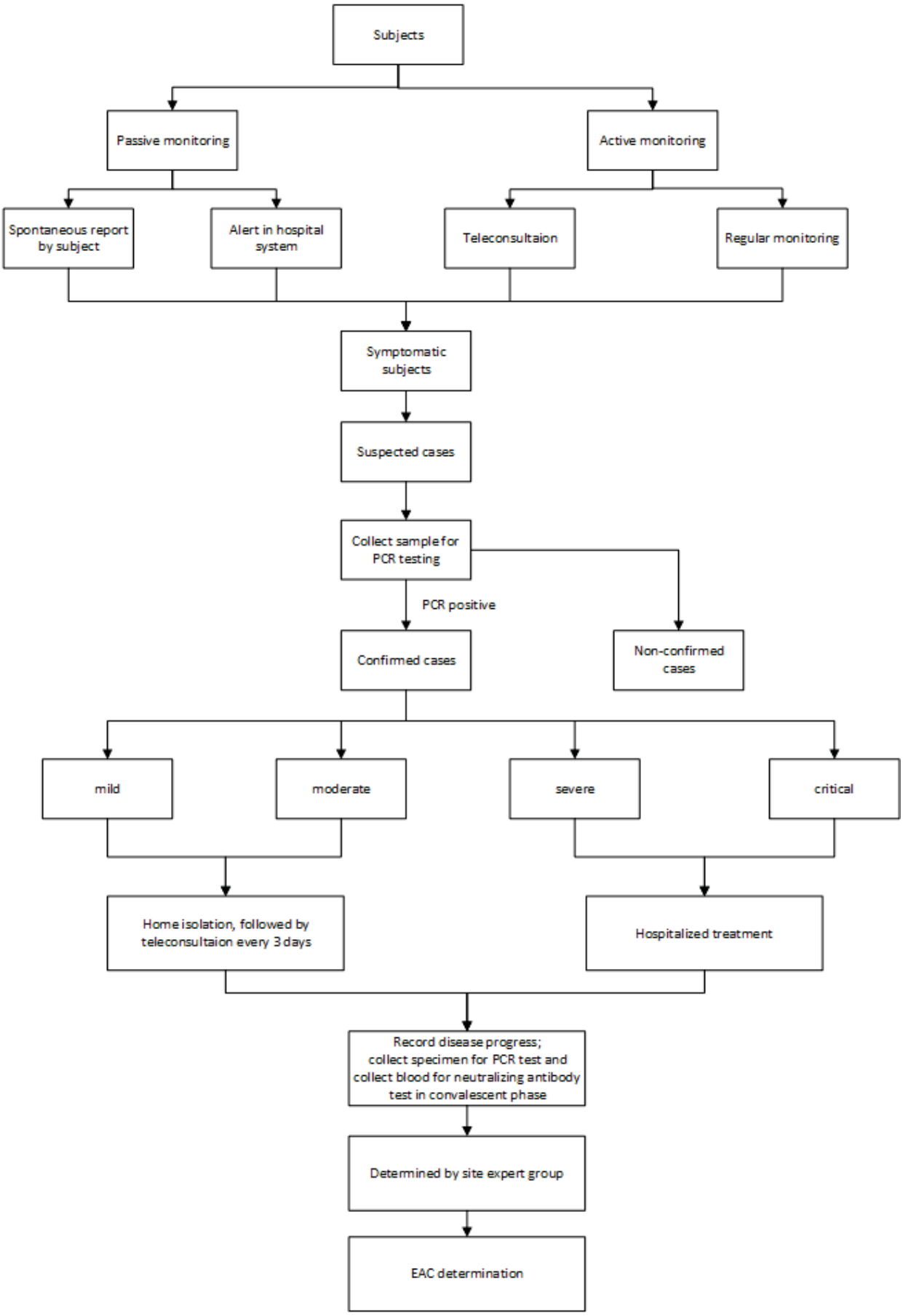
Subjects
Passive monitoring
Active monitoring
Spontaneous report by subject
Alert in hospital system
Teleconsultaion
Regular monitoring
Symptomatic subjects
Suspected cases
Collect sample for PCR testing
PCR positive
Confirmed cases
Non-confirmed cases
mild
moderate
severe
critical
Home isolation, followed by teleconsultaion every 3 days
Hospitalized treatment
Record disease progress; collect specimen for PCR test and collect blood for neutralizing antibody test in convalescent phase
Determined by site expert group
EAC determination

Table 4. Schedule of Events

Visit number	1	2	3	4	5	6	7	8	9	10	11, 13, 14	12, 15, 18	16, 17, 19, 20	21
Day (safety visit)	D0 ✍	D3 ☎	D7 ☎	D14 ☎	D21 ✍	D24 ☎	D28 ☎	D35 ✍	D42 ☎	D49 ✍	D81 D141 D171 ☎	D111(M3) D201 (M6) ; D291 (M9) ✍	D231 D261 D321 D351 ☎	D381 (M12) ✍
Visit (window +/- days)	0d	-2d	+2d	+3d	+7d	-2d compare to V5	+2d compare to V5	+10d compare to V5	+3d compare to V5	+10d compare to V7	+3d compare to V7	+10d compare to V7	+3d compare to V7	+10d compare to V7
SCREENING/BASELINE														
Study Informed consent[1]	✓													
Inclusion/exclusion criteria evaluation	✓[7]				✓[7]									
Demographics	✓													
Medication history	✓				✓									
Measured height	✓				✓									
Review contraception[2]	✓				✓									
EDC Randomization registry	✓													
TREATMENT														
Administer study drug	✓				✓									
SAFETY ASSESSMENTS														
Vital signs specifically RR, HR, BP, body temp/ O2 sat	✓				✓			✓		✓				
Body weight	✓				✓									
Physical Examination[6]	✓[6]				✓[6]			✓[6]		✓[6]				
Post-vaccination observation at site[4]	✓				✓									
Post-vaccination phone call	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant medication	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse events	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Diary Card[5]	✓				✓					✓				
LABORATORY TESTING														
COVID-19 PCR[7]	✓							✓[7]						
Pregnancy test	✓[3]				✓[3]									
Neutralizing Antibody Test	✓							✓		✓[8]		✓[8]		✓[8]

