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Supplementary appendix 2

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Zeng G, Wu Q, Pan H, et al. Immunogenicity and safety of a third dose of CoronaVac, and immune persistence of a two-dose schedule, in healthy adults: interim results from two single-centre, double-blind, randomised, placebo-controlled phase 2 clinical trials. *Lancet Infect Dis* 2021; published online Dec 7. https://doi.org/10.1016/S1473-3099(21)00681-2.

项目名称：新型冠状病毒灭活疫苗（Vero 细胞）I/II期临床试验

方案名称：评价新型冠状病毒灭活疫苗（Vero 细胞）在 18-59 岁健康人中的安全性和免疫原性的随机、双盲、安慰剂对照I/II期临床试验

研究产品名称：新型冠状病毒灭活疫苗（Vero 细胞）

申办者：北京科兴中维生物技术有限公司

研究方：江苏省疾病预防控制中心（江苏省公共卫生研究院）

统计方：北京康特瑞科统计科技有限责任公司

方案编号：PRO-nCOV-1001

方案版本日期：2020 年 12 月 25 日

版本号：1.5

方案批准人：高强

批准人签字：高强

批准日期：2020年 12 月 25日

北京科兴中维生物技术有限公司
SINOVAC RESEARCH & DEVELOPMENT CO., LTD.

主要研究者签字

我同意：

- 承担正确指导在本地区进行该项临床研究的职责。
- 确保本研究按照试验方案及临床研究标准操作规程进行。
- 确保参与本项目的人员充分了解研究产品信息和其它本试验方案中规定的研究相关的职责和义务。
- 确保在未经申办者和伦理委员会（IEC）的审查和书面批准的情况下，不对试验方案做任何更改，除非需要消除对受试者的即刻危害或出于遵从注册管理当局的要求（例如：项目的行政管理方面）。
- 我完全熟悉试验方案中所描述的正确使用该疫苗的方法，完全了解申办者所提供的其它信息，包括但不限于以下内容：现行的研究者手册（IB）或等效文件、研究者手册增补件（如果有）。
- 我熟悉并将遵守《药物临床试验质量管理规范》（GCP）、《疫苗临床试验质量管理指导原则（试行）》和所有现行的法规要求。

主要研究者姓名：朱凤才

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日期：2020 年 12 月 30 日

Project Title: Phase I/II Clinical Trial for COVID-19 Vaccine (Vero Cell), Inactivated

Protocol Title: A Randomized, Double-Blinded, Placebo-Controlled, Phase I/II Clinical Trial, to Evaluate the Safety and Immunogenicity of the COVID-19 Vaccine (Vero Cell), Inactivated in Healthy Adults Aged 18~59 Years

Product Name: COVID-19 Vaccine (Vero Cell), Inactivated

Sponsor: Sinovac Research & Development Co., Ltd.

Research Organization: Jiangsu Provincial Center for Disease Control and Prevention (Public Health Research Institute of Jiangsu Province)

Statistical Organization: Beijing KEY TECH Statistical Technology Co., Ltd.

Protocol No.: PRO-nCOV-1001

Protocol version/date: December 25, 2020

Version No.: 1.5

Protocol approver: Gao Qiang

Signature of approver:

Approval date: MM/DD/YY

北京科兴中维生物技术有限公司
SINOVAC RESEARCH & DEVELOPMENT CO., LTD.

Signature of Principal Investigator

I hereby agree to:

- Assume the responsibility for properly instructing the Clinical Research in this region.
- Ensure that the Research is carried out in accordance with the Trial Protocol and standard operating procedure for clinical research.
- Ensure that the personnel involved in the Project have a full knowledge of the research product information, as well as other responsibilities and obligations in connection with the Research as specified in the Trial Protocol.
- Ensure that no change will be made to the Trial Protocol without review and written approval of the Sponsor and the Independent Ethics Committee (IEC), unless it is necessary to eliminate the immediate hazard to the subjects or as required by the registration authority (for example: in terms of administration of the Project).
- I am thoroughly familiar with the methods for properly using the Vaccine as described in the Trial Protocol and have a full knowledge of other information provided by the Sponsor, including but not limited to the following: the current Investigator's Brochure (IB) or equivalent document and Supplementary Documents to the Investigator's Brochure (if any).

- I am familiar with and will comply with the *Good Clinical Practice* (GCP), *Guidelines for Quality Management of Vaccine Clinical Trial (Trial)* and all prevailing regulatory requirements.

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Revision History of the Protocol

S/N	Original version No./version date/revision part	Current version No./version date/revision description
1	Version 1.4 /June 30, 2020/4. Preclinical Research and Laboratory Evaluation of Vaccine	In Version 1.5/December 25, 2020, reproductive development toxicity test on rats was updated.
2	Version 1.4 / June 30, 2020 /5. Preliminary Clinical Trial	In Version 1.5/December 25, 2020, immunization persistence results after two doses of immunization and immunogenicity results after three doses of immunization were added.
3	Version 1.4 / June 30, 2020 / 6.2 Vaccine stability	In Version 1.5/December 25, 2020, stability research findings were supplemented.
4	Version 1.4/June 30, 2020/8.2.1 Phase I test endpoint	In Version 1.5/December 25, 2020, "Positive rate of IgG and IgM antibodies 6 months after the full-course vaccination of test vaccine", "positive rate of antinuclear antibody on Day 194 after the first dose of test vaccine" and "positive rate of antinuclear antibody on Day 208 after the first dose of test vaccine" were added in exploratory endpoint.
5	Version 1.4 / June 30, 2020 / 8.2.2 Phase II test endpoint	In Version 1.5/December 25, 2020, relevant test endpoint for booster immunization 6 months after Day 0, Day 14 and Day 0, Day 28 schedule was added.
6	Version 1.4 / June 30, 2020 / 8.3.2 Phase II research plan & 10.1 Visit plan & 10.6 Sample collection plan	6-month booster immunization after the second dose of vaccination was added into day 0, 14 and day 0, 28 primary immunization schedule in Version 1.5 / December 25, 2020/research plan. Besides, the corresponding visit and sample collection were added in the visit plan.
7	Version 1.4 / June 30, 2020 / 10.7.7 Report on serious adverse events (SAE)	In Version 1.5/December 25, 2020, the reporting requirements for serious adverse events were revised according to 2020 New GCP.
8	Version 1.4/June 30, 2020 /10.11.1 Analysis set	In Version 1.5/December 25, 2020, the division of data analysis set was revised according to the revision of this

S/N	Original version No./version date/revision part	Current version No./version date/revision description
		immunization schedule.
9	After version 1.5 is approved, version 1.4 is null and void	
10	Version 1.3/June 25, 2020	In Version 1.4/June 30, 2020, the enrollment method for the third dose was changed to enrollment of 30 subjects under Day 0, Day 14, Day 42 schedule, and another 30 subjects were enrolled under Day 0, Day 28, Day 56 schedule; the third dose was given after it was confirmed that the above subjects were safe.
11	Version 1.3/June 25, 2020	In Version 1.4 / June 30, 2020, "blood collection on D3 before and after the third dose of immunization" was added for 60 subjects numbered C001 ~ C030 and D001 ~ D030.
12	After version 1.4 is approved, version 1.3 is null and void	
13	Version 1.2/April 14, 2020	In Version 1.3/June 25, 2020, "5. Preliminary Clinical Trial" was added.
14	Version 1.2/April 14, 2020	In Version 1.3/June 25, 2020, immunization schedule for some subjects vaccinated with the third dose was added in phase II clinical trial.
15	Version 1.2/April 14, 2020	In Version 1.3/June 25, 2020, the observation time of 3-dose immunization schedule was extended from 6 months to 12 months during phase II clinical trial.
16	After Version 1.3 is approved, Version 1.2 is null and void	
17	Version 1.1/ April 14, 2020/8.6 Test suspension and termination criteria	In Version 1.2/April 14, 2020, "After each dose of vaccination, statistics were given on adverse reaction of the subjects, and the test was suspended or terminated according to the following criteria" was added in "8.6 Test suspension and termination criteria" This criterion is determined as the suspension and termination criteria for vaccination groups.
18	Version 1.1/April 14, 2020/9.2 Subject exclusion criteria	In Version 1.2/April 14, 2020, "(Only for Phase I)" was deleted from "(7) IgG or IgM screening result was positive (only for Phase I);" "(only for Phase I)" was deleted from "(7) RT-PCR result of throat

S/N	Original version No./version date/revision part	Current version No./version date/revision description
		or anal swabs was positive (only for Phase I)"
19	Version 1.1/ April 14, 2020/Table 9, Tables 13-16, Tables 19-22	In Version 1.2/April 14, 2020, "Anti-nuclear antibody test" was added in Table 9; "anti-nuclear antibody test, IgG and IgM screening, RT-PCR test of throat and anal swabs" was added in "Tables 13-16"; the collection time of informed consent and demographic information was changed into visit 0; "anti-nuclear antibody" was added in Tables 19-22
20	After Version 1.2 is approved, Version 1.1 is null and void	
21	Version 1.0/April 11, 2020 2.6 Organization for the Trial Sample Test	In Version 1.1/April 14, 2020, antinuclear antibody (ANA) test was added.
22	Version 1.0/April 11, 2020 8.2.1 Endpoints of phase I trial	In Version 1.1/April 14, 2020/exploratory endpoint, "Positive rate of antinuclear antibody on Day 7/14/21/28/42 after the first dose of test vaccine (emergency immunization schedule); positive rate of antinuclear antibody on Day 28/35/42/56 after the first dose of test vaccine (routine immunization schedule)" was added.
23	Version 1.0/April 11, 2020 9.2 Exclusion Criteria for Subjects	In Version 1.1/April 14, 2020, "with SARS record in self-report" was added in exclusion criteria.
24	Version 1.0/April 11, 2020 9.2 Exclusion Criteria for Subjects	In Version 1.1/April 14, 2020, "Platelet count (PLT)" was added in routine blood indexes for laboratory screening.
25	Version 1.0/April 11, 2020 10.1 Visit plan	In Version/April 14, 2020, the time of visit 0 in Tables 11 and 12 was changed from "D-14~0" into "D-7~0".
26	Version 1.0/April 11, 2020 10.5 Safety Follow-up and Observation	In Version 1.1/April 14, 2020, "The investigator paid a visit and collected safety data on Day 0-7" was changed into "the investigator paid a visit (not less than 2 face-to-face visits in Phase I)".
27	Version 1.0/April 11, 2020 10.6 Sample collection	In Version 1.1/April 14, 2020, "Serum shall be separated from venous blood samples for serum antibody (neutralizing antibody/IgG/IgM) test and serum inflammatory factor + antinuclear

S/N	Original version No./version date/revision part	Current version No./version date/revision description
		antibody test in time, placed into 2 tubes (no less than 1ml for single serum tube A in phase I and no less than 0.5ml in phase II, and tube B for backup serum), and recorded" was changed into "Serum shall be separated from blood samples for serum antibody (neutralizing antibody/IgG/IgM) test, placed into 2 tubes (no less than 1ml for serum tube A in phase I and no less than 0.5ml in phase II, and tube B for backup serum), and recorded".
28	Version 1.0/April 11, 2020 10.7.1 Safety Observation Indexes	In Version 1.1/April 14, 2020, "Platelet count (PLT)" was added in routine blood indexes.
29	Version 1.0/April 11, 2020 10.7.6 Handling of Adverse Events	In Version 1.1/April 14, 2020/test observation, subjects who developed fever, with cough and other respiratory symptoms should be seen immediately at the designated hospitals, throat swabs/sputum and anal swabs should be collected if necessary. Besides, imaging examinations such as CT should be performed to analyze and determine if the disease was caused by COVID-19 infection. In case of novel coronavirus infection, it shall be treated according to SAE, and the presence of ADE phenomenon was especially analyzed.

List of Abbreviations of the Protocol

PROTOCOL TITLE	A Randomized, Double-Blinded, Placebo-Controlled, Phase I/II Clinical Trial, to Evaluate the Safety and Immunogenicity of the SARS-CoV-2 Inactivated Vaccine in Healthy Adults Aged 18~59 Years
SPONSOR	Sinovac Research & Development Co., Ltd.
PROJECT PHASE	Phase I/II
OBJECTIVE(S)	To evaluate the safety and immunogenicity of SARS-CoV-2 vaccine
EXPERIMENTAL DESIGN OF THE TRIAL	A randomized, Double-blinded, Placebo-Controlled, Phase I/II Clinical Trial
PLANNED SAMPLE SIZE	Total of 744 subjects， with 144 in the phase I and 600 in the phase II clinical trial
SUBJECT SELECTION CRITERIA	Healthy adults aged 18-59 years, with equal percentage of each gender
NAME AND FORMULATION OF DRUG	SARS-CoV-2 Inactivated Vaccine -Inactivated SARS-CoV-2 -Aluminum hydroxide, disodium hydrogen phosphate, sodium dihydrogen phosphate, sodium chloride, etc.
DOSAGE AND SCHEDULE	Dosage: 0.5ml per dose Phase **I** Emergency Immunization Schedule: Day 0,14 Routine Immunization Schedule: Day 0,28 Phase **II** Emergency Immunization Schedule: Day 0,14,42 or Day 0,14 Routine Immunization Schedule: Day 0,28,56 or Day 0,28 A booster dose is given 6 months after the days 0, 14 or days 0, 28 primary immunization schedule in the phase II trial.
ROUTE OF ADMINISTRATION	Intramuscularly, deltoid region
CHALLENGE SCHEDULE, if applicable	None
BLOOD SAMPLE COLLECTION	The blood-collection time points for different vaccination schedules were listed below: **The schedule of day 0,14 (Phase I)**

	Blood collection on day 0(-7),3,7,14,17,21,28,42,194 **The schedule of day 0,28 (Phase I)** Blood collection on day 0(-7),3,7,28,31,35,42,56, 208 **The schedule of day 0,14,42 (Phase II)** Blood collection on day 0,28,42,45,70, 222,402 **The schedule of day 0,14 (plus the 6-month booster dose, Phase II)** Blood collection on day 0,28,42,194; 1 month and 6 months after the booster dose. **The schedule of day 0,28,56 (Phase II)** Blood collection on day 0,56,59,84, 236,416 **The schedule of day 0,28 (plus the 6-month booster dose, Phase II)** Blood collection on day 0,56, 208; 1 month and 6 months after the booster dose
PARAMETERS OF SAFETY	**Primary Endpoint** – Incidence of adverse reactions occurred from Day 0 to Day 28 after each dose. **Secondary Endpoints** – Incidence of adverse reactions 7 days after each dose of vaccination; – Phase I : Incidence of abnormal laboratory index (blood routine test, blood chemistry test, and urine routine test) on the 3th day after each dose of vaccination in phase I; – Incidence of SAEs from the beginning of the vaccination to 6 months post the whole-schedule vaccination. **Exploratory Endpoints** – Phase I : The change of IL-6, IL-2, and TNF-α in serum 7 days after each dose of vaccination in phase I; – Phase I: The positive rate of serum antinuclear antibody on the 7/14/21/28/42/194th day after the first dose vaccination (emergency schedule); – Phase I : The positive rate of serum antinuclear antibody on the 28/35/42/56/208th day after the first dose vaccination (routine schedule); – Phase II: The positive rate of serum antinuclear antibody on the 28/42/70 th day after the first dose vaccination (days 0,14,42 emergency schedule);