IgM & IgG antibody, cytokines (IL-2, IL-6, IL-4, TNF-α, IFN-γ and other cytokines)	Will be done only in case subject contacted COVID-19 Virus
COVID-19 case monitoring	**During D0-D215, all subjects are visited once a week through phone call.** **For suspected COVID-19 cases, visit every 1-3 days until healed.**

1. Consent process completed and form signed before any study-related procedures are conducted.
2. Counseling on avoidance of pregnancy for women of childbearing potential.
3. Urine pregnancy test must be completed within 24 hours prior to vaccination for women of childbearing potential. If urine pregnancy test is positive, subject is not eligible unless local laboratory performed serum pregnancy test is negative.
4. All subjects will be observed for a minimum of 30 minutes following vaccination.
5. Paper diaries will be used as solicited events diary and a memory aid (vaccination card) for unsolicited events
6. On Visit 1 standard physical examination should be performed prior to the first study vaccination, but if subject's medical history is known based on medical records, a limited, targeted physical examination may be performed instead of standard scope PE prior to the first study vaccination by a study clinician, however in any case neurologic component of PE and physical examination of head/upper respiratory tract must be performed. On visits other than 1 limited, targeted physical examination may be performed if assessed by investigator as needed.
7. COVID-19 PCR will be performed at discretion of the investigator for suspected cases, once every two weeks at site with conditions.
8. Only applies to the 900 or more subjects at the site where allocated sample size is greater than 900.

8. Safety Definitions, Reporting, and Monitoring

8.1. General precautions

The clinical trial was conducted at multicenter Before the start of the trial, the sponsor shall strictly examine the trial site in accordance with GCP requirements, focusing on whether the environmental facilities of the trial site meet the requirements of "Vaccination Management Standards" and "Guiding Principles for Quality Management of Vaccine Clinical Trials". The first aid facilities and first aid equipment in the first aid room are complete and effective, and the first aid doctors have corresponding qualifications and capabilities. Emergency related personnel (emergency doctors, emergency nurses, ambulance drivers, etc.) are trained to be qualified and familiar with the transfer routes and procedures of the agreed hospital. They are on standby at the trial site during vaccination. The trial site shall be equipped with an ambulance. The ambulance shall be parked in a fixed position to keep the vehicle in good condition and in an emergency and shall be under the command and transfer of the emergency response team at any time. During the vaccination period, the agreement hospital will make daily preparations for medical personnel, instruments and equipment, first aid drugs and first aid sites to ensure that the subjects can receive timely treatment. The trial site shall formulate an emergency plan, stipulate personnel responsibilities, contact numbers, rescue routes and other measures to ensure timely handling of unexpected adverse events, and ensure effective contact between subjects and investigators so that any adverse events can be reported and handled quickly.

8.2. Risk Prevention Measures Related to COVID-19

(1) Consideration of the trial site

Since December 2019 during the " COVID-19" pandemic, each site has confirmed many patients with majority of cases in villages and towns, which is defined as -risk areas.

Investigators during recruitment should confirm whether there are new COVID-19 cases or suspected cases in the same village/community by investigating or inquiring volunteers. Whether fever (axillary temperature > 37.0 ℃), dry cough, fatigue, nasal obstruction, runny nose, sore throat, myalgia, diarrhea, shortness of breath and dyspnea occurred in the near future;

(2) Strengthen the management and personal protection of subjects during the study period

The trial site shall strictly disinfect each functional area of clinical research according to regulations, and regularly open windows for air-ventilation. Strict implementation of independent areas and special passages, recipients and their accompanying personnel waiting in relative zones, to avoid contact with research doctors, nurses and other personnel; all functional areas and public places should be equipped with hand disinfectants and temperature measuring devices. Recipients entering the clinical research site and their accompanying personnel are required to be equipped with masks to disinfect their hands and measure their body temperature.

During the first dose of inoculation, the on-site investigators shall remind the subjects to strengthen their own protection. If COVID-19 pandemic occurs locally, the subjects shall be provided with

necessary protective materials such as masks, alcohol, etc. in time, and attention to the health status of the subjects shall be attracted, especially the symptoms related to COVID-19.

(3) Detection of COVID-19 RT-PCR

Subjects need to be tested for COVID-19 RT-PCR before vaccination on D0, D21, D35 and D49, and once per two weeks after D49 at the site with conditions. Clinicians need to ask the subjects again in detail whether they have fever, dry cough, fatigue and other symptoms in the near future. If the above symptoms exist, the subjects are arranged to go to the agreement hospital for CT examination according to the protection requirements of COVID-19. If the examination results have CT imaging characteristics of COVID-19, samples are collected for etiological examination. If there are no symptoms such as fever, dry cough and fatigue, the subject should be home isolated under the arrangement of local CDC according to the requirements of COVID-19 prevention and control plan.

(4) Surveillance of disease process of COVID-19.

The purpose of monitoring the infection of COVID-19 or other coronaviruses in subjects is to find people with potential risks of ADE or VED after injection of COVID-19 vaccine, and to take timely treatment and intervention measures to reduce the risk of aggravation of patients' illness.

The responsible unit on the research site shall inform the medical institutions of the information on the subjects with COVID-19 vaccination, so as to assist doctors to make correct judgment on the patient's condition and potential risks. In addition to collecting nasopharyngeal swabs, alveolar fluid and serum samples of subjects for etiological detection of COVID-19, medical institutions also need to collect blood samples for antibody level detection. The responsible units and medical institutions on the research site should pay close attention to the progress of the subject's condition, and contact the superior medical or testing institutions which have capacity of testing IL-2, IL-6, IL-4, TNF-α, IFN-γ and other cytokines to get ready for sample delivery and testing. When the subject's condition progresses rapidly and has a tendency to ADE or VED, blood samples are collected and sent to a hospital or institution that can carry out the test to help diagnose whether ADE or VED exists.

After unblinding, if the subjects in the experimental group suffer from diseases caused by COVID-19 again, and the disease progresses rapidly, indicating the high probability of ADE or VED. Doctors should be advised to take immune intervention measures to prevent inflammatory storms, or to transfer to a superior hospital in time to prevent more serious injuries due to improper treatment.