	– Phase II: The positive rate of serum antinuclear antibody on the 28/42/194th day after the first dose vaccination (days 0,14,194 emergency schedule); – Phase II: The positive rate of serum antinuclear antibody on the 56/84th day after the first dose vaccination (days 0, 28,56 routine schedule); – Phase II: The positive rate of serum antinuclear antibody on the 56/208th day after the first dose vaccination (days 0,28, 208 routine schedule).
PARAMETERS OF IMMUNOGENICITY	**Primary Endpoint** – The seroconversion rate of neutralizing antibodies 14 days (emergency schedule)/28 days (routine schedule) after the two-dose vaccination. **Secondary Endpoints** – The seropositive rate, GMT, and GMI of neutralizing antibodies 14 days (emergency schedule)/28 days (routine schedule) after two-dose vaccination; – The seroconversion rate, seropositive rate, GMT and GMI of neutralizing antibodies 28 days after the two doses (emergency schedule); – Phase II: The seroconversion rate, seropositive rate, GMT, and GMI 28 days after the third dose (only for days 0,14,42 and days 0,28,56 schedule); – Phase II: The seropositivity rate, GMT, and GMI 14 day (emergency schedule)/28 days (routine schedule) after the booster dose (only for days 0,14 and days 0,28 schedule); – Phase I: The seroconversion rate, seropositive rate, GMT, and GMI 7/14/21 days after the first dose vaccination (emergency schedule); – Phase I: The seroconversion rate, seropositive rate, GMT, and GMI 28/35/42 days after the first dose vaccination (routine schedules); – Phase I: The seropositive rate of IgG, IgM antibodies 7/14/21/28/42 days after the first dose vaccination (emergency schedule); – Phase I: The seropositive rate of IgG, IgM antibodies 28/35/42/56 days after the first dose vaccination (routine schedule). **Exploratory Endpoints** – Phase I: Positive rate of specific T cell response 14 days after vaccination (IFN-γ detection using Elispot);

	– The seropositive rate and GMT of neutralizing antibody at 6 months after the second dose (only for the days 0,14 and days 0,28 schedule); – Phase II: The seropositive rate, GMT, and GMI of neutralizing antibody at 12 months after the third dose (only for the days 0,14,42 and days 0,28,56 schedule); – Phase II: The seropositive rate and GMT of neutralizing antibody at 14 days (emergency schedule) or 28 days (routine schedule) after the booster dose (only for the days 0,14 and 0,28 schedule); – Phase II: The seropositive rate and GMT of neutralizing antibody at 6 months after the booster dose (only for the days 0,14 and 0,28 schedule)

List of Vocabulary Abbreviations

ADE	Antibody Dependent Enhancement
AE	Adverse Event
ALB	Albumin
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CDC	Center for Disease Control and Prevention
CDE	Center for Drug Evaluation
CFDA	China Food and Drug Administration
CK	Creatine Kinase
COVID-19	Corona Virus Disease 2019
CPK	Creatine Phosphokinase
NMPA	National Medical Products Administration
CFDI	Center for Food and Drug Inspection
CRF	Case Report Form
eCRF	Electronic Case Report Form
ELISA	Enzyme-Linked Immune-sorbent Assay
ELISPOT	Enzyme-Linked Immuno-spot Assay
EDC	Electronic Data Capture
FAS	Full Analysis Set
GCP	Good Clinical Practice
IEC	Independent Ethics Committee
ITT	Intention-to-Treat
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
PI	Principal Investigator
PPS	Per Protocol Set
PT	Preferred Term
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SOC	System Organ Class
SOP	Standard Operation Procedure
SS	Safety Set
SUSAR	Suspected Unexpected Serious Adverse Reaction

Summary of the Clinical Protocol

The COVID-19 Vaccine, Inactivated developed by Sinovac Research & Development Co., Ltd. (hereinafter referred to as "SINOVAC") is capable to induce the body to produce active immunity and prevent the disease caused by SARS-CoV-2. The results of the preliminary immunogenicity research show that the COVID-19 Vaccine, Inactivated can produce a good neutralizing antibody response in animals, which preliminarily proves the effectiveness of the vaccine. At the same time, a comprehensive safety evaluation has been conducted in animals, the preliminary results of which show that the new vaccine is safe for animals. The Clinical Trial Protocol is hereby formulated in accordance with relevant requirements of the *Provisions of Drug Registration*[1], *Good Clinical Practice* (GCP)[2], *Technical Guidelines for Clinical Trial of Vaccines*[3], *Guidelines for Quality Management of Vaccine Clinical Trial (Trial)*[4] and *Technical Guidelines for Research and Development of Vaccine for Prevention of SARS-CoV-2 (Trial)*[5].

The main objective of the Trial is to evaluate the safety and immunogenicity of the test vaccine. The randomized, double-blinded and placebo-controlled experiment design is applied. 144 healthy adults aged 18~59 year are selected as the subjects of phase I clinical trial. Upon informed consent, physical examination and screening based on the inclusion/exclusion criteria, the subjects are enrolled to be vaccinated by 2 doses respectively according to the emergency immunization schedule of day 0,14 and the routine immunization schedule of day 0,28. 72 subjects are enrolled for each immunization schedule in stages of medium and high doses respectively, each with 36 subjects, who are vaccinated by the test vaccine or placebo respectively at the ratio of 2:1. According to the occurrence of the solicited and non-solicited adverse events, and of the abnormal indexes of blood routine examination, blood biochemistry and routine urine test, the vaccination in the stage of high dose may be conducted only 0~7 days after the first dose in the stage of medium dose is vaccinated when the safety observation is completed and the safety is confirmed by DMC.

The immediate reaction within 30 minutes after each dose of vaccination is observed, the local and systemic solicited adverse events within 0~7 days and the non-solicited adverse events from the beginning of the vaccination to 28 days after the whole-schedule vaccination are collected, and the SAE monitoring from the beginning of the vaccination to 6 months after the whole-schedule vaccination is completed.

The blood of volunteers was sampled at different times before and after immunization to test the blood routine, blood biochemistry, urine routine, serum inflammatory factors and anti-nuclear antibodies and evaluate the safety of the vaccine; test the serum neutralizing antibody, IgG and IgM antibodies and IFN-γ secretory reaction of specific T cells and evaluate the immunogenicity and immunization persistence of the vaccine.

According to the occurrence of the solicited and non-solicited adverse events, and of the abnormal indexes of blood routine examination, blood biochemistry and routine urine test, phase II clinical trial may be started only 0~7 days after the first high dose of phase I clinical trial is vaccinated when the safety observation is completed and the safety is confirmed by DMC. 600 healthy adults aged 18~59 years were selected as the subjects of the clinical trial for Phase II clinical trial. Upon informed consent, physical examination and screening based on the inclusion/exclusion criteria, the subjects are enrolled to be vaccinated according to Day 0, Day 14, Day 42 or Day 0, Day 14 emergency immunization schedule or Day 0, Day 28, Day 56 or Day 0, Day 28 routine immunization schedule. 300 subjects were enrolled for each immunization schedule, randomized into 3 groups by a ratio of 2:2:1 and were vaccinated by the medium dose, high dose or placebo respectively. The immunization schedule for the subjects numbered C001~C150 was Day 0, Day 14 and Day 42, while that for the subjects numbered C151~C300 was Day 0, Day 14. The immunization schedule for the subjects numbered D001~D150 was Day 0, Day 28 and Day 56, while that for the subjects numbered D151~D300 was Day 0 and Day 28. The subjects given the third dose of Day 0, Day 14, Day 42 and Day 0, Day 28, Day 56 immunization schedule were enrolled in phases, and a total of 30 subjects numbered C001 ~ C030 were given the

third dose first, and 30 subjects numbered D001 ~ D030 were given the third dose based on the abnormalities in blood routine and blood biochemical indexes and the occurrence of adverse events on Day 0 ~3 after vaccination. After it was preliminarily confirmed safe, a total of 30 subjects numbered D001~D030 were given the third dose. It is confirmed safe through assessment, the subjects numbered C031 ~ C150 and D031 ~ D150 may be given the third dose based on the abnormalities in blood routine and blood biochemical indexes and the occurrence of adverse events of 30 subjects in each of the above groups on Day 0~7 after vaccination.

The adverse immediate reaction within 30 minutes after each dose of vaccination was observed; the local and systemic solicited adverse events on Day 0~7 and the non-solicited adverse events on Day 0~28 (Day 0~14 for the first dose under the emergency immunization schedule) after each vaccination were collected, and the SAE monitoring from the beginning of the vaccination to 6 months after full-course vaccination. The blood of volunteers is sampled at different times before and after immunization to test the serum neutralizing antibody for evaluating the immunogenicity and immunization persistence. Volunteers numbered C001~C030 and D001~D030 were required to have blood collected on D3 before and after the third dose for laboratory testing to evaluate the safety of the vaccine. If the blood routine and blood biochemical indexes before the immunization for the third dose were abnormal and had a clinical significance (Grade 2 or higher), the subjects would not be given the third dose.

Based on the immunogenicity results 6 months after 2 doses of vaccination in this study, the subjects under Day 0, Day 14 (C151~C300) and Day 0, Day 28 (D151~D300) 2-dose primary immunization schedules were given 1 dose of booster immunization 6 months after primary immunization. The adverse immediate reactions within 30 min after booster immunization were observed; local and systemic solicited adverse events on Day 0~7 and the non-solicited adverse events on Day 0~28 after inoculation were collected; and the SAE monitoring 6 months after inoculation was completed.

The Clinical Protocol will be under sole responsibility of the Investigator upon approval by the Independent Ethics Committee. The Monitor designated by the Sponsor

will conduct monitoring of the whole research process and the Data Monitoring Committee (DMC) will be established for risk assessment of the clinical trial to ensure that the Trial is carried out in a safe and standard way.

Contents

1 Introduction

The COVID-19 Vaccine (Vero Cell), Inactivated (hereinafter referred to as "COVID-19 Vaccine") developed by Sinovac Research & Development Co., Ltd. (hereinafter referred to as "SINOVAC") is capable to induce the body to produce active immunity and prevent the disease caused by SARS-CoV-2. The results of the preliminary immunogenicity research show that the COVID-19 Vaccine, Inactivated can produce a good neutralizing antibody response in animals, which preliminarily proves the effectiveness of the vaccine. At the same time, a comprehensive safety evaluation has been conducted in animals, the preliminary results of which show that the COVID-19 Vaccine is safe for animals. The Clinical Protocol is hereby formulated to evaluate the safety and immunogenicity of the COVID-19 Vaccine.

2 Participating Organizations and their Responsibilities

2.1 Organization Responsible for the Clinical Trial

2.1.1 Responsibilities

The organization responsible for the Clinical Trial is Jiangsu Provincial Center for Disease Control and Prevention (Public Health Research Institute of Jiangsu Province), the main responsibilities of which are as follows:

- Participating in the formulation of tables and cards required by the Vaccine Clinical Trial Protocol and the Trial;
- Participating in the drafting of informed consent for vaccination, the preparation of SOP for site operation of the Clinical Trial, and the application for approval by the Independent Ethics Committee; organizing the selection and assessment of the site for the Clinical Trial that meets the requirements of GCP, and filing with the "Record Management Information Platform for Drug Clinical Trial Institutions" of the National Medical Products Administration;
- Organizing the implementation of the Clinical Trial, and performing quality control over its implementation process;
- Instructing the site, reporting Serious Adverse Events occurring during the Clinical Trial to the provincial medical products administration, Sponsor and

Independent Ethics Committee in a timely manner, and carrying out investigation and handling;

- Participating in database locking and keeping a backup of the locked database for verification;
- Reporting the implementation progress of the Clinical Trial to relevant administrative departments and writing the summary report of the Clinical Trial.

2.1.2 Organization Introduction

Jiangsu Provincial Center for Disease Control and Prevention (Public Health Research Institute of Jiangsu Province), as a non-profit public institution engaged in disease control and prevention under direct leadership of Jiangsu Commission of Health, is established by merger of former Jiangsu Provincial Sanitation and Anti-epidemic Station (Jiangsu Institute for Tuberculosis Control), Jiangsu Provincial Institute for Occupational Disease Prevention and Treatment (Jiangsu Provincial Hospital for Occupational Disease Prevention and Treatment), Health Propaganda & Education Institute of Jiangsu and Jiangsu Provincial Institute for Dermatology Prevention and Treatment (Jiangsu Provincial Monitoring Center for Venereal Disease), later adding Jiangsu Provincial Sanitation Test Center and Public Health Research Institute of Jiangsu Province, and is a first-class provincial disease control and prevention institution in China. The Center is currently governing 31 institutes (departments and offices), including the specialty disciplines such as prevention and control of acute infectious diseases, prevention and control of venereal diseases and AIDS, prevention and control of chronic non-communicable diseases, prevention and control of occupational diseases, food safety and evaluation, toxicology and function evaluation, physical and chemical testing, pathogenic microorganism research, health education and health promotion, and public health information. It has strong capabilities in scientific research, monitoring, testing, prevention and control. In recent years, Jiangsu Provincial Center for Disease Control and Prevention has made fruitful achievements in responding to various public health emergencies and emerging infectious diseases,

as well as in the follow-up scientific research. The Center has presided over and participated in the clinical research of more than 100 vaccines, such as common vaccines or other biological products for influenza, epidemic hemorrhagic fever, rabies, chickenpox, leprosy gills, meningitis, hepatitis B, tuberculosis, typhoid fever, diphtheria pertussis tetanus, haemophilus influenzae and interferon, as well as new vaccines such as the world-leading Ebola vaccine, enterovirus 71 vaccine, hepatitis E vaccine, HPV vaccine, pandemic influenza vaccine, staphylococcus aureus vaccine and influenza A H1N1 vaccine. The Institute for Vaccine Clinical Evaluation has 8 senior professional titles, 3 intermediate professional titles, 2 primary professional titles, 11 physicians and 2 laboratory technicians.

2.2 Site Organization of the Clinical Trial

2.2.1 Responsibilities

The site of the Clinical Research is located in Suining County and the research site organization is the Center for Disease Control and Prevention of Suining County, the main responsibilities of which are as follows:

- Cooperating in the assessment and filing of the test site;
- Organizing personnel with corresponding expertise and rich clinical research experience to participate in the work on the research site, and all participants to read and understand the content of the research protocol in detail and strictly observe the protocol to ensure that there is sufficient time to complete the clinical research within the time limit as specified;
- Organizing the on-site implementation, including the organization and selection of subjects, obtaining the *Informed Consent* signed by subjects, screening and enrollment, vaccination, safety visit, sample collection, serum separation, sample cryopreservation and submission;
- Data input and ensuring that all collected data are true, accurate, complete and legal;

- Accepting the monitoring and inspection by the Monitor or Inspector dispatched by the Sponsor, and the inspection and visit by the medical products administration to ensure the quality of the Clinical Research;
- Ensuring that subjects are properly handled when they suffer adverse reactions/events during the research, and in case of serious adverse reactions/events, taking appropriate treatment measures for the subjects immediately, and reporting to the Sponsor, Independent Ethics Committee and provincial medical products administration;
- Keeping relevant clinical trial data during the Clinical Trial.

2.2.2 Organization Introduction

The Center for Disease Control and Prevention of Suining County is located 200m to the north of the intersection of Suihe North Road and Yongchang Road in Suining County, with 54 persons as the authorized personnel force and 48 as the actually permanent staff. Among them, there are 42 health professionals, 28 college graduates or above, 9 junior college graduates, 5 technical secondary school graduates, 10 senior technical professionals and 7 intermediate technical professionals. The Center consists of 10 departments, namely General Department, Health Education Department, Disease Control Department, Quality Control Department, Emergency Response Office, Endemic and Parasitic Disease Prevention and Control Department, Health Department, Health Laboratory Department, Chronic Non-communicable Disease Control and Prevention Department, and Outpatient Department of CDC. It has been awarded the Advanced Collective of Disease Control and Prevention in Xuzhou and the Progress Award of Disease Control and Prevention in Xuzhou for many times. The Center's laboratory has passed the "Laboratory Qualification Accreditation" and "Food Inspection Qualification Accreditation" organized by the Quality and Technology Supervision Bureau of Jiangsu.

The Center for Disease Control and Prevention of Suining County has always been focused on laboratory construction, and now has advanced detection and testing instruments and equipment such as gas chromatography - mass spectrometer, atomic

absorption spectrometer, ion chromatography, atomic fluorescence spectrometer and PCR detector. In 2017, the government invested more than RMB 2 million for the Center to add flow injection analyzer, automatic biochemical analyzer, five-category globulimeter and other equipment. In 2017, the Center's laboratory successfully passed the provincial laboratory qualification accreditation and participated in the external proficiency testing and laboratory comparison for 9 times, all with excellent performance. At present, the Center has 143 test items passing the qualification accreditation or recognition, and the coverage of laboratory accreditation is 80%.

The Center for Disease Control and Prevention of Suining County has undertaken many projects for consecutive years, including the Measles, Rubella and Parotitis Immunity Level Monitoring and Etiology Surveillance Project, the Fifth Round Global Fund Malaria Project, the Global Fund AIDS Project, the National Normal Iodine Program, the Comprehensive Mosquito-borne Disease Monitoring Project in Jiangsu, the Adult Tobacco Epidemic Survey in China and the National Residents' Health Literacy Monitoring Project.