(5) Persistent monitoring and long-term safety follow-up of COVID-19 antibodies

According to the requirements of the protocol, the subjects are followed up for a long-term safety period of 12 months, during which serious adverse event information, including disease information caused by COVID-19, is collected through telephone follow-up and active report by the subjects.

8.3. Handling and Reporting of Serious Adverse Events

Monitoring and reporting of adverse events in vaccine clinical trials are jointly completed by subjects, adverse event investigators, trial sites and responsible institutions at different observation time points with different stages.

The sponsor is the main body responsible for monitoring, evaluating and SAE reporting safety information of vaccine clinical trials. The person shall be designed as the administrator of clinical trial safety information monitoring and SAE reporting, and work with investigators to establish SOPs for clinical trial safety information monitoring and SAE reporting, know well the latest status of the safety information of the whole clinical trial, and timely report updates to all clinical trial institutions/ investigators and regulatory authorities.

If it is difficult to make a judgment on the correlation between SAE and vaccine or there is doubt about the judgment, when it is necessary to make a new judgment, the expert meeting shall make a judgment after argumentation.

(1) On-site treatment measures

Emergency plans for SAE treatment in clinical trials shall be established at the trial site, and all relevant personnel shall be trained. If the subjects show serious adverse events, the investigators shall immediately take appropriate measures for the subjects and record them. The investigators must take relevant approaches to know in time any clinically significant diseases/events related to vaccination. According to relevant national regulations, the subjects should be received appropriate treatment in time in the designated hospitals.

investigators at the trial site should follow up serious adverse events/reactions until the symptoms disappear or stabilize. The progress and outcome of all symptoms will be recorded in detail, and all drug treatments and medical treatments will be recorded at each follow-up. investigators should truthfully record serious adverse events on eCRF, which shall be evaluated and discussed in the final report after the test is completed or terminated.

During the whole observation process, if the subjects suffer from physical injuries caused by serious adverse reactions related to vaccination, which is confirmed by the expert investigation team, the sponsor will give corresponding compensation.

(2) Reporting Procedures for Serious Adverse Events

✓ Reporting Procedures of investigators

Any serious adverse event, whether related to the investigational vaccine, the investigator must submit the first report of the "Serious Adverse Event Report Form" to the drug administration department, the sponsor and the ethics committee by fax, e-mail or EDC system or personal delivery within 24 hours after learning about it. Subsequently, the follow-up report of the "Serious Adverse Event Report Form" shall be submitted regularly until the end of the event. All information is reported in the "Serious Adverse Event Report Form" in the form of written reports, including description of adverse reactions/events, onset time and type, duration, intensity, causal

relationship with vaccination, results, treatment methods (symptomatic treatment) and other relevant clinical and laboratory data.

When receiving the report of serious adverse events/reactions, the researcher shall, together with the sponsor, comprehensively consider the duration, scope, intensity, outcome and the wishes of the subject to decide whether the subject should continue to participate in the test or terminate the test in advance.

✓ **the sponsor's reporting procedure**

During the clinical trial of drugs, sponsors need to quickly report unexpected and serious adverse reactions (SUSAR) that are definitely related to or suspicious of the tested drugs in the form of case-by-case safety reports according to the Standards and Procedures for Rapid Reporting of Safety Data during Clinical Trial of Drugs. If the researcher and the sponsor cannot reach an agreement on the judgment of the causal relationship between adverse events and drugs, either party's judgment cannot exclude those related to the test drugs, and the sponsor should also make a quick report.

For SUSAR that is fatal or life-threatening, the sponsor should report it as soon as possible after the first knowledge, but not more than 7 days, and report it within the following 8 days to improve the follow-up information (Note: the day when the sponsor first learned it is the 0th day). For SUSAR that is not fatal or life-threatening, the sponsor should report it as soon as possible after the first knowledge, but not more than 15 days. For other potential serious safety risk information, the sponsor should also report to the national drug evaluation agency as soon as possible, and at the same time make medical and scientific judgment on each situation. After the first report, the sponsor shall continue to track the serious adverse reactions and submit relevant new information or changes to the previous report in a timely manner in the form of a follow-up report. The reporting time limit shall be within 15 days from the date of obtaining the new information.

8.4. Outcome of Serious Adverse Events

The outcomes of serious adverse events include: (1) disappearance of symptoms (sequelae); (2) Symptoms disappear (no sequelae); (3) Symptoms persist; (4) Death

8.5. Safety Oversight (DSMB)

Safety oversight will be conducted by a DSMB that is an independent group of experts that monitors subject safety and advises the sponsor. The DSMB members will be separate and independent of study personnel participating in this trial and should not have scientific, financial or other conflict of interest related to this trial. The DSMB will consist of members with appropriate expertise to contribute to the interpretation of the data from this trial.

DSMB members are multidisciplinary, including experts in clinical medicine, statistics and clinical trial management.

Responsibilities:

✓ Monitoring of safety: review the post-immunization safety report of the subjects according to

DSMB by laws and monitoring plan. If it is found that there's an increase in the risk of subjects during the trial, DSMB needs to report to PI and Sponsor immediately.

- ✓ Monitoring of effectiveness: Review the interim analysis results according to DSMB bylaws thus to monitor the effectiveness and assist to make decision on early termination of the trial.
- ✓ Monitoring of trial quality: monitor the quality of trial by reviewing data, including protocol compliance, recruitment status, dropout of subjects and data integrity, etc.

The DSMB will review study progress and subject, clinical, safety, and reactogenicity data at the following time points.

- Data review for safety at study specific time frames.
- After all 14-day post second study vaccination safety data are available for all study subjects.
- Interim review meeting: Review the blinded safety data for the interim report for this trial. The data will be provided in a standard summary format. The DSMB may be asked to provide recommendations in response to questions posed by the sponsor.
- Final review meeting: After clinical database lock to review the cumulative unblinded safety and efficacy data for this trial. The data will be provided in a standard summary format. The DSMB may be asked to provide recommendations in response to questions posed by the sponsor.
- Ad hoc, for evaluation of immediate concerns regarding observations during this trial, or as needed.

The DSMB is independent, each data element that the DSMB needs to assess will be clearly defined. The DSMB will review applicable data to include, but not limited to, study progress and subject, clinical (total number of COVID-19 confirmed cases), safety, and analytical data. Reports may include enrollment and demographic information, medical history, concomitant medications, physical assessments, clinical laboratory values, dosing compliance, and solicited events and AE/SAEs. Additional data may be requested by the DSMB, and interim statistical reports may be generated as deemed necessary and appropriate by the sponsor. The DSMB may receive data in aggregate and presented by treatment arm. The DSMB may also be provided with expected and observed rates of the expected AEs in an unblinded fashion, and may request the treatment arm be unblinded for an individual subject if required for safety assessment. The DSMB will review grouped and unblinded data in the closed session only. The DSMB will meet and review this data at scheduled time points or ad hoc as needed during this trial as defined in the DSMB charter. As an outcome of each review/meeting, the DSMB will make a recommendation as to the advisability of proceeding with study vaccinations (as applicable), and to continue, modify, or terminate this trial.

9. Statistical Considerations

In addition to study protocol, a separate statistical analysis plan (SAP) will be written to describe the details of statistical methods. SAP will be finalized before the database is locked.

9.1. Hypothesis

Primary hypothesis:

In the healthy population who are older than 18 years, 95% confidence interval (CI) of vaccine efficacy (VE) after 14 days following two-dose vaccinations is larger than 30% in vaccine groups compared with placebo (point estimate of VE is achieves 50%).

9.2. Analysis sets

(1) Analysis Set for Efficacy

Full Analysis Set (FAS): includes all subjects who follow intent to treat (ITT) principle, undertake randomization, received at least one dose of vaccine and have ⩾1 follow up for case surveillance.

COVID-19 cases included in FAS analysis: initial occurrence post first-dose vaccination and involvement in efficacy assessment in FAS analysis and COVID-19 cases confirmed by etiological and serological evidence, and deaths caused by COVID-19.

modified Full Analysis Set (mFAS): It is a subset of FAS population, and includes all subjects who take two doses of vaccination and have at least 1 follow-up for efficacy after all course immunization.

Per Protocol Set (PPS): being a subset of mFAS, the subjects in PPS are more compliant to the protocol, including all subjects who meet the inclusion/exclusion criteria, undertake randomization, receive 2 doses of vaccination according to the protocol requirements, and have ⩾1 follow up in 14 days after the 2nd vaccination for case surveillance. Among them, subjects who meet the following conditions should be excluded from PPS: (1) they do not meet the selection criteria; (2) The subjects received the wrong vaccination or incorrect dose of vaccine; (3) For those whose vaccination time exceeds the window, the researcher, the sponsor and the statistician shall jointly agree on the time exceeding the window before unblinding; (4) any other conditions which potentially affect the evaluation of vaccine efficacy.

Confirmed COVID-19 cases included in PPS; initial occurrence after 14 days following 2-dose vaccination, involvement in efficacy assessment in data set and COVID-19 cases confirmed by etiological and serological evidence, and deaths caused by COVID-19.

(2) Analysis Set for Immunogenicity

Full Analysis Data Set (FAS): includes all subjects from immunogenicity subset who follow ITT principle, undertake randomization, receive at least one dose of vaccine, and have pre-vaccination immunogenicity data.

Per-protocol set (PPS): It is a subset of FAS. The subjects in this data set are more compliant to the protocol, meet the inclusion/exclusion criteria, participate in randomization, receive 2 doses of vaccine according to the requirements of the protocol, and have serum-testing results before and after immunization. The subjects in this data set are included in PPS set. Among them, subjects who meet the following conditions are not allowed to involve the PPS data set: (1) they do not meet the selection criteria and meet the exclusion criteria; (2) Those who fail to obtain follow up data and

information after vaccination; (3) Serious lack of information and data after randomization; (4) The subject received the wrong inoculation or incorrect dose; (5) Other investigators consider it needs to be excluded. For those whose vaccination time exceeds the window or whose blood collection time exceeds the window after exemption, the researcher, the sponsor and the statistician shall jointly agree on the exceeding window time before blindness.

(3) Safety analysis data set

Safety Analysis Data Set (SS): includes all subjects who receive vaccination after randomization.

9.3. Statistical Methods

(1) General considerations

Quantitative data will be described by mean, median, standard deviation, minimum and maximum. Frequency and percentage will be used to describe qualitative data and ordinal data.

All analysis will be performed by using SAS 9.4 or later version.

(2) Subject disposition and demographics

The number of subjects randomized, discontinued and completed in each group will be summarized. The discontinued subjects will be listed, including the reason for discontinuation. The number of subjects in the analysis sets will be presented as well.

The demographics of all subjects will be summarized by groups.

(3) Efficacy analysis

The number of cases of admission, dropout, elimination, blood collection, dropout reasons, combined medication and combined vaccines in the experimental and placebo groups shall be described. The percentage of dropout and concomitant medication in the experimental and placebo groups shall be compared with χ^2 test or Fishers exact test.

Protection efficacy (FAS, mFAS and PPS analysis):

The person-year incidence rate of COVID-19 after 14 days following two-dose of vaccination will be calculated in Vaccine-1, Vaccine-2 and placebo groups. Vaccine efficacy from person-year incidence rate of Vaccine-1 and Vaccine-2 with the corresponding 95% CIs will be estimated. The differences between Vaccine-1, Vaccine-2 and placebo will be compared by using Poisson regression model. The person-year incidence rate is calculated by (Number of COVID-19 cases / Person years in exposure of all subjects) $\times$100%. In the calculation of person years in exposure, the start date is after 14 days following the 2nd dose. The end date is the diagnosed date of COVID-19 case for ones who are confirmed as COVID-19 cases or last follow-up date for others. Vaccine efficacy (VE)= 1-(person-year incidence in vaccine group/ person-year incidence in placebo group).