It has successively undertaken phase I clinical trial of the typhoid A paratyphoid conjugate vaccine of Royal (Wuxi) Bio-pharmaceutical Co., Ltd., phase III clinical trial of Influenza Vaccine (Split Virion), Inactivated, Quadrivalent of Shanghai Institute of Biological Products Co., Ltd. and phase Ib clinical trial of recombinant staphylococcus aureus vaccine (escherichia coli) of Olymvax Biopharmaceuticals Inc. On June 27-28, 2018, it accepted the GCP site inspection by the former Center for Food and Drug Inspection of China Food and Drug Administration.

2.3 Sponsor of the Clinical Trial

2.3.1 Responsibilities

The Sponsor of the Clinical Trial is Sinovac Research & Development Co., Ltd., the main responsibilities of which are as follows:

- Providing the preliminary clinical trial protocol and approving the final protocol with signature and seal.

- Providing approval documents for the Clinical Research, the Investigator's Brochure for the Clinical Trial (preclinical safety information of the product), executive standards for products and other site application documents.
- Providing vaccines for the Clinical Research and issuing the acceptable verification report.
- Evaluating and selecting the responsible organization and site of the Clinical Trial, assigning the Monitor to perform the assessment and accreditation of the site of the Clinical Trial and the monitoring duties according to the GCP requirements, and being ultimately responsible for the quality of the Clinical Trial.
- Participating in the investigation and handling of the cases with abnormal reaction to vaccine, and providing medical treatment and relevant compensation for the cases with clinically proven abnormal reaction related to the vaccination according to relevant regulations. For other cases, please refer to the Working Agreement.
- Providing funds for the Clinical Research.

2.3.2 Organization Introduction

Sinovac Research & Development Co., Ltd., as the former R&D Center of Sinovac Biotech Co., Ltd. and a biological high-tech enterprise solely-invested and established by Sinovac Biotech (Hong Kong) Limited, was incorporated in 2009, with the registered capital of USD 9.60 million. The Company is a Zhongguancun high-tech enterprise and Zhongguancun gold seed enterprise.

SINOVAC is specialized in the research, development and technical services of vaccines for human use and related products to provide technical support for the prevention and control of serious infectious diseases. Relying on the Group's advantages in vaccine research and development and industrialization over the years, the Company has gradually formed a research and development mode with enterprises as the main body of research and development and the combination of the efforts of enterprises, universities and research institutions, and built the virus isolation

identification technology platform, cell factory platform, microcarrier fermentation technology platform, virus purification technology platform, bacterial fermentation and purification platform, polysaccharide-protein combination technology platform, freeze-drying technology platform, animal evaluation platform, quality control platform and diagnostic reagent raw materials development platform, the expertise of which complements each other's advantages with cross penetration to promote the stable and efficient progress of Company's research and development.

SINOVAC has undertaken 2 special projects of national major new drug development and one science and technology program in Beijing, and obtained 12 authorized patents for invention in China. The clinical research of the 23-valent pneumopolysaccharide vaccine developed by the Company has been successfully completed and its industrialization has been realized in Sinovac. The Company is developing DPT polio Hib series combined vaccine, 13-valent pneumococcus conjugate vaccine, recombinant hepatitis B vaccine and other varieties.

2.4 Organization 1 for the Trial Sample Test

2.4.1 Responsibilities

Traditional Chinese Medicine Hospital of Suining County, the main responsibilities of which are as follows:

- Performing blood routine examination, blood biochemistry and routine urine test.

2.4.2 Organization Introduction

The Traditional Chinese Medicine Hospital of Suining County is a tertiary general traditional Chinese medicine hospital integrating medical treatment, first aid, teaching, scientific research, prevention, health care and rehabilitation with advanced equipment, powerful technology, complete specialties and orderly management. It is a "Baby Friendly Hospital" named by the Ministry of Health, a teaching hospital of Nanjing University of Chinese Medicine, a "Safe Hospital" in Jiangsu, a demonstration unit of "Safe Consumption" in Jiangsu, a member of the "Cooperative Development Consortium of Traditional Chinese Medicine Hospitals in Nanjing Metropolitan Area" in Jiangsu, and a "Technical Collaboration Hospital of Traditional Chinese Medicine

Hospitals in Jiangsu". In recent years, it has been awarded the "People's Satisfaction Hospital" and "Civilized Unit" in Xuzhou.

The Hospital is divided into south and north areas, where the south area has a floor area of 36.4mu and a building area of 48,000m^2. There are 28 clinical departments, 10 medical laboratories, 14 wards, 400 approved beds and 715 actually open beds. There are currently 1,177 employees, including 283 with intermediate and senior titles, 2 doctoral students and 11 postgraduates. The Hospital is well equipped with all kinds of modern diagnostic and treatment equipment, currently with 510 pieces of modern diagnostic and treatment equipment at a value over RMB 10,000. The north area of the Hospital is an important livelihood project in Suining County and is expected to be put into use in 2020 according to the requirements and construction standards of a tertiary hospital. The completion of the branch will make the Hospital the largest and most complete modern hospital with green gardens, ecological environment protection, low carbon and energy saving in Suining County, and provide reliable guarantee for the construction of a tertiary traditional Chinese medicine hospital leading in the North Jiangsu Region.

2.5 Organization 2 for the Trial Sample Test

2.5.1 Responsibilities

The Center for Disease Control and Prevention of Suining County, the main responsibilities of which are as follows:

- IgG and IgM screening of volunteers before enrollment;
- PT-PCR nucleic acid tests by throat swab and anal swab of volunteers.

2.5.2 Organization Introduction

See Section 2.2.2.

2.6 Organization 3 for the Trial Sample Test

2.6.1 Responsibilities

National Institutes for Food and Drug Control, the main responsibilities of which are as follows:

- Test of serum neutralizing antibody, IgG, IgM and anti-nuclear antibodies in

enrolled subjects.

2.6.2 Organization Introduction

National Institutes for Food and Drug Control is a public institution directly under the National Medical Products Administration, the national statutory body and the supreme technical arbitration body for testing the quality of medicines and biological products, and the "WHO Collaborating Center for Drug Quality Assurance" designated by the World Health Organization. In accordance with the laws, it implements the approval and registration inspection, import inspection, supervision inspection and safety assessment of medicines, biological products, medical devices, food, health food, cosmetics, experimental animals, packing materials and other products in various fields, as well as lot release of biological products, is responsible for the research, distribution and management of culture and virus seed used for the reference material and production verification of national drugs and medical devices, and carries out related technical research.

2.7 Organization 4 for the Trial Sample Test

2.7.1 Responsibilities

Jiangsu Huatai Vaccine Engineering Technology Research Co., Ltd., the main responsibilities of which are as follows:

- Detecting the IFN-γ secretion by T cell response;
- Detecting the serum inflammatory factor.

2.7.2 Organization Introduction

Jiangsu Huatai Vaccine Engineering Technology Research Co., Ltd., as a wholly state-owned holding company in Taizhou Pharmaceutical High-tech Industrial Development Zone with the registered capital of RMB 50 million, is mainly engaged in research and development of vaccine engineering technology, research and development of biological products, clinical evaluation, technology transfer and consultation. The Company has 22 professional service staff, including 2 doctors and 10 masters. Relying on the Administrative Committee of Taizhou Pharmaceutical

High-tech Industrial Development Zone, the Company has established partnership with Chinese Academy of Medical Sciences, National Institutes for Food and Drug Control, Nanjing University, Jiangsu Provincial Center for Disease Control and Prevention and Vaccine Research and Development Center of Taiwan Health Research Institute, and has a number of expert consultants. Its existing laboratories cover an area of 13,000m^2, including the testing laboratory, large-scale instrument sharing laboratory, R&D incubation laboratory, phase I clinical evaluation base, vaccine production pilot line and bulk filling workshop. In addition, there is an office service space of 6,000m^2. The Vaccine Engineering Center has established a vaccine research and development technology center, a pilot production base for biological products, a vaccine clinical evaluation center and a biological product testing center, and has the qualifications and abilities to independently provide external technical services.

The Company is in technical cooperation with 20 enterprises for biological products under research, mainly including Qyuns Therapeutics Co., Ltd., Ab&b Bio-Tech Co., Ltd. JS, Jiangsu Rec-Biotechnology Co., Ltd. and Jiangsu Saihua Biological Technology Co., Ltd., with 420 R&D personnel. There are more than 350 sets of main instruments and equipment, including ultra-performance liquid chromatograph, separation flow cytometer, molecular interaction instrument, purifier, ultra-speed centrifuge, fluorescence quantitative PCR and biochemical analyzer, with a value of more than RMB 40 million.

Ongoing research projects of the cooperators of the Company mainly include VERO rabies vaccine, VLP cervical cancer vaccine, quadrivalent influenza vaccine, monoclonal antibody drugs and Biosimilar products, including 4 Class I innovative drugs. It has obtained 8 approval documents for new drug clinical trials in recent years, and completed phase I clinical evaluation experiment of Ebola, anthrax, cholera vaccine projects.

2.8 Monitor

2.8.1 Responsibilities

The Clinical Research Department of Sinovac Biotech Co., Ltd. is responsible for

the monitoring of the Clinical Trial.

- Conducting monitoring of the Clinical Trial according to GCP, protocol and SOP;
- Assisting the Sponsor in undertaking the screening and training of the institutions for the Clinical Trial, holding kick-off meeting and other work;
- Verifying the test process and progress;
- Verifying the signing of informed consent;
- Verifying the qualifications of the investigators and the effectiveness of the implementation equipment;
- Verifying the transportation, storage, distribution, use, return and disposal of the vaccines for the Clinical Trial;
- Verifying the collection, storage and transportation of biological samples;
- Verifying the handling of adverse events;
- Verifying the logicality of the original records and the report documents in the Trial;
- Completing the monitoring after the Trial, etc.

2.8.2 Organization Introduction

Since its establishment in 2002, Sinovac Clinical Research Department has independently undertaken the organization, implementation, monitoring, data and statistical analysis management of many clinical trials, including inactivated hepatitis A vaccine, hepatitis A and B combined vaccine, SARS vaccine, H1N1 vaccine, H5N1 vaccine, EV71 vaccine, 23-valent pneumococcus vaccine, varicella vaccine, inactivated poliomyelitis vaccine, and quadrivalent influenza vaccine, making it experienced in clinical trial organization, implementation and management.

2.9 Organization for Data Management

2.9.1 Responsibilities

Meida Kelin (Nanjing) Medicine Technology Co., Ltd. is responsible for clinical trial data management.

- Formulating the Data Management Plan and Data Validation Plan according to protocol requirements;
- Providing EDC and other related online services;
- Carrying out data management in accordance with the *Technical Guidelines for Clinical Trial Data Management* during the Trial, and confirming that all data reports and records are correct and complete;
- Conducting data cleaning, raising questions about research data, and assisting investigators in verification and clarification;
- Preparing the data management report.

2.9.2 Organization Introduction

Meida Kelin (Nanjing) Medicine Technology Co., Ltd. established in September 2014, is a Contract Research Organization (CRO) mainly engaged in the outsourcing of data related services in clinical trials for domestic and foreign pharmaceutical companies. It has now offices in Shanghai, Beijing, Xi'an and Shenyang, and is in a strategic partnership with the CRO Clinical Service Center providing all-round services. It has provided data management, statistical analysis and drug safety alert services for phases I~IV and bioequivalence clinical trials of the innovative drugs and generic drugs of dozens of domestic and foreign pharmaceutical companies. It has:

- Standard Operating Procedure (SOP) and strict quality management system that meet the requirements of ICH-GCP/FDA 21 CFR part 11/international or domestic clinical trials;
- Personnel familiar with the clinical trial design, implementation, data management and statistical analysis experience in China, US, EU, Japan, South Korea and other countries, and with relevant drug management regulations and implementation rules;

  Complete education and training system.

2.10 Organization Responsible for Statistical Analysis

2.10.1 Responsibilities

Beijing KEY TECH Statistical Technology Co., Ltd. is responsible for the

statistical analysis of the Clinical Trial.

- Writing the randomization, sample size and statistical analysis parts of the Clinical Trial Protocol;
- Writing the statistical analysis plan according to Clinical Trial Protocol;
- Conducting the randomization and blinding of the Clinical Trial;
- Carrying out the statistical analysis according to the proposed statistical analysis plan and writing the statistical analysis report.

2.10.2 Organization Introduction

Beijing KEY TECH Statistical Technology Co., Ltd. (referred to as "KEY TECH"), incorporated in August 2017 in Beijing, is a wholly domestic-funded company engaged in data management and statistical analysis services of clinical trial. It focuses on the biostatistics service of clinical research, and mainly provides, with respect to registered clinical trials, the statistical strategy consultation for drug research plan throughout the whole process, the statistical design and statistical analysis, etc. KEY TECH has currently set up offices in Beijing, Xi'an and Nanning, now with 43 employees, who have mainly graduated from the Fourth Military Medical University, Peking University, Sichuan University and other first-class universities in China. At present, there are 21 statisticians/statistical programmers, 18 data managers, 1 quality control person and 3 non-business personnel among the employees. In terms of education background, there are 3 doctors, 6 masters and 34 bachelors.

Since its establishment, KEY TECH have assisted the Sponsor in obtaining 8 approval documents for clinical trial, completed 18 new drug applications, including 5 Class I new drugs of biological products, and obtained the approval for marketing of 5 products in the applied projects, including the first 13-valent pneumonia vaccine in China, nasal spray influenza vaccine, the second Adalimumab monoclonal antibody product in China, the third quadrivalent influenza vaccine in China and varicella vaccine. KEY TECH signed an agreement with Abbott in 2019 for statistical consulting services in the Asia Pacific Region, establishing long-term partnership with leading innovative pharmaceutical companies at home and abroad.

2.11 Data Monitoring Committee

The Data Monitoring Committee consists of specialists in clinical medicine, epidemiology and statistics.

Its main responsibilities are as follows:

– Performing safety data review and clinical trial risk assessment to ensure that the Trial is carried out in a safe and standard way.

3 Background and Principle

3.1 Summary

Since December 8, 2019, several cases of pneumonia for unknown cause were reported in Hubei, with most of the patients working or living in South China Seafood Wholesale Market where live animals are sold. At early stage, this pneumonia presented severe symptoms of acute respiratory infection, with some patients rapidly developing to acute respiratory distress syndrome (ARDS). This pneumonia, which was later proved to be human-to-human transmission, escalated rapidly in early January 2020, and there were cases found in provinces of China and more than 20 other countries, including Japan, Singapore and US. Chinese Center for Disease Control and Prevention (CDC) identified a novel coronavirus from a patient's throat swab sample on January 7, 2020. The World Health Organization (WHO) declared the pneumonia outbreak caused by the novel coronavirus to be a public health emergency of international concern (PHEIC) on January 31, 2020. WHO declared the outbreak to enter the international pandemic phase on March 12, 2020.

As shown by research, the novel coronavirus gene sequences were most closely associated with two SARS-like coronaviruses from bat (bat-SL-CoVZC45 and bat-SL-CoVZXC21)[6]. International Committee on Taxonomy of Viruses (ICTV) declared the official class name of this novel coronavirus as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) on February 12, 2020, while WHO declared the official name of the disease caused by the virus as COVID-19 on the same day.

3.2 Virology

Coronavirus (COV) is an important pathogen of human and vertebrate that can infect the respiratory tract, gastrointestinal tract, liver and central nervous system of humans, livestock, birds, bats, mice and many other wild animals. Since the outbreak of Severe Acute Respiratory Syndrome (SARS) in 2003 and Middle East Respiratory Syndrome (MERS) in 2012, the possibility for COVs to transmit from animals to humans has been proved. COVs belongs to the Coronavirinae subfamily of the Nidovirales coronavirus family, which includes four genera: α-coronaviruses, β-coronaviruses, γ-coronaviruses, and δ-coronaviruses[7].

SARS-CoV-2 is from genus β that is enveloped with round or oval and often pleomorphic particles in the diameter of 60-140nm, and is a plus-stranded RNA virus. Its gene characteristics are clearly different from those of SARSr-COV and MERSr-COV. The present research shows that it has more than 85% homology with bat SARS-like coronavirus (bat-SL-COVZC45). SARS-CoV-2 could be found in respiratory epithelial cells in about 96h when isolated and cultured in vitro, while in about 6 days when isolated and cultured in Vero E6 and Hun-7 cell lines.

So far, the full-length genome sequences among virus samples are almost identical, suggesting that no significant virus variation has taken place. Close monitoring of SARS-CoV-2 also shows that no significant variation has been found in viruses isolated from the environment, previously isolated from humans and recently isolated[8]. However, there is still the possibility of future mutation or recombination in which the virulence may increase or decrease.

The understanding of physicochemical properties of coronavirus mainly comes from the researches of SARS-COV and MERS-COV. The virus is sensitive to ultraviolet and heat. At 56℃ for 30 minutes, diethyl ether, 75% ethanol, chlorine-containing disinfectant, peracetic acid, chloroform and other lipid solvents can effectively inactivate the virus, but chlorhexidine cannot[9].

3.3 Clinical Manifestation

According to the current epidemiological survey, the incubation period is 1-14 days, mostly 3-7 days, with fever, fatigue and dry cough as the main manifestations. A

few patients have symptoms such as nasal congestion, runny nose, sore throat, myalgia and diarrhea. Critical patients often develop dyspnea and/or hypoxemia one week after attack, with rapid development to acute respiratory distress syndrome, septic shock, incorrigible metabolic acidosis, haemorrhagic and coagulation dysfunction in severe cases. It is worth noting that the course of the disease in the severe and critical patients may present moderate to low fever, and even no obvious fever.

Some cases of children and newborns show atypical symptoms, such as vomiting, diarrhea and other digestive tract symptoms or only mental weakness and polypnea. Mild patients only show low fever, fatigue, etc., without pneumonia.

The prognosis of most patients is favorable and a few patients are in critical condition. The elderly and those with chronic underlying diseases have a poor prognosis. The clinical course of pregnant and birth-giving women with COVID-19 is similar to that of patients of the same age, and children have relatively mild symptoms[9].

3.4 Epidemiological Characteristics

Transmission routes and susceptible groups

The main source of infection of COVID-19 is the patients infected by SARS-CoV-2, and asymptomatic carriers may also become the source of infection. The main routes of transmission are respiratory droplets and contact transmission, the virus is transmitted through the droplets produced during patients' cough, sneeze and talk, susceptible people inhaling them will be infected, and the population is generally susceptible. Exposure to high concentration of aerosol in a relatively closed environment for a long time presents the possibility of aerosol transmission.

The fecal-oral transmission route remains to be determined. Recently, SARS-CoV-2 was detected in the feces of the confirmed patients in Wuhan, Shenzhen and even the US in the first case, indicating that the virus can replicate and exist in the digestive tract and suggesting that fecal-oral transmission is possible[10], but it has not been established that eating food contaminated by the virus will cause infection and transmission. There is also a view that the virus in feces may be retransmitted by aerosol formed by droplets containing the virus, and further investigation is needed.

It has been currently reported that there is the case where the mother is a confirmed

COVID-19 patient and the newborn is with positive viral nucleic acid by throat swab 30h after birth, suggesting that SARS-CoV-2 may cause neonatal infection through mother-to-child transmission[11].

Epidemic Status of COVID-19 in China

As of 24:00 on June 11, 2020 (Beijing time), there have been 83,064 confirmed cases of COVID-19 in China, with 4,624 deaths[12]. As pointed out in the *Joint Investigation Report of China-WHO on Novel Coronavirus Pneumonia (COVID-19)*[13], among the 55,924 laboratory confirmed cases reported, the median of age is 51 years old, the age range is 2 days~100 years old, and the interquartile range is 39~63 years old. Most of the cases (77.8%) are in the range of 30~69 years old. Among them, males account for 51.1%, cases from Hubei for 77% and peasants or manual workers for 21.6%.

In China, human-to-human transmission of COVID-19 mainly occurs within families. Detailed information on continuous transmission among family members in some provinces can be obtained from cluster case surveys and some family transmission case studies. There are 1,836 cases in total in Guangdong and Sichuan, and the reported 344 cluster cases involve 1,308 cases, of which 78%~85% occur in family members. Research on the transmission within family members is ongoing, but preliminary findings in Guangdong estimate that the second-generation secondary attack rate in family members is about 3%~10%. As the pandemic continues, community cluster infections are also increasing with hospital cluster attack, although family cluster infections are dominant[13].

Epidemic Status of COVID-19 in the World

As of 2:25 p.m. on June 13, 2020 (CEST), a total of 7,553,182 COVID-19 confirmed cases and 423,349 deaths had been reported across the world. The countries with a high incidence of COVID-19 infection are the US (2,010, 391 cumulative confirmed cases), Brazil (802,828 cumulative confirmed cases), Russia (520, 129 cumulative confirmed cases), India (308,993 cumulative confirmed cases), the United Kingdom (292,954 cumulative confirmed cases), Spain (243,209 cumulative confirmed cases), Italy (236,305 cumulative confirmed cases), Peru (214,788 cumulative confirmed cases), German (186,022 cumulative confirmed cases), Iran (182,545 cumulative confirmed cases) and Turkey (175,218 cumulative confirmed cases). The COVID-19 has spread to global 216 countries around the world, leading to a global

COVID-19 pandemic.[12]

3.5 Vaccine Research and Development

There are no approved specific therapies or vaccines against COVID-19. According to the data published by WHO, there were 119 candidate vaccines under development, 110 candidate vaccines in preclinical studies, and 9 candidate vaccines in clinical trials, including 1 candidate vaccine in phase I clinical trials, 2 candidate vaccines in phase II clinical trials, and 6 candidate vaccines in phase I/II clinical trials as of May 15, 2020. According to the technical route, 48 of the candidate vaccines are recombinant protein vaccines (mainly subunit vaccines and virus-like particles); 30 are nucleic acid vaccines (including 20 mRNA vaccines and 10 DNA vaccines); 27 are vector vaccines (using 9 vectors, including adenovirus, influenza virus, poxvirus, measles virus vector, vesicular stomatitis virus, yellow fever virus, rabies virus, Newcastle disease virus and avian paramyxovirus); 8 are inactivated vaccines (under development in China, Japan, USA and Kazakhstan); 2 are attenuated live vaccines (under development in India); 4 are other vaccines (therapeutic vaccines).

4 Preclinical Research and Laboratory Evaluation of Vaccine

4.1 Safety Research

The toxicity test of single administration in rats, active systemic anaphylaxis test in guinea pigs, toxicity test of repeated administration in rats, toxicity test of repeated administration in macaca fascicularis and reproductive development toxicity test in rats have been carried out for the test vaccine, the results of which are as follows:

4.1.1 Toxicity test of single administration in rats

Test objective: to evaluate the possible acute toxicity in Sprague-Dawley (SD) rats within 14 days after single intramuscular injection of COVID-19 Vaccine, so as to provide animal experimental data for subsequent research.

Experimental design: according to the body weight of animals measured before administration, 20 animals with similar body weight and quarantine inspection passed were selected for the test, with half males and half females, which were randomly

divided into 2 groups by sex section, namely the test group and the negative control group. The rats in the test group were intramuscularly injected with the proposed clinical high-dose vaccine by 0.5ml/1200SU/rat and the rats in the negative control group were intramuscularly injected with normal saline by 0.5ml/rat, which were observed for 14 days after the administration and further observed by gross anatomy.

Test results: No death or near-death was observed in the animals of both the test group and the negative control group, and no abnormalities were observed in clinical observation. The body weights of the animals in all groups normally increased, and no statistical differences were observed in the body weights of animals in the test group when compared with the animals in the negative control group of same sex during the same period, and no significant effects of drug administration on animal intake were observed. Visual observations of pathological gross autopsy showed that no abnormities were seen in major organs and tissues of the animals in all the groups.

Conclusion: No abnormalities associated with administration were seen in SD rats inoculated with high-dose vaccines in clinic, and the maximum tolerated dose (MTD) in SD rats was greater than or equal to 1,200 SU/1 dose/rat.

4.1.2 Active systemic anaphylaxis test in guinea pigs

Test objective: to observe the immediate systemic anaphylaxis in guinea pigs sensitized by intramuscular injection of COVID-19 Vaccine (once every other day, for 3 times in total) and stimulated by intravenous injection on D19 and/or D26, so as to provide animal experimental data for clinical research of the test article.

Experimental design: according to the body weight of animals measured before administration, animals with similar body weight were selected, and 36 Hartley guinea pigs were randomly divided into 4 groups, i.e., low-dose test group, high-dose test group, negative control group and positive control group, respectively sensitized by intramuscular administration on D1, D3 and D5 and stimulated by intravenous administration on D19 (14 days after the last sensitization) and D26 with 0.5ml/1200SU/dose test article, normal saline and human hemoglobin. The first 3 animals in each group were stimulated by intravenous injection in the feet, and the

stimulation dose in each group was twice the sensitization dose. Clinical observation was performed after administration. The experimental design is shown in the table below:

Table 1 Experimental Design of Active Systemic Anaphylaxis in Guinea Pigs

Group	Test article/ control	Qty. of animals	Sensitization (i.m) D1,D3,D5		Stimulation (i.v) D19 and D26	
			Dosage of administration	Capacity of administration (mL/Nr.)	Dosage of administration	Capacity of administration (mL/Nr.)
1	Negative control	4	0	0.5	0	1
2	Positive control	4	20 mg/Nr.	0.5	40 mg/Nr.	1
3	Low-dose test article	4	0.1 dose/Nr.	0.05	0.2 dose/Nr.	0.1
4	High-dose test article	4	1 dose/Nr.	0.5	2 doses/Nr.	1

Test results: no abnormal reaction was observed in general clinical observation. The body weight of animals in each group was in normal growth according to the weighing before grouping, before the last sensitization and before administration on the day of stimulation respectively. The low-dose group, high-dose group and negative control group all showed negative anaphylaxis. The positive control group was stimulated on D19 and D26 and showed positive anaphylaxis.

Conclusion: no allergic reaction was found in SD rats inoculated with high-dose vaccines in clinic.

4.1.3 Toxicity test of repeated administration in rats

Test objective: to evaluate the toxicity and determine target organs for toxicity and recovery of toxic reaction in SD rats after repeated intramuscular injection of COVID-19 vaccine, determine the safe dose for repeated administration, and provide basic data for clinical trial and application of the test articles.

Experimental design after administration of three doses: according to the body weight of animals measured before grouping, 150 animals with similar body weight and satisfactory quarantine inspection results were selected, which were randomized into 7 groups by sex for the main test groups (1~4 groups, i.e. low-dose test group, high-dose test group, negative control group and adjuvant control group) and satellite groups

(5~7 groups, i.e. low-dose test group, high-dose test group and negative control group). There were 15 animals per sex in each main test group and 5 animals per sex in each satellite group. The rats in the low-dose test group, high-dose test group, negative control group and adjuvant control group were administrated by intramuscular injection of 0.5ml/300SU/dose of test article, 0.5ml/1200SU/dose of test article, 0.5ml/dose of normal saline and 0.5ml/dose of adjuvant respectively on D1, D8 and D15, and safety observation was performed until 4 weeks after the last administration. Test indexes include: clinical observation such as anaphylaxis and local injection reaction, body weight/body temperature/food intake/ophthalmic testing, cliniopathological markers (blood counts, coagulation function, blood biochemistry and urine analysis), immunological indexes (T lymphocyte subsets, cytokines and antibodies) and pathological examination (gross anatomical observation and histopathological examination).

Experimental design after administration of four doses: 80 SD rats (half males and half females) aged 5-6 weeks were selected and randomized into 2 experimental groups according to body weight: negative control group (CN group) and COVID-19 vaccine group (T group), with 40 animals in each group, including 30 animals in the main test group and 10 animals in the satellite group. The doses were administered intramuscularly at a dose of 1,200 SU/0.5 ml/rat/dose. Doses were administered at weeks 0, 1, 2 and 3 respectively, totaling to 4 doses as per 0.5 ml/rat, with a recovery period of 2 weeks. The testing indexes were the same as 3 doses.

Test results: after 3 or 4 doses were administrated, no abnormalities were found in the test animals of each group during index observation; body temperature did not abnormally rise after administration; body weight fluctuated in a small range; no change related to administration was found. After 3 doses were administrated, no definite abnormality related to administration was found in the fibrinogen measured on D2 and D4 and in the blood cell counts measured on D4. At last dose had been administrated during test on 4 doses, 12 test animals showed muscle interstitial inflammatory cell infiltration at the injection sites, including one with fibroblast hyperplasia. At the end of the recovery period, 3 animals showed muscle interstitial inflammatory cell

infiltration at the injection sites.

Test conclusions: The COVID-19 vaccine was given to rats by repeated intramuscular injections once a week for consecutive 3 or 4 times. During administration and at the end of the recovery period, no systemic toxic reactions were observed in animals at doses of 300 SU/rat and 1,200 SU/rat. It was determined that no observed adverse effect level (NOAEL) was 1,200SU/rat. Local irritation related to aluminum adjuvant was seen at some local injection sites, and no immunotoxic reactions were observed.

4.1.4 Toxicity test of repeated administration in macaca fascicularis

Test objective: to evaluate the possible toxicity and target organ in macaca fascicularis after 4 weeks of repeated intramuscular injection of COVID-19 Vaccine, as well as the recovery of toxicity after 4 weeks of withdrawal, so as to provide animal experimental data for clinical research of the test article.

Experimental design: according to the body weight of animals measured before grouping, 40 animals were randomly divided into 4 groups by sex section, i.e. low-dose test group, high-dose test group, negative control group and adjuvant control group, with 10 macaca fascicularis in each group, half males and half females, which were administrated by intramuscular injection of 0.5ml/300SU/dose of test article, 0.5ml/1200SU/dose of test article, 0.5ml/dose of normal saline and 0.5ml/dose of adjuvant respectively on D0, D7 and D14, and safety observation was performed until 14 days after the last administration for euthanasia anatomy. Test indexes include clinical observation such as anaphylaxis and local injection reaction, body weight/body temperature/electrocardiogram/blood pressure/ophthalmic testing, cliniopathological markers (blood counts, coagulation function, blood biochemistry and urine analysis), immunological indexes (T lymphocyte subsets, cytokines, C-reaction protein, alexin and antibodies) and pathological examination (gross anatomical observation and histopathological examination).

Result: During the test, no death or near death was observed in the animals of each group. Clinical observations showed no abnormalities related to drug administration

and no abnormal changes in body weight, body temperature, electrocardiogram, blood pressure or eye examination resulted from drug administration. No abnormal clinicopathological indexes or immunological indexes associated with drug administration were observed. Pathological examination showed that, on Day 3 after the last administration (Day 18), granulomatous inflammation or single cell infiltration was visible locally in 5/6, 6/6 and 5/6 animals in the adjuvant control and low/high-dose groups respectively, with mild to moderate lesions; this change was considered a local reaction caused by accumulation of aluminum adjuvant, which was an expected reaction caused by intramuscular injection of a vaccine containing aluminum adjuvant. At the end of the 2-week recovery period, macrophage granulomatous inflammation was still visible locally in 3/4, 4/4 and 4/4 of the animals in the adjuvant control group and low/high-dose groups respectively, suggesting that the local irritant response of drug administration had not recovered.

Test conclusions: The COVID-19 vaccine was given to machin by repeated intramuscular injections once a week for consecutive 2 weeks, totaling to 3 doses. During administration and at the end of the 2-week recovery period, no systemic toxic reactions were observed in animals at doses of 300 SU/rat and 1,200 SU/rat. It was determined that no observed adverse effect level (NOAEL) was 1,200SU/rat. Local irritation related to aluminum adjuvant was seen at some local injection sites, and no immunotoxic reactions were observed.

4.1.5 Reproductive development toxicity test in rats

Test objectives: evaluate the effects of repeated intramuscular injection of COVID-19 Vaccine in SD rats before mating to duration of pregnancy until lactation period on the fertility of male and female rats, and on the development of pregnant/lactation female rats, fetus and fetal rats, understand the effect of the vaccine on the development of teratogenic fetal rats and offspring rats, and study the antibody level in the blood of fetus or offspring rats, so as to provide reference for the safe administration to special population in the Clinical Trial.