Vaccine efficacy after 14 days following two-dose vaccination will be evaluated based on mFAS and PPS. The VE from mFAS population is the primary result, and the efficacy from PPS population is a sensitivity analysis result.

Furthermore, the same statistical methods will be employed to estimate the VE after one dose based on FAS population. Kaplan-Meier plot will be used to depict the incidence of COVID-19 from FAS population.

The same statistical methods as above are used to evaluate VEs against severe cases of COVID-19 and deaths accompanied by COVID-19.

(4) Immunogenicity analysis (FAS and PPS analysis):

Statistical description: The antibody titer should be logarithmically transformed. Minimum value, maximum value, median and quartile spacing, GMT and 95% CI should be shown.

Comparison of antibody levels before immunization: Logarithmic conversion was carried out on antibody titers, and two independent sample T tests (normal and homogeneous variance) or corrected T tests (normal but uneven variance) shall be used to compare the GMT of neutralizing antibodies against COVID-19 before immunization between the experimental and placebo groups with various ages.

Comparison of antibody levels after immunization:

- ✓ calculate the antibody 4-fold increase rate and 95% CI of anti-SARS-CoV-2 antibody in the experimental and placebo groups with various ages after immunization, and make superiority comparison. If the lower limit of 95% CI of antibody 4-fold increase rate is ≥ 10%, the superiority hypothesis is valid;
- ✓ calculate 95% CI of GMT ratio of anti-SARS-CoV-2 antibody in the experimental and placebo group after immunization. If the lower limit of 95% CI ratio is ≥ 1.1, the superiority hypothesis is valid;
- ✓ calculate the GMI and 95% CI of anti-SARS-CoV-2 antibody in the experimental group after immunization.

(5) Safety analysis (SS analysis)

Describe the frequency and number and incidence of adverse reactions/events. If a subject manifest the same adverse reaction/events repeatedly, the description on this adverse reactions/evens should indicate the most severity, the closest relationship with vaccination and the earliest starting time. However, in the list of adverse reactions/events, all adverse reactions/events will be listed.

Using χ^2 test or correct χ^2 test or Fishers exact test, the incidence of total adverse reactions, systemic adverse reactions, local adverse reactions and unexpected adverse reactions in the experimental and placebo groups within 30 minutes, 0-7 days and 8-28 days after inoculation of each dose were compared χ^2 test or correct χ^2 test or Fishers exact is used to compare the difference of SAE incidence rate between the experimental and placebo groups within 360 days after the whole inoculation. The rank sum of two independent samples is used to compare the average grade of adverse reactions in the experimental and placebo groups.

In the analysis of adverse events/reactions stratified by symptoms and SAE, MedDRA coding is used to carry out comparative analysis of SOC level and PT level respectively.

9.4. Sample size

9.4.1. Calculation of sample size for vaccine efficacy study

The sample size required for phase III in vaccine efficacy study should meet the following requirements: ① For trial vaccine-1 or trial vaccine-2, the point estimation value of any vaccine efficacy is over 50%; ② the lower limit of 95% CI of any vaccine efficacy of trial vaccine-1 or trial vaccine-2 is no less than 30%.

Assume VEs of both vaccine-1 and vaccine-2 could reach 0.6. If 95% CI of any one of the two vaccines' efficacy is larger than 0.3, the vaccine will be considered to be successful. The statistical power achieves 90% when the number of COVID-19 cases in any one vaccine and placebo groups is 150. There are vaccine-1 and vaccine-2 groups in this trial. It will be analyzed when the number of COVID-19 cases in any one vaccine and placebo groups achieves 150.

The sample size required for each vaccine group was calculated by reference to document [15] according to the confirmed cases' cumulative number of COVID 19 epidemic situation in UAE and several other research sites since Jan. 2020 and the trend of newly diagnosed cases per day most recently, assuming the annual incidence rate of placebo group, P1 is 850/100,000, and the ratio of trial vaccine -1, trial vaccine -2 and placebo control group is 1:1:1.

N2=T/[（C+1-π1）×P1]=150/[（1+1-0.6）×0.0085]=12605 cases

In the above formula, π1 is the point estimation of VE, and C is the sample proportion of the test group and the control group.

If the drop-off rate is estimated as 15%, a total of 12605/(1-0.15)×3=44488 cases were needed in the three groups. Considering the per capita distribution in the multi-center study site, 45,000 cases were planned and 15,000 cases in each group and the samples cases were allocated according to features of each site.

9.4.2. Estimation of Sample size for Immunogenicity Study

The estimation of sample size should meet the needs of immunogenicity hypothesis analysis.

(1) Superiority test based on seroconversion rate of antibody after immunization

Referring to the relevant data of Phase I and Phase II clinical trials of this product (the current data are all hypotheses and will be revised later according to the results of Phase I and Phase II clinical trials), the 4-fold growth rate of IgG antibody in placebo group is 10%, the actual difference D1 of the 4-fold growth rate of IgG antibody in test group and control group is 0.30, and the superiority margin δ = 0.20). The hypothesis can only be considered as valid when four-fold growth rate of antibody and GMT both reach the superiority. In order to control the probability of overall type I

error, the probability of type I error (= 0.025/2=0.0125 (One-sided) at each superiority comparison; power 0.90; z test is used for the calculation of test statistic, designed as ration of 1: 1. It is calculated about 445 cases for each group, and 900 cases for each test group according to the estimation of 50% dropouts.

Table 5. Sample Size Required for Antibody Seroconversion rate Superiority test under Different Parameters

Probability level (one-sided)	Superiority Margin	Control rate p2	Rate difference D_1	Power $1-\beta$	Calculate sample size per group	Consider the sample size after 50% dropouts
0.0125	0.20	0.05	0.30	0.90	377	760
0.0125	0.20	0.10	0.30	0.90	445	900

(2) GMT superiority test based on antibody post-immunization

Referring to the relevant data of Phase I and Phase II clinical trials of this product (the current data are all hypotheses and will be revised later according to the results of Phase I and Phase II clinical trials), the standard deviation of antibody titer is set to be about 0.50 (logarithmic scale). The hypothesis can only be considered as valid when the antibody seroconversion rate and GMT both meet superiority. In order to control the probability of overall type I error, the probability of type I error (= 0.025/2 = 0.0125 (one-sided) at each superiority comparison; power is 0.90; The Superiority margin = 0.079 (logarithmic scale, i.e. GMT test group/GMT control group ≥ 1.2 after immunization); The difference D between the average antibody titres (logarithmic scale) of the test group and the control group is 0.20. The standard deviation is 0.5; The experimental group and the control group is designed at a ratio of 1: 1. It is calculated about 425 cases for each group, and 850 cases for each group according to the estimation of 50% dropouts.

Table 6. Sample Size Required for Antibody GMT Superiority Test under Different Parameters

Probability level (One-sided)	Standard deviation (logarithmic scale)	Superiority Margin (Logarithmic Scale)	Mean difference (logarithmic scale)	Power $1-\beta$	Calculate each group Sample size	Estimated sample size after 50% dropouts
0.0125	0.50	0.041 (ratio 1.1)	0.20	0.90	247	500
0.0125	0.50	0.079 (ratio 1.2)	0.20	0.90	425	850

According to the principle of maximizing the sample size, taking into account the factors of dropouts and the distribution of the number of subjects on the multi-center research site.

9.5 Interim analysis

Two interim analyses are planned in this trial when 1/3 and 2/3 of expected COVID-19 cases are observed. Early stopping for efficacy is considered in the interim analysis. Lan DeMets O'Brien-Fleming spending function is employed to control the family-wise type I error within 5% of two-sided. When the number of COVID-19 cases in any one vaccine (vaccine-1 or vaccine-2) and placebo groups achieves 50, the first interim analysis will be performed and the corresponding nominal significance level is α_1=0.0001 (one-sided). When 100 COVID-19 cases in any one vaccine (vaccine-1 or vaccine-2) and placebo groups are observed, the second interim analysis will be conducted and the corresponding nominal significance level is α_2=0.0060 (one-sided). If the null hypothesis is not rejected in the two interim analyses, the nominal significance level of final analysis is α_3=0.0231 (one-sided). In the practical clinical trial, the nominal significance level will be calculated based on the number of COVID-19 cases observed at the interim analysis from pre-specified Lan DeMets O'Brien-Fleming spending function.

The interim analyses will be performed by DSMB.

Since CNBG's COVID-19 inactivated vaccine clinical trial project is following 1 (vaccine 1):1 (vaccine 2):1 (control) three-group settings, in order to ensure the integrity of the clinical trial, the research team cannot access to any information regarding the number of endpoint cases in either the vaccine group or the control group, therefore, the number of cases occurred in individual group can only be unblinded and monitored independently by the DSMB.

When the total number of cases in some vaccine group (such as vaccine 1) and the placebo group reaches 50, the DSMB will conduct the first interim analysis. If the vaccine's efficacy reaches statistical criterion in the first interim analysis, it could suggest that the corresponding vaccine satisfies the basic regulatory requirement on the efficacy of an inactivated SARS-CoV-2 vaccine.

If some vaccine group could not reach statistical criteria at the first interim analysis, the cases will be continuously monitored until 100 cases between the vaccine group and place group, and the second interim analysis will be activated accordingly. If the vaccine's efficacy reaches statistical criterion in the second interim analysis, it could suggest that the corresponding vaccine satisfies the basic regulatory requirement on the efficacy of an inactivated SARS-CoV-2 vaccine.

If some vaccine group could not reach statistical criteria in the two interim analyses, the cases will be continuously monitored until 150 cases, and the final analysis will be conducted, if the

vaccine's efficacy reaches statistical criterion, it could suggest that the corresponding vaccine satisfies the basic regulatory requirement on the efficacy of an inactivated SARS-CoV-2 vaccine, otherwise, the efficacy will be considered as inconclusive.

If vaccine 1 (or vaccine 2) is conditionally approved for marketing authorization based on interim analysis data from a pivotal clinical efficacy trial, then the cases should be continuously monitored post-marketing authorization, until 150 cases are monitored across vaccine 1 (or vaccine 2) study group and placebo group in order to complete the clinical trial.

9.6 Data and Safety Monitoring Board

Data and Safety Monitoring Board (DSMB) will be constructed in this trial. It will perform interim analysis as planned in the protocol, monitor study safety and operation to protect the interest of participating subjects from ethical and safety concerns and ensure the rationality of the study. DSMB consists of one clinician, one epidemiologist and one statistician who are independent of sponsor and have no conflict of interest with the sponsor. DSMB will evaluate the safety and efficacy of the study product and make sure the acceptable risk-benefit ratio of the subjects under exposure. It will be responsible for the proposal regarding trial plan, the safety evaluation and measures to protect subjects' interests. The sponsor will make decision according to DSMB proposal.

The composition, responsibility, management and meeting organization of DSMB will be described in DSMB charter.

10. Ethical and Regulatory Matters

This clinical trial will be conducted by the Sponsor, the Investigator, and delegated Investigator staff and Sub-investigator, in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the ICH guidelines for good clinical practice (GCP), all applicable laws, rules and regulations.

10.1. Independent Ethics Committee and Regulatory Authorities

The ICH-GCP (E6 (R2)) guidelines require that approval must be obtained from an Independent Ethics Committee (IEC) prior to participation of human patients in research studies. Prior to the study onset, the protocol, informed consent, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to the patient or the patient's legal guardian must be approved by the IEC. Documentation of the relevant national IEC approval and of the IEC compliance with ICH Guideline E6 will be maintained by the site and will be available for review by the Sponsor or its designee or by the authorized members of regulatory agencies.

The respective Ethics Committees approvals should be signed by the IEC Chairman or designee and must identify the IEC name and address, the clinical protocol by title and/or protocol number and the date approval and/or favorable opinion was granted. Also a list of the EC members who attended the meeting when the Protocol/ Protocol amendment was discussed, including names and qualifications, needs to be provided by the EC to the investigator or the sponsor/ his representative.

If any alterations, other than changes of administrative nature only, are made to the study protocol, a formal protocol amendment will be issued and submitted to relevant IEC for approval. The amendment will not be implemented until IEC approval, except in cases where immediate implementation is necessary to eliminate or prevent imminent hazard to the patients.