Experimental design: according to the body weight of animals measured before

administration, the animals were randomly divided into 4 groups by sex section, i.e. low-dose test group, high-dose test group, negative control group and adjuvant control group, with 28 males and 56 females in each group, which were administrated with 0.5ml/300SU/dose of test article, 0.5ml/1200SU/dose of test article, 0.5ml/dose of normal saline and 0.5ml/dose of adjuvant respectively. The male rats were administrated for 4 times before mating, on D1, D8 and D15 respectively. Female rats were administrated for 3 times before mating, on D1, D8 and D15 respectively. Female and male rats started mating in a cage one week after the end of the administration to male rats, and female rats were administrated once respectively on gestational day 6 (GD6) and on postnatal day 7 of offspring rats (PND7). 1/2 of the pregnant rats in each group had a cesarean section on GD20 for fetal examination (appearance, viscera and bone examination), and the remaining 1/2 in the same group were given natural delivery and euthanized at the end of lactation period. Clinical observations were made during the test, and the parental male and female rats were examined for body weight, food intake and reproductive capacity; the necropsied male rats had a caesarean section on GD20 to examine the development of embryo-fetal rats, appearance of fetal rats, bone and viscera; the sperm viability, counting and morphology of parental male rats were examined, and the histopathology of main reproductive organs of parental male and female rats were examined; the survival, body weight, body and emission development index of F1 offspring rats after delivery were examined; the serum of male rats and fetal rats necropsied on GD20 and parturient female rats and F1 offspring rats were tested for specific IgG antibodies and neutralizing antibodies against SARS-CoV-2.

Test results: the COVID-19 Vaccine, Inactivated was repeatedly injected into SD rats by means of intramuscular injection at doses of 300 SU/rat and 1,200 SU/rat before mating to the embryonic implantation and parturition, and there were no effects on the fertility of male and female rats as well as growth and development of F1 offspring rats, no obvious adverse reaction on the pregnant / lactant female rats, no developmental toxicity and teratogenicity of embryo-fetal rats and no effects on the growth and development of F1 offspring rats. Besides, the specific IgG antibodies and neutralizing antibodies against SARS-CoV-2 can be detected in the serum of male rats and fetal rats

as well as parturient female rats and F1 neonatal rats necropsied on GD20 in the high/low-dose groups of the test articles, with a detectable rate of 100%.

4.2 Immunogenicity Research

By intraperitoneal immunization of mice and intramuscular immunization of rats from inactivated novel coronavirus using different dosages, adsorption ways and immunization schedules, blood samples were collected at different times to determine the titer of serum neutralizing antibody and IgG antibody after immunization, evaluate the immunogenicity of the COVID-19 Vaccine (Vero Cell), Inactivated (hereinafter referred to as "COVID-19 Vaccine") and determine the formulation, dosage and immunization schedules of the vaccine according to the immunogenicity results.

Research design:

- Determination of aluminum adsorption and non-aluminum adsorption processes for the vaccine

1200SU/0.5ml, 600 SU/0.5ml, 300 SU/0.5ml and 150 SU/0.5ml COVID-19 Vaccine with aluminum adjuvant and 1200SU/0.5ml, 600 SU/0.5ml and 300 SU/0.5ml COVID-19 Vaccine without aluminum adjuvant were respectively prepared by two different processes, which were used for intraperitoneal immunization of mice as per 10 mice/group and 0.5ml/mouse, and for immunization by one dose, the serum was sampled on D7, D14 and D21 after immunization; for day 0,7 and day 0,14 immunization by two doses, the serum was sampled on D14, D21 and D28 to test the titer of IgG antibody in serum. Negative control animals were also set. By comparing the antibody levels, the immunogenicity of the vaccines prepared by two different processes was compared, with the specific research design shown in the table below:

Table 2 Comparative Research Design for Immunogenicity of Aluminum Adsorption/Non-aluminum Adsorption COVID-19 Vaccine

Dosage (SU/0.5ml)	COVID-19 Vaccine, Inactivated				Non-aluminum adsorption COVID-19 Vaccine, Inactivated			
	Vaccine lot no.	Immunization by one dose	Day 0,7 immunization by two doses	Day 0,14 immunization by two doses	Vaccine lot no.	Immunization by one	Day 0,7 immunization by two doses	Day 0,14 immunization by two doses

						dose		
1200SU	20200303-1	10	10	10	20200303-5	10	10	10
600 SU	20200303-2	10	10	10	20200303-6	10	10	10
300SU	20200303-3	10	10	10	20200303-7	10	10	10
150 SU	20200303-4	10	10	10	/	/	/	/

- Determination of immunization dosage and schedules of COVID-19 Vaccine

Mouse test groups: 4 dose groups with antigen content of 300SU/0.5ml, 600SU/0.5ml, 1200SU/0.5ml and 2400SU/0.5ml (corresponding lot no. as 20200213-1~4) were for intraperitoneal immunization of mice as per 10 mice/group and 0.5ml/mouse by emergency and routine immunization schedules.

Rat test groups: 4 dose groups with antigen content of 300SU/0.5ml, 600SU/0.5ml, 1200SU/0.5ml and 2400SU/0.5ml (corresponding lot no. as 20200213-1~4) were for intramuscular immunization of rats as per 5 rats/group and 0.5ml/rat by emergency and routine immunization schedules. Vaccine diluent was also provided as negative control. The immunization and blood sampling are shown in Table 3.

Table 3 Research Design for Immunization Dosage and Schedules of COVID-19 Vaccine

Immunization Procedure	Immunization Procedure	Blood sampling time	Qty.
Emergency immunization schedule	Day 0 immunization	Blood collection on day 7, 14, 21, 28, 35, 42	10 mice and 5 rats
	Day 0,7 immunization	Blood collection on day 14, 21, 28, 35, 42	10 mice and 5 rats
	Day 0,3,7 immunization	Blood collection on day 7, 14, 21, 28, 35, 42	10 mice and 5 rats
Routine immunization schedule	Day 0,14 immunization	Blood collection on day 21, 28, 35, 42	10 mice and 5 rats
	Day 0,14,28 immunization	Blood collection on day 35, 42	10 mice and 5 rats

The proposed dosage of COVID-19 Vaccine for the Clinical Trial was determined by analyzing the immunization dosage, neutralizing antibody titer and enzyme labelled antibody titer. At the same time, the immunization effects of one dose, two doses and three doses were compared to determine the immunization schedule.

Research results:

- Determination of aluminum adsorption and non-aluminum adsorption

processes for the vaccine

After intraperitoneal immunization of mice by one dose of COVID-19 Vaccine with and without aluminum adjuvant, a certain level of anti-SARS-CoV-2 enzyme labelled antibody could be produced in the mice on D7 after primary immunization. The antibody level of 1200SU/0.5ml vaccine without aluminum adjuvant was comparable to that of 300SU/0.5ml vaccine with aluminum adjuvant. The immunogenicity of the vaccine with aluminum adjuvant was obviously better than that of the vaccine without aluminum adjuvant.

- Determination of immunization dosage and schedules of COVID-19 Vaccine

(1) For the same immunization schedule, different dose groups were for immunization of the same species of animals, and the neutralizing antibody titer was detected at the same blood collection point. There was a good dose-effect relationship between the immunization dosage and the neutralizing antibody titer produced.

(2) For the same dose groups, different immunization schedules (one dose, two doses and three doses) were used for immunization of the same species of animals, and the enzyme labelled antibody titer was detected at the same blood collection point. The immunization effect using the schedules of two and three doses on mice was lower than that using the schedule of one dose. The immunization effect using the schedules of two and three doses on rats was higher than that using the schedule of one dose. The immunization effect using the schedules of two and three doses was equivalent due to the short interval among three doses.

(3) For the same dose groups and the immunization schedule of two doses (day 0,7 and day 0,14) at different time points, the enzyme labelled antibody level of the day 0,14 immunization schedule was one order of magnitude higher than that of the day 0,7 immunization schedule on D21, indicating that the interval of more than 14 days is required between two doses in the Clinical Trial.

(4) For different dose groups and the same immunization schedule of two doses, the neutralizing antibody levels under 1200SU and 2400SU were basically the same.

Research conclusion: the formulation of aluminum adjuvant was selected, the dosages determined to be used for the Clinical Research were 300SU/dose, 600SU/dose

and 1200SU/dose, and the immunization schedule of two doses was selected.

4.3 Challenge Protection Research

Test objectives: to evaluate the animal protective effect of COVID-19 Vaccine under challenge of SARS-CoV-2 after immunizing animals with COVID-19 Vaccine according to different immunization schedules and dosages, and evaluate the existence of Antibody Dependent Enhancement (ADE), so as to provide animal experimental data for clinical research and application.

Experimental design: rhesus monkeys were immunized by COVID-19 Vaccine according to different immunization schedules and dosages, novel coronavirus seed was used to challenge the animals 21~42 days after the first immunization, the protective effect of the vaccine was evaluated according to the results of observation of clinical symptoms, serum detection, viral load test and histopathological examination of the rhesus monkeys, and the existence of ADE under different antibody levels was observed, with the research design shown in the table below:

Table 4 Experimental Design of Challenge Protection Effect

Group S/N	Group	Immunization schedule (day)	Sample dosage	Number of days of challenge after first immunization (day)	Number of days of euthanasia (after challenge)	Qty. of animals
1	3 doses-vaccine	0,7,14	High dose (1200SU/0.5ml)	23	7	4
			Medium dose (600SU/0.5ml)	22	7	4
2	3 doses-adjuvant	0,7,14	/	21	7	2
3	Model group	/	/	21	7	2
4	2 doses-vaccine	0,14	High dose (1200SU/0.5ml)	23	7	4
			Medium dose (600SU/0.5ml)	22	7	4

2-dose test results: no significant rise in body temperature was seen in the model group after the challenge, and high levels of virus were detected in throat swabs, anal swabs and lung tissue. Lung tissue showed severe interstitial pneumonia lesions. There was no significant difference between the adjuvant group and the model group; compared with the model group, 2 (n=4) had a body temperature over 40°C, 3 (n=4)

tested negative for throat swab virus on Day 3, Day 5 and Day 7 after challenge, 4 (n=4) tested negative for lung tissue virus on Day 7 after challenge, and all 4 showed mild interstitial pneumonia in the medium-dose group, suggesting that the medium-dose vaccine had a significant protective effect, and no ADE was observed; in the high-dose group compared with the model group, there was no abnormal body temperature, and 3 (n=4) tested negative for throat swab virus on Day 3, Day 5 and Day 7 after challenge. 4 (n=4) tested negative for lung tissue virus on Day 7 after challenge, and all 4 showed mild interstitial pneumonia, suggesting that the medium-dose vaccine had a significant protective effect, and no ADE was observed.

The changes of antibody levels in each group of rhesus monkeys are shown in Table 5. Based on the results of immune protection in the medium-dose group challenge suggested that neutralizing antibody titers greater than or equal to 1:48 after 2 doses of immunization had significant protective effect.

Table 5 Changes in Antibody Levels of Rhesus Monkeys in Each Group after COVID-19 Vaccination

	Animal No.	Day 0 after immunization	Day 7 after immunization	Day 14 after immunization	Day 21 after immunization	Day 3 after challenge	Day 5 after challenge	Day 7 after challenge
Medium-dose group	**K21**	<8	<8	4	64	64	48	256
	K22	<8	<8	4	128	48	64	128
	K23	<8	<8	6	48	32	96	1024
	K24	<8	<8	32	64	256	128	1024
GMT	/	/	/	7.4	70.8	70.8	78.4	430.5
High-dose group	**K17**	<8	<8	16	128	1024	512	512
	K18	<8	<8	16	256	256	512	512
	K19	<8	<8	4	96	512	1024	512
	K20	<8	<8	<4	64	192	256	1024
GMT	/	/	/	6.7	119.1	400.7	512.0	608.9
Adjuvant group	**K9**	<8	<8	<4	<4	<4	4	8
	K10	<8	<8	<4	<4	<4	<4	<8
GMT	/	/	/	/	/	/	/	/
Model group	**K15**	<8	<8	<4	<4	<4	6	12
	K16	<8	<8	<4	<4	<4	8	8
GMT	/	/	/	/	/	/	6.9	9.8

3-dose test results: no significant rise in body temperature was observed in the animals of the model group after challenge, and no abnormalities were observed in the adjuvant, medium-dose and high-dose groups in body temperature. WBC decreased and LYMPH% increased after all groups of animals were infected, and there was no

significant difference between the medium/high-dose groups and the model group. Blood biochemical tests on all the groups of animals on D0 and D14 after immunization and when the animals were put to death showed that all the indexes were within the normal range. High levels of virus were detected in throat swabs, anal swabs and lung tissue for the model group. In the medium-dose group, the average level of virus in throat and anal swabs decreased on Day 7 after challenge compared with the model group; in the high-dose group, throat and anal swabs were tested negative for virus on Day 7 after challenge; 3 (n=4) in the medium-dose group were tested negative for virus in lung tissue on Day 7 after challenge, and all 4 in the high-dose group were tested negative for virus in lung tissue on Day 7 after challenge.

Both the model and adjuvant groups were negative for neutralizing antibodies on Day 21 after immunization. In the medium-dose group, the neutralizing antibody GMT was 1:61.3 and reached 1:400.7 on Day 7 after challenge. In the high-dose group, the neutralizing antibody GMT was 1:50.1 and reached 1:145 on Day 7 after challenge, as shown in Table 6.

Table 6 Changes in Antibody Levels of Rhesus Monkeys in Each Group after COVID-19 Vaccination

	Animal No.	Day 0 after immunization	Day 7 after immunization	Day 14 after immunization	Day 21 after immunization	Day 3 after challenge	Day 5 after challenge	Day 7 after challenge
Medium-dose group	K5	<8	<8	6	64	32	384	1024
	K6	<8	<8	4	24	32	64	512
	K7	<8	<8	48	384	128	512	768
	K8	<8	<8	6	24	32	64	64
GMT		/	/	9.1	61.3	45.3	168.5	400.7
High-dose group	K1	<8	<8	12	48	24	96	256
	K2	<8	<8	16	64	96	512	384
	K3	<8	<8	6	32	24	48	96
	K4	<8	<8	6	64	16	48	48
GMT		/	/	9.1	50.1	30.7	103.2	145.9
Adjuvant group	K9	<8	<8	<4	<4	<4	4	8
	K10	<8	<8	<4	<4	<4	<4	<8
GMT		/	/	/	/	/	/	/
Model group	K15	<8	<8	<4	<4	<4	6	12
	K16	<8	<8	<4	<4	<4	8	8
GMT		/	/	/	/	/	6.9	9.8

Pathological findings of some animals are detailed in Fig. 1-6.