In the same way, approval from regulatory authorities (RA) should be granted before beginning the study. The investigator or the sponsor representative must provide to the regulatory authorities the name and address of the EC along with a statement from the EC that it is organized according to GCP and the applicable laws and regulations. Amendments will be submitted to RA too for approval.

10.2. Responsibilities of the Sponsor

The Sponsor of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial according to ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the e-CRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AE documentation, IP allocation, patient compliance with the instructions, IP accountability, concomitant therapy use, and quality of data.

10.3. Responsibilities of the Investigator

The Investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki (version as of October 2013) as well as with the ICH Note for Guidance on Good Clinical Practice (ICH, Topic E6, R2, 2016), relevant site SOPs and applicable regulatory requirements. These documents state that the informed consent of subjects is an essential precondition for participation in the clinical study.

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the e-CRF, Discrepancy Resolution Form [DRF] or other appropriate

instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data, particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Sub-investigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Sub-investigators shall be appointed and listed in a timely manner. The Sub-investigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

In 1998, the US Food and Drug Administration (FDA) introduced a regulation (21 CFR, Part 54) entitled “Financial Disclosure by Clinical Investigators.” For studies conducted in any country that could result in a product submission to the FDA for marketing approval and which contribute significantly to the demonstration of efficacy and safety of the drug (named “covered studies” by the FDA), the Investigator and all sub-Investigators are obliged to disclose their financial interest which they or their spouses and dependent children may have in the Sponsor. This information is required during the study and until 12 months after its completion.

10.4. Subject Information and Consent

An unconditional prerequisite for a subject participating in the study is his/her or their legal representative written informed consent. Adequate information must therefore be given to the subject by the Investigator/ designated personnel before informed consent is obtained. A subject information sheet in the local language and prepared in accordance with the Note for Guidance on Good Clinical Practice (ICH, Topic E6 (R2)) will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to this written information, the Investigator or his designate will inform the subject verbally. In doing so, the wording used will be chosen so that the information can be fully and readily understood by laypersons. The subject information sheet will be revised whenever important new information becomes available that may be relevant to the consent of subjects.

The patient must be informed that his/her personal trial-related data will be used by CNBG and his subsidiaries (sponsor) in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/ her medical records may be examined by authorized monitors or Clinical Quality Assurance auditors appointed by CNBG and his subsidiaries (sponsor), by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

The Informed Consent Form must be also signed and personally dated by the subject and by the Investigator/person designated by the Investigator to conduct the informed consent discussion. Provision of consent will be confirmed in the CRF by the Investigator. The signed and dated declaration of informed consent will remain at the Investigator's site and must be safely archived

by the Investigator so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated information and consent should be provided to the subject prior to participation.

10.5. Compensation to Subjects

Appropriate insurance coverage is provided by China National Biotec Group (CNBG) in line with legal requirements and GCP guidance. Details can be asked at the investigator's site (certificates and conditions in the Investigator Site File).

Insurance coverage will be provided by a local insurance provider.

10.6. Patient Confidentiality

The investigator(s) will respect and protect the confidentiality of the patient in all possible ways. Patient identification, other than patient number, initials and date of birth, will not appear in any Case Report Form (CRF) pages or other documents given to the Sponsor. Only the investigator and the persons authorized to verify the quality and integrity of the study will have access to patient records where the patient can be identified.

Ensure that the personal secrets of the subjects will not be disclosed under the conditions of testing, biological sample collection, reporting and publication, etc. Only the subject code, blood sample number, blood collection time and test index are recorded in the blood sample. It is strictly limited to the main testers to obtain electronic or written copies.

10.7. Amendment to Patient Related Information

Should a Protocol amendment become necessary, the patient information and consent form may need to be revised to reflect the changes to the Protocol. It is the responsibility of the investigator to ensure that an amended consent form is reviewed and has received approval/ favorable opinion from the IRB / IEC and CA and/or the regulatory authority has provided approval / has been notified (depending on local laws and regulations), and that it is signed by all patients subsequently entered in the trial and those currently in the trial, if affected by the amendment.

10.8. Direct Access to Source Documentation

Source data are all the information in original records and certified copies of original records of clinical findings, observations, or other activities in the study, which are necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (originals or certified copies).

Source Documents are original documents, data, and records (e.g., hospital records, spirometry records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, and pharmacy records or prescriptions, laboratory reports or, computer printouts from the laboratory websites). All of them are expected

to be reviewed signed, dated and assessed by investigator. The source documents must contain study participation information.

It is the Investigator's obligation to collect and present of all relevant medical data in the patient's medical file. Sponsor name and trial number, patient identification (name, date of birth, address, etc.), information that the informed consent was obtained prior any screening procedures, visit dates, patient number, treatment information (treatments assignment, treatment dates, number of unused therapeutic units), medical history, concomitant diseases, efficacy data, safety data, concomitant medications and date and reason of completion of the study.

Source records should be preserved for the maximum period of time required by local requirements.

All information recorded on the CRFs for this study must be consistent with the patient's source documentation.

Besides the monitor of the Contract Research Organization (CRO), regulatory authorities, members of ethics committees and the Sponsor's clinical quality assurance group or any other Sponsor's representative, may carry out source data checks and/or on-site audits or inspections. Direct access to source data will be required for these audits and inspections; they will be carried out giving due consideration to data protection and medical confidentiality. The investigator will assure the CRO, authorities and the sponsor of the necessary support at all times.

11. Study Management

11.1. Case Report Form Handling

The data recorded during the course of this study must be documented in the CRF and/or the "Serious Adverse Events (SAE)" form, and must be forwarded to the sponsor or appointed designee. Then they should be processed, evaluated and stored in anonymous form in accordance with data protection regulations.

The investigator must ensure that the CRFs and any other associated documents contain no mention of any subject names. The CRFs must be completely filled in. They are regulatory documents and must be suitable for submission to authorities.

For eCRFs all data must be derived from source documents. Clinical data will be captured via electronic data capture (EDC) using the CTMS, a web-based tool. The investigator site staff will enter and edit the data via a secure network, with secure access features (username, password and secure identification or username and password – an electronic password system). A complete electronic audit trail will be maintained. The investigator will approve the data using an electronic signature (Ref: 21 CFR Part 11), and this approval is used to confirm the accuracy of the data recorded. The electronic CRFs (eCRFs) will be used, the investigator's data will be accessible from the investigator's site throughout the trial. Relevant medical history prior to enrolment will be documented at the baseline visit. Thereafter during the trial, narrative statements relative to the patient's progress

during the trial will be maintained. The electronic CRFs must be kept current to reflect patient status at each phase during the course of the trial. The patients must not be identified on the electronic CRF by name. Appropriate coded identification (i.e. Patient Number) must be used. The investigator must make a separate confidential record of these details (patient identification code list) to permit identification of all patients enrolled in a clinical trial in case follow-up is required. While a trial is ongoing and until the access to the database has been terminated, there will be no Documentation of Changes (DOCs).

All changes will be requested from the investigator through the EDC system. If a change is necessary once the investigator has no further access to the database, a DOC will be sent to the investigator for confirmation of the change. The investigator's signature is requested to show he/she agrees with the change that was made. The original DOC is kept by the investigator. Copies of the electronic CRF together with all data changes made will be supplied to the investigator at the end of the trial. The investigator will be responsible for retaining all records pertaining to the trial as specified in the appropriate contract.

11.2. Source Data and Subject Files

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

The investigator has to keep a written or electronic subject file for every subject participating in the clinical study. In this subject file, the available demographic and medical information of a subject has to be documented, in particular the following: name, date of birth, sex, height, weight, subject history, concomitant diseases and concomitant drug (including changes during the study), statement of entry into the study, study identification, randomization number, the date of informed consent, all study visit dates, predefined performed examinations and clinical findings, observed AEs, and reason for withdrawal from the study, if applicable.

It should be possible to verify the inclusion and exclusion criteria for the study from the available data in this file.

It must be possible to identify each subject by using this subject file. Additionally, any other documents with source data, especially original printouts of data that were generated by technical equipment have to be filed. This includes but not limited to ECG tracings, X-ray films, CT and MRI scans, laboratory value listings and QoL questionnaires, etc. All these documents have to bear at least the subject identifier and the printing date printed by the recording device to indicate to which subject and to which study procedure the document belongs. The medical evaluation of such records should be documented as necessary and signed/dated by the investigator.

Computerized subject files will be printed whenever source data verification is performed by the monitor. Printouts must be signed and dated by the investigator, countersigned by the monitor and kept in a safe place.

Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the case; also, current medical records must be available.

Data on the patient dairies are considered source data and have to be stored along with the patient file. The data of the dairies will be forwarded to the sponsor or a CRO appointed by the sponsor for data entry into the data base.

11.3. Investigator Site File and Archiving

The Investigator will be provided with an Investigator Site File at the start of the study. This file contains all relevant documents necessary for the conduct of the study. This file must be safely archived after termination of the study. It is the responsibility of the Investigator to ensure that the subject identification sheets are stored for at least 15 years beyond the end of the clinical study. All original subject files must be stored for the longest possible time permitted by the regulations at the hospital, research institute, or practice in question. If archiving can no longer be maintained at the site, the Investigator should notify the Sponsor.

11.4. Monitoring, Quality Assurance and Inspection by Authorities

This study is to be conducted in accordance with the ICH Note for Guidance on Good Clinical Practice (ICH, Topic E6 (R2), 2016). The appointed clinical monitor will arrange regular visits to the study center(s) to check progress with the study and to check CRF completion.

During monitoring visits, the monitors will:

- Help resolve any problems;
- Examine CRF for omission of data, compliance and possible AEs;
- Discuss inconsistencies in the study data;
- Ensure that all study materials are correctly stored and dispensed;
- Check adherence to the obligations of the investigator;
- Review consent forms, in particular the date of consent and signature;
- Perform source data verification as described below.

In line with International Conference on Harmonization (ICH)-Good Clinical Practice (GCP) guidelines, monitoring will include verification of data entered in the CRF against original subject records. This verification will be performed by direct access to the original subject records, and the Sponsor guarantees that subject confidentiality will be respected at all times. Participation in this study will be taken as agreement to permit direct source data verification.

The investigator/ institution will permit trial-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all related source data / documents. eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must

be available at all times for review by the sponsor's clinical trial monitor or a CRO appointed by the sponsor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate (CRA) / on site monitor and auditor may review all CRFs/eCRFs, and written informed consents.

11.5. Changes to the Study Protocol

Changes to, or formal clarifications of, the study protocol must be documented in writing.

Major changes to the protocol will be described in a "Protocol Amendment". It will be submitted to the relevant Ethics Committee(s)/Institutional Review Board(s) and to authorities, where required. Approval/favorable opinion from the relevant Ethics Committee(s)/Institutional Review Board(s) will be required prior to implementation of the amendment.

Any amendment affecting the subject requires the subject's informed consent prior to implementation.

Changes of administrative or technical nature will be recorded in a document entitled "Administrative Change to Study Protocol". It will be sent for information to the relevant Ethics Committee(s)/ Institutional Review Board(s) or to authorities, if so required. Amendments and administrative changes will be signed by all signatories of the protocol.

All Investigators will acknowledge the receipt and confirm by their signature on the Amendment or Administrative Change Signature Sheet that they will adhere to the Amendment/Administrative Change. This sheet will be issued in duplicate and after signing, one will be filed in the Investigator Site File and one in the Study Master File.

11.6. Study Report and Publication Policy

After conclusion of the study, an integrated clinical and statistical study report shall be written by the Sponsor.

The respective EC and competent authority need to be notified about the end of the trial (last patient/patient out) or early termination of the trial.

China National Biotec Group (CNBG) is as much as possible dedicated to support process of free exchange of relevant scientific information. Any publication of the result of this trial must be consistent with the CNBG publication policy. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a general rule, no trial results should be published prior to finalization of the Clinical Trial Report (CTR).

The present trial will be published in a clinical trial registry indicating the trial dates and indication as well as the number of sites and location. The patient identity should be kept confidential.

12. References

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