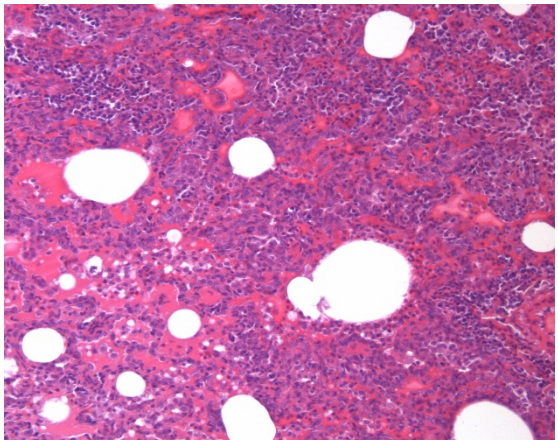


Fig. 1 Model Group K15 Minor Lobe of Right Lung Severe Interstitial Pneumonia H.E.×100

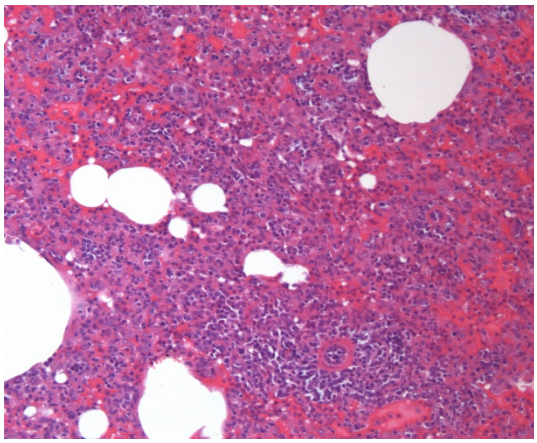


Fig. 2 Adjuvant Group K10 Middle Lobe of Right Lung Severe Interstitial Pneumonia H.E.×100

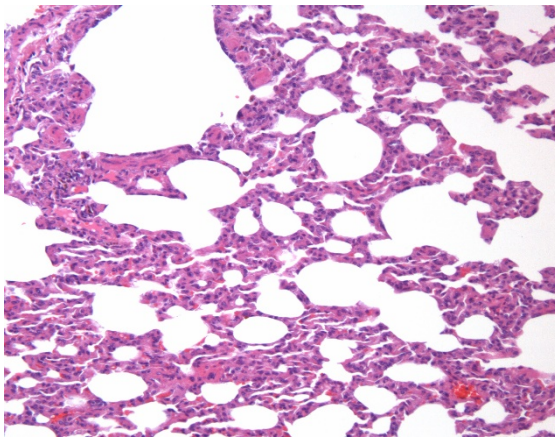


Fig. 3 Medium-dose Group K21 Superior Lobe of Right Lung Mild Interstitial Pneumonia H.E.×100

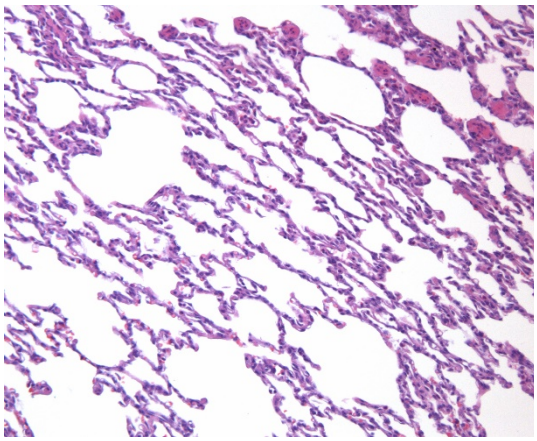


Fig. 4 Medium-dose Group K22 Inferior Lobe of Left Lung No Abnormality Seen H.E.×100

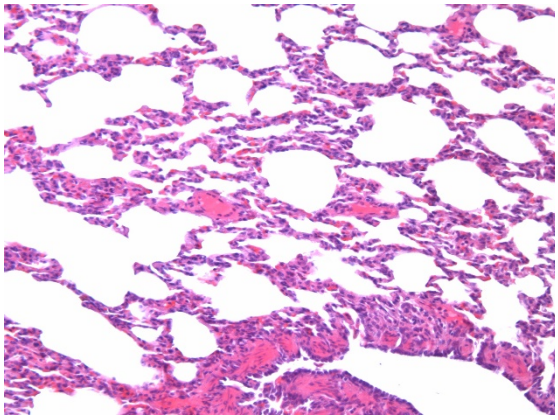


Fig. 5 High-dose Group K17 Inferior Lobe of Right Lung Mild Interstitial Pneumonia H.E.×100

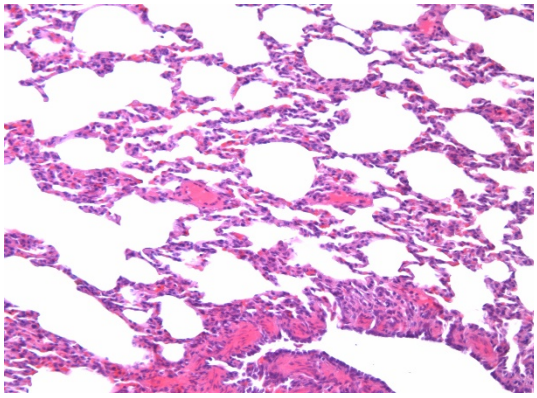


Fig. 6 High-dose Group K19 Inferior Lobe of Left Lung No Abnormality Seen H.E.×100

Test conclusions: The COVID-19 vaccine had apparently protective effects, and no ADE phenomenon was observed.

4.4 Cross Neutralizing Research

A cross neutralizing test of different viruses was conducted on the serum of

patients infected with SARS-CoV-2 in the acute phase and in the recovery phase. The preliminary results showed that the overall neutralizing antibody level in the serum in the acute phase was not high, and a certain proportion of serum neutralizing antibody was negative. The overall neutralizing antibody level in the serum in the recovery phase was higher than that in the acute phase, and the preliminary data showed that 100% serum neutralizing antibody in the recovery phase was positive, which could suggest that the neutralizing antibody played a certain protective role in the recovery process of patients.

The neutralizing antibody titer of the animal serum of the monkeys immunized by vaccine was also preliminarily detected, the results of which showed that good neutralizing antibody titer could be produced by the vaccine when the non-vaccine strain virus was used for detecting the neutralizing antibody, and it had a good dose-effect relationship with different immunization dosages and schedules.

The cross neutralizing test will be continued.

5. Preliminary Clinical Trial

5.1 Safety Evaluation

(1) Phase I clinical trial

Adverse event

In phase I clinical trial, a total of 143 subjects aged 18~59 years were included into the SS set, including 72 in Day 0, Day 14 emergency immunization schedule and 71 in Day 0, Day 28 routine immunization schedule. According to the analysis results, the overall incidence of adverse reaction was 25.00%, and the incidence of adverse reaction was 29.17%, 37.50% and 8.33% respectively in test vaccine group, high-dose group and placebo group from the vaccination to Day 28 after full-course immunization, and the difference in incidence between groups was not statistically significant. Adverse reactions are mainly systemic diseases and various reactions at the administration site according to system organ classes (SOC), mainly manifested as pain at the inoculation site, followed by weakness. The adverse reaction level was mainly grade 1, with an incidence rate of 25.00%, and no Grade 2 adverse reaction occurred.

The incidence rate of Grade 3 adverse reaction was only 1.39%.

The overall incidence of adverse reaction was 14.08% under routine schedule, and the incidence of adverse reaction was 12.50%, 16.67% and 13.04% respectively in medium-dose group, high-dose group and placebo group of test vaccine from the vaccination to Day 28 after full-course immunization, without statistically significant differences between groups Adverse reactions are mainly systemic diseases and various reactions at the administration site, mainly manifested as pain at the inoculation site and the difference in the incidence of each adverse reaction between groups was not statistically significant. All adverse reactions were Grade 1.

In the phase I clinical trial, from the beginning of vaccination to 6 months after full-course immunization, the overall incidence of serious adverse events under the emergency schedule was 1.39% (1/72), i.e., one subject in the placebo group had one serious adverse event, namely colorectal polyp; the overall incidence of serious adverse events under the routine schedule was 1.41% (1/71), i.e., one subject in the high-dose group had 2 serious adverse events, namely goiter and papillary thyroid carcinoma. All of the above adverse events occurred on Day 28 after two doses of vaccine and were not related to vaccination.

Laboratory inspection

For the emergency immunization schedule, the incidence of abnormalities in laboratory indicators of clinical significance was 8.33%, 8.33% and 4.17% respectively in medium/high-dose groups of test vaccine and placebo group on Day 3 after each dose of vaccine, dominant by Grade 1. For the routine immunization schedule, the incidence of abnormalities in laboratory indicators of clinical significance was 8.33%, 8.33% and 4.35% respectively in medium/high-dose groups of test vaccine and placebo group on Day 3 after each dose of vaccine, dominant by Grade 1.

Inflammatory factor

For the first dose of the emergency immunization schedule, the average level of TNF-α in the high-dose group on Day 7 after vaccination was 2 times that before

vaccination (P<0.0006); for the second dose, the average level of IL-2 in the high-dose group on Day 7 after vaccination was 0.5 times that before vaccination (P=0.0102), and the average level of TNF-α was about 1.4 times that before vaccination (P=0.0060); for the second dose of the routine immunization schedule, the average level of serum TNF-α in the high-dose group on Day 7 after vaccination was about 0.5 times that before vaccination (P<0.0001), and the actual changes in all the above inflammatory factors were small, and neither substantial increase in serum inflammatory factors nor signals related to immunopathological reactions were found.

(2) Phase II clinical trial

In phase II clinical trial, a total of 600 subjects aged 18~59 years (C001-C300 & D001~D300) were included into the SS set, including 300 in emergency immunization schedule (Day 0, Day 14, Day 42 or Day 0, Day 14) and 300 in routine immunization schedule (Day 0, Day 28, Day 56 or Day 0, Day 28).

The overall incidence of adverse reaction was 31.67% under emergency schedule (C001-C300), and the incidence of adverse reaction was 33.33%, 35.00% and 21.67% respectively in medium/high-dose groups of test vaccine and placebo group from the vaccination to Day 28 after two doses, without statistically significant differences between groups. Adverse reactions are mainly systemic diseases and various reactions at the administration site according to system organ classes (SOC), mainly manifested as pain at the inoculation site, followed by weakness. The incidence of medium/high-dose groups of test vaccine and placebo group was 20.83%, 25.83% and 10.00% respectively (high-dose group>medium-dose group > placebo group), and the differences were statically significant. The difference in the incidence of the adverse reactions other than pain at the inoculation site between groups was not statistically significant. The overall adverse reaction was mainly Grade 1, without Grade 3 adverse reaction.

The overall incidence of adverse reaction was 19.00% under routine schedule (D001-D300), and the incidence of adverse reaction was 19.17%, 19.17% and18.33% respectively in medium/high-dose groups of test vaccine and placebo group from the

vaccination to Day 28 after two doses, without statistically significant differences between groups. Adverse reactions are mainly systemic diseases and various reactions at the administration site according to system organ classes (SOC), mainly manifested as pain at the inoculation site, followed by weakness. The incidence of medium/high-dose groups of test vaccine and placebo group was 17.50%, 16.67% and 16.67% respectively, and the differences in various adverse reactions between groups were not statistically significant. The adverse reaction was mainly Grade 1, and the incidence was 19.17%, 19.17% and 18.33% respectively in medium/high-dose groups of test vaccine and placebo group, without Grade 3 adverse reaction.

In the phase II clinical trial, from the beginning of vaccination to 6 months after full-course immunization, the overall incidence of serious adverse events under day 0, 14 emergency schedule (C151-C300) was 2.67% (4/150); the incidence of serious adverse events in medium-/high-dose groups was 3.33% (2/60), and that of the placebo group was 0%. In the medium-dose group, 3 serious adverse events occurred in 2 subjects, including 1 subject with hand fracture and nail injury and 1 subject with hemorrhoids; in the high-dose group, 2 adverse events occurred in 2 subjects, including 1 subject with soft tissue injury and 1 subject with glandular cystitis; 0, the overall incidence of serious adverse events was 0.67% under day 0, 28 routine schedule (D151-D300), and only one subject in the medium-dose group had a serious adverse event, namely protrusion of intervertebral disc. All of the above adverse events were not related to vaccination.

5.2 Immunogenicity Evaluation

5.2.1 Immunogenicity of two doses

The results of phase I clinical trial showed that, under the emergency immunization schedule, the positive conversion rate was 45.83%, 50.00% and 0% respectively and neutralizing antibody GMT was 5.6, 7.7 and 2.0 respectively in test vaccine medium-dose group, high-dose group and placebo group on Day 14 after two-dose inoculation; under the routine immunization schedule, the positive conversion rate was 83.33%, 79.17% and 4.35% respectively and neutralizing antibody GMT was 19.0,

29.6 and 2.2 respectively in test vaccine medium-dose group, high-dose group and placebo group on Day 28 after full-course vaccination.

The results of phase II clinical trial showed that, under the emergency immunization schedule (C001-C300), the positive conversion rate was 92.37%, 98.32% and 3.33% respectively and neutralizing antibody GMT was 27.6, 34.5 and 2.3 respectively in test vaccine medium-dose group, high-dose group and placebo group on Day 14 after two-dose inoculation; under the routine immunization schedule (D001-D300), the positive conversion rate was 97.44%, 100% and 0% respectively and neutralizing antibody GMT was 44.1, 65.4 and 2.0 respectively in test vaccine medium-dose group, high-dose group and placebo group on Day 28 after two-dose inoculation, suggesting that both the emergency immunization schedule and the routine immunization schedule of COVID-19 vaccine had good immunogenicity. On Day 14 after two doses under emergency immunization schedule (C001-C300), the positive conversion rate in the high-dose group was 98.32%, slightly higher than that in the middle-dose group (92.37%) (P=0.0296), and GMT 34.5 in the high-dose group was comparable to 27.6 in the middle-dose group (P=0.1051); on Day 28 after two doses under routine immunization schedule (D001-D300), the positive conversion rate was 100% in the high-dose group and 97.44% in the middle-dose group (P=0.1218), and GMT was 65.4 in the high-dose group, higher than that in the middle-dose group (44.1) (P=0.0006). In summary, the difference in neutralizing antibody GMT after immunization was less than 1.5 times between the medium and high dose groups, and the positive conversion rate was more than 90% in both groups.

The immunogenicity from phase II was significantly superior to that from phase I because the manufacturing process of vaccine for phase II clinical trial was optimized based on the vaccine for phase I clinical trial. The cell factory process was upgraded into bioreactor process, so the immunogenicity of the vaccine was significantly improved.

5.2.2 Immunization persistence of two doses

The results of the phase II clinical trial 6 months after immunization under day 0,

14 two-dose primary immunization schedule (C151-C300) showed that the positive rate of the medium/high-dose groups and the placebo group were 16.95%, 24.14% and 0% respectively, and the GMT was 4.1, 4.8 and 2.0 respectively. The difference in the positive rate between the groups was statistically significant (P=0.0056), and the positive rate in the medium/high-dose groups were comparable, with no statistically significant difference (P=0.3356); the GMT difference was statistically significant (P<0.0001) in each group, and the difference was not statistically significant (P=0.3574) in the medium/high-dose groups with comparable GMT. The positive rate of neutralizing antibody and GMT change trends within 6 months after immunization under day 0, 14 two-dose primary immunization schedule are shown in Fig. 7~8.

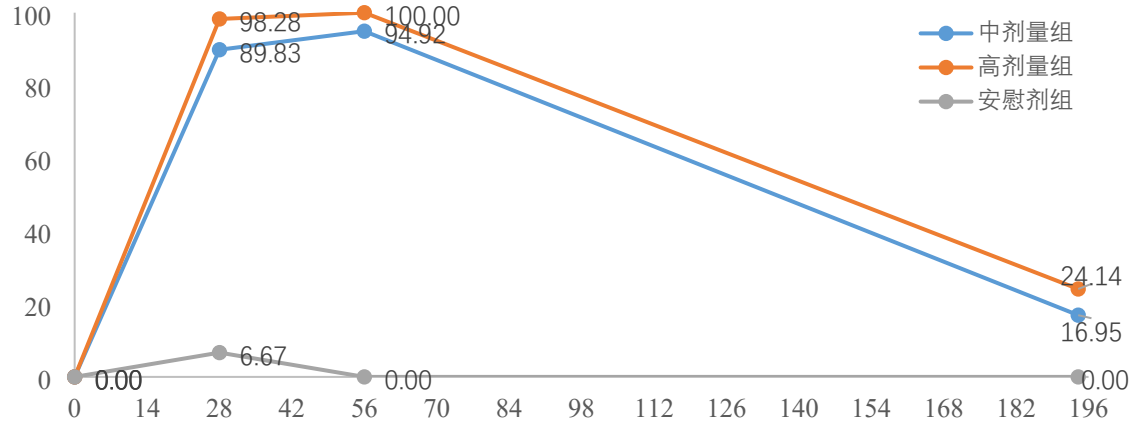


Fig. 7 Positive Rate of Neutralizing Antibody at Different Time Points of Day 0, Day 14 Two-dose Basic Immunization Schedule for Phase II Clinic Trial of COVID-19 Vaccine for Adults

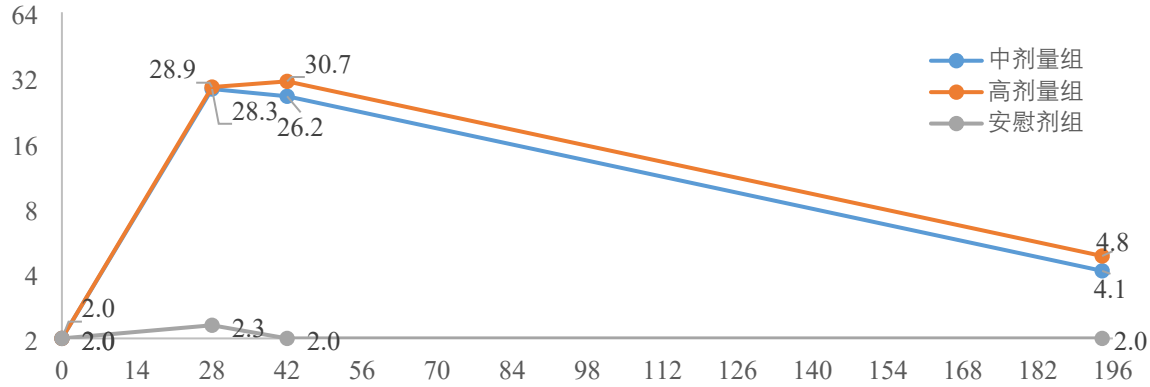


Fig. 8 GMT of Neutralizing Antibody at Different Time Points of Day 0, Day 14 Two-dose Basic Immunization Schedule for Phase II Clinic Trial of COVID-19 Vaccine for Adults

The results of the phase II clinical trial 6 months after immunization under Day 0,

Day 28 two-dose primary immunization schedule (D151-D300) showed that the positive rate of the medium-/high-dose groups and the placebo group were 35.19%, 46.43% and 0% respectively, and the GMT was 6.7, 7.1 and 2.0 respectively. The difference in the positive rate between the groups was statistically significant (P<0.0001), and the positive rate in the medium-/high-dose groups were comparable, with no statistically significant difference (P=0.2305); the GMT difference was statistically significant (P<0.0001) in each group, and the difference was not statistically significant (P=0.7579) in the medium-/high-dose groups with comparable GMT. The positive rate of neutralizing antibody and GMT change trends within 6 months after immunization under day 0, 28 two-dose primary immunization schedule are shown in Fig. 9~10.

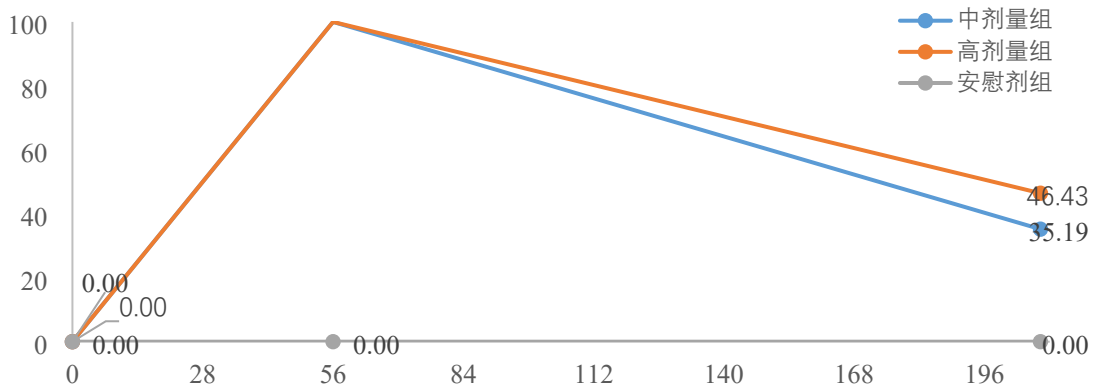


Fig. 9 Positive Rate of Neutralizing Antibody at Different Time Points of Day 0, Day **28 Two-dose Basic Immunization Schedule for Phase II Clinic Trial of COVID-19 Vaccine for Adults**

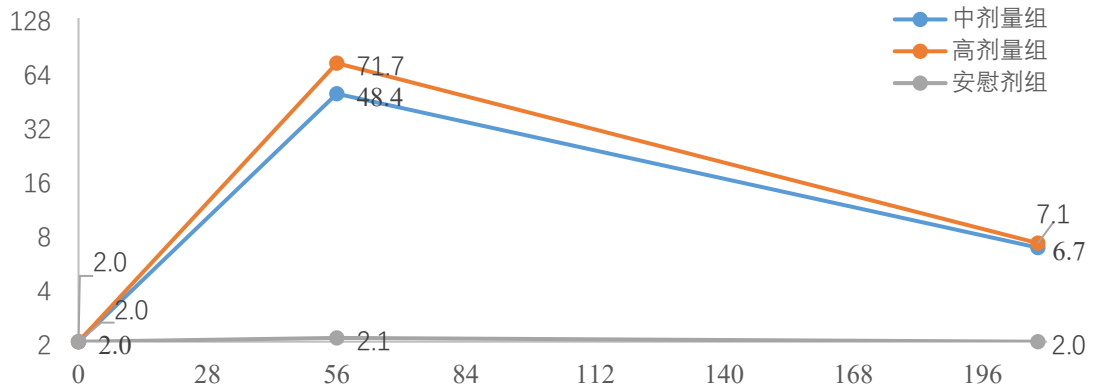


Fig. 10 GMT of Neutralizing Antibody at Different Time Points of Day 0, Day 28 Two-dose Basic Immunization Schedule for Phase II Clinic Trial of COVID-19 Vaccine for Adults

5.2.2 3 Immunogenicity

The immunogenicity results of the phase II clinical trial under Day 0, Day 14, Day

42 three-dose primary immunization schedule showed that all the subjects were negative for neutralizing antibodies before immunization, indicating the baseline antibody level was balanced and comparable. The positive conversion rate/positive rate was 94.83%, 93.22% and 98.15% respectively in the medium-dose group on day 14 after the second dose of immunization, on Day 28 after the second dose of immunization and on day 28 after the third dose of immunization, with the GMT of 27.0, 22.2 and 45.8 respectively; the positive conversion rate/positive rate was 98.33%, 98.33% and 98.28% in the high-dose group, with the GMT of 40.8, 29.1 and 74.2 respectively. The positive conversion rate/positive rate of neutralizing antibody in the medium/high-dose groups was comparable, and the differences were not statistically significant (P=1.0000); the GMT of the high-dose group was higher than the medium-dose group, and the differences were not statistically significant (P=0.0052).

Table 7 Immunogenicity of Phase II Clinic Trial of COVID-19 Vaccine for Adults under Day 0, Day 14, Day 42 Three-dose Basic Schedule (Neutralizing Antibody)

Time	Index	Medium-dose group	High-dose group	Placebo group	P value (3 groups)	P value (Medium vs high)
Before immunization	N	54	58	26		
	Positive rate n (%)	0(0.00)	0(0.00)	0(0.00)	1.0000	1.0000
	GMT	2.0	2.0	2.0	NA	NA
Second dose Day 14 after immunization	N	58	60	30		
	Positive rate n (%)	55 (94.83)	59 (98.33)	0 (0.00)	**<0.0001**	0.3601
	Positive conversion rate n (%)	55 (94.83)	59 (98.33)	0 (0.00)	**<0.0001**	0.3601
	GMT	27.0	40.8	2.2	<0.0001	0.0272
	GMI	13.5	20.4	1.1	<0.0001	0.0272
Second dose Day 28 after immunization	N	59	60	30		
	Positive rate n (%)	55 (93.22)	59 (98.33)	0 (0.00)	<0.0001	0.2068
	Positive conversion rate n (%)	55 (93.22)	59 (98.33)	0 (0.00)	<0.0001	0.2068
	GMT	22.2	29.1	2.0	<0.0001	0.0762
	GMI	11.1	14.6	1.0	<0.0001	0.0762
Third dosage Day 28 after immunization	N	54	58	26		
	Positive rate n (%)	53 (98.15)	57 (98.28)	0 (0.00)	<0.0001	1.0000
	Positive conversion rate n (%)	53 (98.15)	57 (98.28)	0 (0.00)	<0.0001	1.0000
	GMT	45.8	74.2	2.0	<0.0001	0.0052
	GMI	22.9	37.1	1.0	<0.0001	0.0052

The immunogenicity results of the phase II clinical trial under Day 0, Day 28, Day 56 three-dose primary immunization schedule showed that all the subjects were negative for neutralizing antibodies before immunization, indicating the baseline

antibody level was balanced and comparable. The positive conversion rate/positive rate of neutralizing antibody was 94.92% and 98.11% respectively in the medium-dose group on Day 28 after the second dose of immunization and on Day 28 after the third dose of immunization, with the GMT of 39.6 and 49.7 respectively; the positive conversion rate/positive rate was 100% in the high-dose group, with the GMT of 58.4 and 51.9 respectively. The positive conversion rate/positive rate of neutralizing antibody in the medium/high-dose groups was comparable on Day 28 after third dose, and the differences were not statistically significant (P=1.0000); the GMT of the medium/high-dose groups was comparable, and the differences were not statistically significant (P=0.7794).

Table 8 Immunogenicity of Phase II Clinic Trial of COVID-19 Vaccine for Adults under Day 0, Day 28, Day 56 Three-dose Basic Immunization Schedule (Neutralizing Antibody)

Time	Index	Medium-dose group	High-dose group	Placebo group	P value (3 groups)	P value (Medium vs high)
Before immunization	N	53	48	25		
	Positive rate n (%)	0(0.00)	0(0.00)	0(0.00)	1.0000	1.0000
	GMT	2.0	2.0	2.0	NA	NA
Second dose Day 28 after immunization	N	59	60	30		
	Positive rate n (%)	56 (94.92)	60 (100.00)	0 (0.00)	<0.0001	0.1187
	Positive conversion rate n (%)	56 (94.92)	60 (100.00)	0 (0.00)	<0.0001	0.1187
	GMT	39.6	58.4	2.0	<0.0001	0.0292
	GMI	19.8	29.2	1.0	<0.0001	0.0292
Third dosage Day 28 after immunization	N	53	48	25		
	Positive rate n (%)	52 (98.11)	48 (100.00)	0 (0.00)	<0.0001	1.0000
	Positive conversion rate n (%)	52 (98.11)	48 (100.00)	0 (0.00)	<0.0001	1.0000
	GMT	49.7	51.9	2.0	<0.0001	0.7794
	GMI	24.8	26.0	1.0	<0.0001	0.7794

5.3 Conclusion

COVID-19 Vaccine, Inactivated produced by SINOVAC has good safety and immunogenicity, and can produce antibodies rapidly after two doses of vaccination according to Day 0, Day 14 or Day 0, Day 28 schedule. However, the antibody level have dropped to a low level 6 months after two doses of vaccination. The antibody level after three doses of primary immunization on Day 0, Day 14, Day 42 or Day 0, Day 28, Day 56 were significantly higher than that after two doses of primary immunization, for which evidence of immunization persistence has not been obtained. Besides, the

cellular immune response of the COVID-19 Vaccine, Inactivated remains to be further investigated. No obvious change in the inflammatory factor before and after inoculation was caused; no signal related to immunopathological effect was observed.

According to the CDE's requirements for conditional marketing authorization of COVID-19 vaccine: "If the results of the subsequent clinical trials suggest that the existing immunization schedules and doses are not optimal, research on optimization of immunization schedules and doses should be continued". Considering that the neutralizing antibody level dropped to a low level 6 months after two doses of primary immunization, it was decided to give one dose of booster immunization 6 months after primary immunization and further investigate the immunization effect of the booster immunization schedule, thus providing a basis for the optimal immunization strategy for the subjects who had got two doses of primary immunization (C151-C300 and D151-D300) on Day 0, Day 14 and Day 0, Day 28 in Phase II of this study The above additional studies have been approved by DMC.

6 Introduction of Product Features

6.1 Preparation Technology and Formulation of the Vaccine

The COVID-19 Vaccine, Inactivated is prepared by vaccinating African green monkey kidney cell (referred to as “Vero Cell”) with novel coronavirus (CZ02 strain) through the culture, harvesting of virus solution, virus inactivation, concentration, purification and adsorption of aluminum hydroxide. It is milky white suspension liquid, which may be stratified due to precipitation and is easy to shake off. Its main component is inactivated novel coronavirus (SARS-CoV-2), and its excipients are aluminum hydroxide, disodium hydrogen phosphate, sodium dihydrogen phosphate, sodium chloride, etc. It contains no preservatives. It is packed in penicillin bottles or pre-filled syringes, each with 0.5ml. The vaccination can induce the body to produce the immunity against SARS-CoV-2 to prevent the disease caused by SARS-CoV-2 infection.

The test vaccine is prepared by Sinovac Research & Development Co., Ltd. and has been verified by National Institutes for Food and Drug Control as conforming to

the requirements of the *Regulations for Production and Verification of COVID-19 Vaccine, Inactivated (Draft)*. The vaccine is of injection type, with the specification of 0.5ml/dose. It contains respectively 300SU/0.5ml, 600SU/0.5ml and 1200SU/0.5ml SARS-CoV-2 antigen.

6.2 Vaccine Stability

The thermal accelerated stability study at 25±1℃ on Day 56 and at 37±1℃ on Day 42 has been completed for 6 batches of final products produced by the bioreactor. When stored at 25±1℃, the antigen content after the dissociation at different time points within 42 days (inclusive) met the quality standard, while the antigen content after the dissociation on Day 56 was lower than the quality standard, then the test was terminated; when stored at 37±1℃, the antigen content after the dissociation at different time points within 28 days (inclusive) met the quality standard, while the antigen content after the dissociation at the monitoring point on Day 42 was lower than 50% of the labelled amount for some batches, then the test was terminated.

The long-term stability observation at 2-8℃ for 6 months has been completed for 3 batches of final products produced by the cell factory and no obvious reduction was observed in the antigen content after the dissociation of different batches of final products of COVID-19 vaccine. The long-term stability observation for 6 months has been completed for 3 of 9 batches of final products produced by the bioreactor, and no obvious reduction was observed in the test data. Another 6 batches received 3-month long-term stability observation, no obvious reduction was observed in the antigen content after the dissociation of different batches of final products of COVID-19 vaccine.

According to the results of accelerated stability test, the validity period of vaccine is tentatively determined to be 3 years when stored at 2-8℃.

6.3 Control Vaccine

The Research applies placebo control, which is produced by Sinovac Research & Development Co., Ltd., with its component as aluminum hydroxide diluent and a trace

of milky white precipitated liquid. Its appearance is the same as that of the test vaccine.

It has been verified by National Institutes for Food and Drug Control as conforming to the requirements of the *Regulations for Production and Verification of COVID-19 Vaccine, Inactivated (Draft)*. The vaccine is of injection type, with the specification of 0.5ml/dose. It contains no SARS-CoV-2 antigen.

6.4 Transportation and Storage of Vaccine

The vaccine shall be kept and transported away from light at 2~8℃.

6.5 Inoculation Route and Procedure

The qualified subjects receive intramuscular injection at the lateral deltoid of upper arm, each with 0.5ml test vaccine or control vaccine for single dose. The subjects were inoculated according to emergency immunization schedule (Day 0, Day 14, Day 42 or Day 0, Day 14) or routine immunization schedule (Day 0, Day 28, Day 56 or Day 0, Day 28) as per 0.5ml/dose/times, and the vaccine was shook well before use. The subjects under Day 0, Day 14 and Day 0, Day 28 primary immunization schedules were given 1 dose of booster immunization 6 months after the second dose of vaccination.

6.6 Information of Test Product

Information of test product is shown in the following figure:

Table 9 Information of Test Product

Group	Vaccine name	Packaging	Antigen content	Manufacturer	Phase	Lot No.	Valid until
Medium-dose test Vaccine	COVID-19 Vaccine, Inactivated	Prefilled syringe	600SU/ 0.5ml	SINOVAC	Phase I	20200304	2023.02.28
					Phase II	20200308	2023.03.20
High-dose test Vaccine	COVID-19 Vaccine, Inactivated	Prefilled syringe	1200SU/ 0.5ml	SINOVAC	Phase I	20200310	2023.03.25
					Phase II	20200309	2023.03.21
Placebo Control	Aluminum hydroxide diluent	Prefilled syringe	0SU/ 0.5ml	SINOVAC	Phase I	2020022801	2023.02.27
					Phase II	2020022801	2023.02.27

6.7 Vaccine Packaging

The vaccine will be packed in a labelled box, with the label style shown as follows, and the rules of vaccine numbering on the label can be found in “8.4 Randomization and double-blinding”.

I/II Clinical Trial for COVID-19 Vaccine (Vero Cell), Inactivated
PRO-nCOV-1001
A001
For clinical trial only, stored at 2-8℃
Expiration date:

The packing box should be as follows:

I/II Clinical Trial for COVID-19 Vaccine (Vero Cell), Inactivated
PRO-nCOV-1001
Number segment:
For clinical trial only, stored at 2-8℃
Expiration date:

7 Purpose

To evaluate the safety and immunogenicity of COVID-19 Vaccine, Inactivated developed by SINOVAC for vaccination in adults.

7.1 Phase I Clinical Trial

To evaluate the safety, tolerance and primary immunogenicity of different doses of test vaccine for vaccination in adults according to different immunization schedules.

7.2 Phase II Clinical Trial

To evaluate the immunogenicity and safety of different doses of test vaccine for vaccination in adults according to different immunization schedules, and determine the appropriate dosage and vaccination schedule.

8 Test Design

8.1 Design

8.1.1 Overall design

The randomized, double-blinded and placebo-controlled design is applied.

8.1.2 Sample size and power of test

Phase I clinical trial: according to the *Technical Guidelines for Clinical Trial of Vaccines*[3] and *Provisions of Drug Registration*[1], Phase I clinical trial is a small-scale research (20~30 persons), focusing on the evaluation of vaccine safety. The total sample size of this phase of clinical trial is 144, with 72 for each immunization schedule.

The total number of subjects vaccinated with medium-does and high-dose test vaccine under each immunization schedule is 48. The number of subjects vaccinated with the test vaccine meets the requirement of phase I clinical trial.

Phase II clinical trial: according to the *Technical Guidelines for Clinical Trial of Vaccines*[3] and the *Provisions of Drug Registration*[1], Phase II clinical trial is to observe the immunization effect and safety of different doses of vaccine in the target population. The endpoint is to evaluate the immunogenicity and safety of the test vaccine. The number of cases in the test group is not less than 300. The total sample size of this phase of clinical trial is 600, the number of subjects vaccinated with medium-dose test vaccine, high-dose test vaccine and placebo is respectively 240, 240 and 120, and the number of cases in the test vaccine group is 480. The number of subjects vaccinated with the test vaccine meets the basic requirements of phase II clinical trial.

8.2 Endpoint

8.2.1 Endpoints of phase I trial

8.2.1.1 Primary endpoint

- Incidence of adverse reactions occurred from the beginning of the vaccination to 28 days after the whole-schedule vaccination.

8.2.1.2 Secondary endpoint

- Incidence of adverse reactions 0~7 days after each dose of vaccination;
- Incidence of abnormal laboratory indexes (blood routine test, blood biochemistry test and urine routine test) on the 3rd day after each dose of vaccination;
- Incidence of serious adverse event from the inoculation to 6 months after full-course vaccination;
- The seroconversion rate, seropositive rate, GMT, and GMI of neutralizing antibodies 7/14/21/28/42 days after the first dose of vaccination (emergency schedule);
- The seropositive rate of IgG and IgM antibodies 7/14/21/28/42 days after the first dose of vaccination (emergency schedule);

- The seroconversion rate, seropositive rate, GMT, and GMI of neutralizing antibodies 28/35/42/56 days after the first dose of vaccination (routine schedule);
- The seropositive rate of IgG and IgM antibodies 28/35/42/56 days after the first dose of vaccination (routine schedule).

8.2.1.3 Exploratory endpoint

- Positive rate of T cell response 14 days after vaccination (IFN-γ detection using Elispot);
- Positive rate and GMT of neutralizing antibody 6 months after full-course vaccination of test vaccine.
- Positive rate and GMT of IgG and IgM antibodies 6 months after full-course vaccination of test vaccine.
- The change of interleukin-6 (IL-6), interleukin-2 (IL-2) and tumor necrosis factor-α (TNF-α) in serum 7 days after each dose of vaccination.
- Positive rate of antinuclear antibody on Day 7/14/21/28/42/194 after the first dose of test vaccine (emergency immunization schedule);
- Positive rate of antinuclear antibody on Day 28/35/42/56/208 after the first dose of test vaccine (routine immunization schedule).

8.2.2 Endpoints of phase II trial

8.2.2.1 Primary endpoint

- Positive conversion rate of serum neutralizing antibody on Day 14 (emergency immunization schedule)/Day 28 (routine immunization schedule) after two doses of test vaccine;
- Incidence of adverse reaction on Day 0~28 (Day 0~14 for the first dose under emergency immunization schedule) after each dose;

8.2.2.2 Secondary endpoint

- positive rate, GMT and GMI of serum neutralizing antibody 14 days (emergency immunization schedule)/28 days (routine immunization schedule) after two doses of test vaccine;
- Positive conversion rate, positive rate, GMT and GMI of serum neutralizing

antibody on Day 28 after two dose of test vaccine under emergency immunization schedule;

- Positive conversion rate, positive rate, GMT and GMI of serum neutralizing antibody on Day 28 after three doses of test vaccine for primary immunization (only Day 0, Day 14, Day 42 and Day 0, Day 28, Day 56 schedules);
- Incidence of adverse reactions 0~7 days after each dose of vaccination;
- Incidence of serious adverse event from the inoculation to 6 months after full-course vaccination;

8.2.2.3 Exploratory endpoint

- Positive rate and GMT of neutralizing antibody 6 months after two doses of test vaccine (only Day 0, Day 14 or Day 0, Day 28 schedule);
- Positive rate and GMT of neutralizing antibody 12 months after three doses of test vaccine for primary immunization (only Day 0, Day 14, Day 42 and Day 0, Day 28, Day 56 schedules);
- Positive rate, GMT and GMI of serum neutralizing antibody on Day 14 (emergency immunization schedule)/Day 28 (routine immunization schedule) after booster inoculation of test vaccine (only Day 0, Day 14 and Day 0, Day 28 schedules);
- Positive rate and GMT of neutralizing antibody 6 months after booster immunization of test vaccine (only Day 0, Day 14 and Day 0, Day 28 schedules);
- Positive rate of antinuclear antibody on Day 28/42/70 after the first dose of test vaccine (Day 0, Day 14, Day 42 schedule);
- Positive rate of antinuclear antibody on Day 28/42/194 after the first dose of test vaccine (Day 0, Day 14 schedule);
- Positive rate of antinuclear antibody on day 56/84 after the first dose of test vaccine (Day 0, Day 28, Day 56 schedule);
- Positive rate of antinuclear antibody on day 56/208 after the first dose of test vaccine (Day 0, Day 28 schedule).

8.3 Study Plan

8.3.1 Phase I Study Plan

The clinical trial is a single-center, randomized, double-blind and placebo-controlled one. A total of 144 healthy adults aged 18-59 years are selected as the subjects. Upon informed consent, physical examination and screening based on the inclusion/exclusion criteria, the subjects are enrolled to receive different doses of the test vaccine or placebo according to different immunization schedules and meanwhile receive the test vaccine sequentially in accordance with the principle of medium dose to high dose. The purpose is to evaluate the safety, tolerance and primary immunogenicity of the test vaccine.

The subjects are enrolled according to the emergency immunization schedule of day 0,14 and the routine immunization schedule of day 0,28. A total of 72 subjects are enrolled for each immunization schedule in stages of medium and high doses respectively, each with 36 subjects who are vaccinated by the test vaccine or placebo respectively at the ratio of 2:1. According to the occurrence of the solicited and non-solicited adverse events, and of the abnormal indexes of blood routine examination, blood biochemistry and routine urine test, the vaccination in the stage of high dose may be conducted only 0~7 days after the first dose in the stage of medium dose is vaccinated when the safety observation is completed and the safety is confirmed.

The immediate reaction within 30 minutes after each dose of vaccination is observed, the local and systemic solicited adverse events within 0~7 days and the non-solicited adverse events from the beginning of the vaccination to 28 days after the whole-schedule vaccination are collected, and the SAE monitoring from the beginning of the vaccination to 6 months after the whole-schedule vaccination is completed.

The blood of volunteers was sampled at different times before and after immunization to test the blood routine, blood biochemistry, urine routine, serum inflammatory factors and anti-nuclear antibodies and evaluate the safety of the vaccine; test the serum neutralizing antibody, IgG and IgM antibodies and IFN-γ secretory reaction of specific T cells and evaluate the immunogenicity and immunization persistence of the vaccine.

See Table 10 for details on the Phase I clinical trial study plan.

Table 10 Phase I Clinical Trial Study Plan

Schedule (day)	Medium dose	High dose	Placebo	Total	Blood sampling time (day)	Antibody test/T cell reaction (day)	Blood routine examination, blood biochemistry and routine urine test (day)	Inflammatory factor (day)
0,14	24		12	36	0(-7),3,7,14,17, 21,28, 42,194¶	0*,7,14*,21, 28*, 42,194	0(-7),3, 14,17	0,7,14,21
		24	12	36	0(-7),3,7,14,17, 21,28, 42,194¶	0*,7,14*,21, 28*, 42,194	0(-7),3,14,17	0,7,14,21
0,28	24		12	36	0(-7),3,7,28,31, 35,42,56,208¶	0*,28*,35,42*, 56,208	0(-7),3,28,31	0,7,28,35
		24	12	36	0(-7),3,7,28,31, 35,42,56,208¶	0*,28*,35,42*, 56,208	0(-7),3,28,31	0,7,28,35
Total	**48**	**48**	**48**	**144**				

Remarks: * Test time-point of specific T cells secreting IFN-γ.

8.3.2 Phase II Study Plan

The clinical trial is a single-center, randomized, double-blind and placebo-controlled one. According to the occurrence of the solicited and non-solicited adverse events, and of the abnormal indexes of blood routine examination, blood biochemistry and routine urine test, phase II clinical trial may be started only 0~7 days after the first high dose of phase I clinical trial is vaccinated when the safety observation is completed and the safety is confirmed by DMC. 600 healthy adults aged 18~59 years were selected as the subjects of the clinical trial. Upon informed consent, physical examination and screening based on the inclusion/exclusion criteria, the subjects are enrolled to be vaccinated according to the emergency immunization schedule (Day 0, Day 14, Day 42 or Day 0, Day 14) or routine immunization schedule (Day 0, Day 28, Day 56 or Day 0, Day 28). 300 subjects were enrolled for each immunization schedule, randomized into 3 groups by a ratio of 2:2:1 and were vaccinated by the medium dose, high dose or placebo respectively according to the corresponding immunization schedule. The immunization schedule for the subjects numbered C001~C150 was Day 0, Day 14 and Day 42, while that for the subjects numbered C151~C300 was Day 0, Day 14. The immunization schedule for the subjects numbered D001~D150 was Day 0, Day 28 and

Day 56, while that for the subjects numbered D151~D300 was Day 0 and Day 28. The subjects given the third dose of Day 0, Day 14, Day 42 and Day 0, Day 28, Day 56 immunization schedule were enrolled in phases, and a total of 30 subjects numbered C001 ~ C030 were given the third dose first, and 30 subjects numbered D001 ~ D030 were given the third dose based on the abnormalities in blood routine and blood biochemical indexes and the occurrence of adverse events on Day 0 ~3 after vaccination. After it was preliminarily confirmed safe, a total of 30 subjects numbered D001~D030 were given the third dose. It is confirmed safe through assessment, the subjects numbered C031 ~ C150 and D031 ~ D150 may be given the third dose based on the abnormalities in blood routine and blood biochemical indexes and the occurrence of adverse events of 30 subjects in each of the above groups on Day 0~7 after vaccination.

The immediate reaction within 30 minutes after each dose of vaccination was observed; the local and systemic solicited adverse events on Day 0~7 and the non-solicited adverse events on Day 0~28 (Day 0~14 for the first dose under the emergency immunization schedule) after each vaccination were collected, and the SAE monitoring from the beginning of the vaccination to 6 months after the full-course vaccination was completed. The blood of volunteers is sampled at different times before and after immunization to test the serum neutralizing antibody for evaluating the immunogenicity and immunization persistence. Volunteers numbered C001~C030 and D001~D030 were required to have blood collected on D3 before and after the third dose for laboratory testing to evaluate the safety of the vaccine. If the blood routine and blood biochemical indexes before the immunization for the third dose were abnormal and had a clinical significance (Grade 2 or higher), the subjects would not be given the third dose.

Based on the immunogenicity results 6 months after 2 doses of vaccination in this study, the subjects under Day 0, Day 14 (C151~C300) and Day 0, Day 28 (D151~D300) 2-dose primary immunization schedules were given 1 dose of booster immunization 6 months after primary immunization. The adverse immediate reactions within 30 min after booster immunization were observed; local and systemic solicited adverse events

on Day 0~7 and the non-solicited adverse events on Day 0~28 after inoculation were collected; and the SAE monitoring 6 months after inoculation was completed.

See Table 11 for details on the Phase II clinical trial study plan.

Table 11 Phase II Clinical Trial Study Plan

	Immunization Procedure (day)	**Medium dose**	**High dose**	**Placebo**	**Total**	**Neutralizing antibody & anti-nuclear antibody test (day)**	**Blood routine examination and blood biochemistry * (day)**
Emergency immunization schedule	0,14,42	60	60	30	150	0,28,42,70,222†,402†	42,45
	0,14¶	60	60	30	150	0,28,42,194, 208†,374†	-
Routine immunization schedule	0,28,56	60	60	30	150	0,56,84,236†,416†	56,59
	0,28¶	60	60	30	150	0,56,208, 236†,388†	-
	Total	**240**	**240**	**120**	**600**		

* Only the subjects numbered as C001~C030 and D001~D030 underwent laboratory testing. ¶ The subjects (C151-C300, D151-D300) under Day 0, Day 14 and Day 0, Day 28 immunization schedules underwent 6-month booster immunization. Only neutralizing antibody was tested.

8.4 Randomization and Double-blind

8.4.1 Randomization

Randomized statisticians adopt the block randomization method. The SAS software (Version 9.4) is used to generate randomized blind codes for the subjects in different immunization schedules of Phase I and Phase II clinical trials. The blind code of the research vaccine is a “List of Corresponding Relationships between Random Numbers and Research Vaccines or Placebos”, which is made in duplicate and sealed after blind coding is completed. The original is kept by the investigator for unblinding in the test, and the copy is kept by the Sponsor. The numbers of the vaccines used under the emergency immunization schedule and routine immunization schedule in Phase I clinical trial are A001-A072 and B001-B072 respectively. The numbers of the vaccines used under the emergency immunization schedule and routine immunization schedule in Phase II clinical trial are C001-C300 and D001-D300 respectively.

The randomized statistician uses the SAS software (Version 9.4) to generate a blind code of spare vaccines which are prepared as per the ratio of 1:1:1 for medium dose, high dose, and placebo in phase I clinical trial. The number of spare vaccines is X01-X36. Spare vaccines are prepared according to the ratio of 2:2:1 for medium dose, high dose, and placebo in phase II clinical trial and the number of spare vaccines is Y01-Y60. In case of any discoloration or damage of test vaccines, the vaccinator should report to the responsible person and principal investigator at site who should start the spare vaccine enablement procedure to obtain the number of spare vaccines through the online spare vaccine acquisition system, and replace the research vaccine with the spare vaccine.

All test vaccines and placebos will be labeled blind as described in "6.7 Vaccine Packaging". After enrollment, subjects were inoculated with the blinding vaccine consistent with their study number.

8.4.2 Double-blind

Double-blind design is adopted in this trial. Randomized statisticians and other blind coding personnel who are not involved in the trial are employed for blind coding of the vaccine, that is, paste the printed label on the designated position of each vaccine/placebo according to the blind code. Randomized statisticians supervise the vaccine blind coding, and guide the blind coding operators to label according to the blind code. After the blind coding is completed, the blind code shall be sealed by randomized statisticians. The whole blind coding process must be recorded in writing. The blind coding personnel shall neither participate in other related work of this clinical trial, nor disclose any information about the blind code to any person participating in this clinical trial.

8.4.3 Emergency unblinding

Randomized statisticians shall prepare emergency letters during blind coding. Each letter shall contain a random password for unblinding, and each random password can correspond to any study number. The group of the study number can be fed back through the online unblinding system. Each random password represents an opportunity

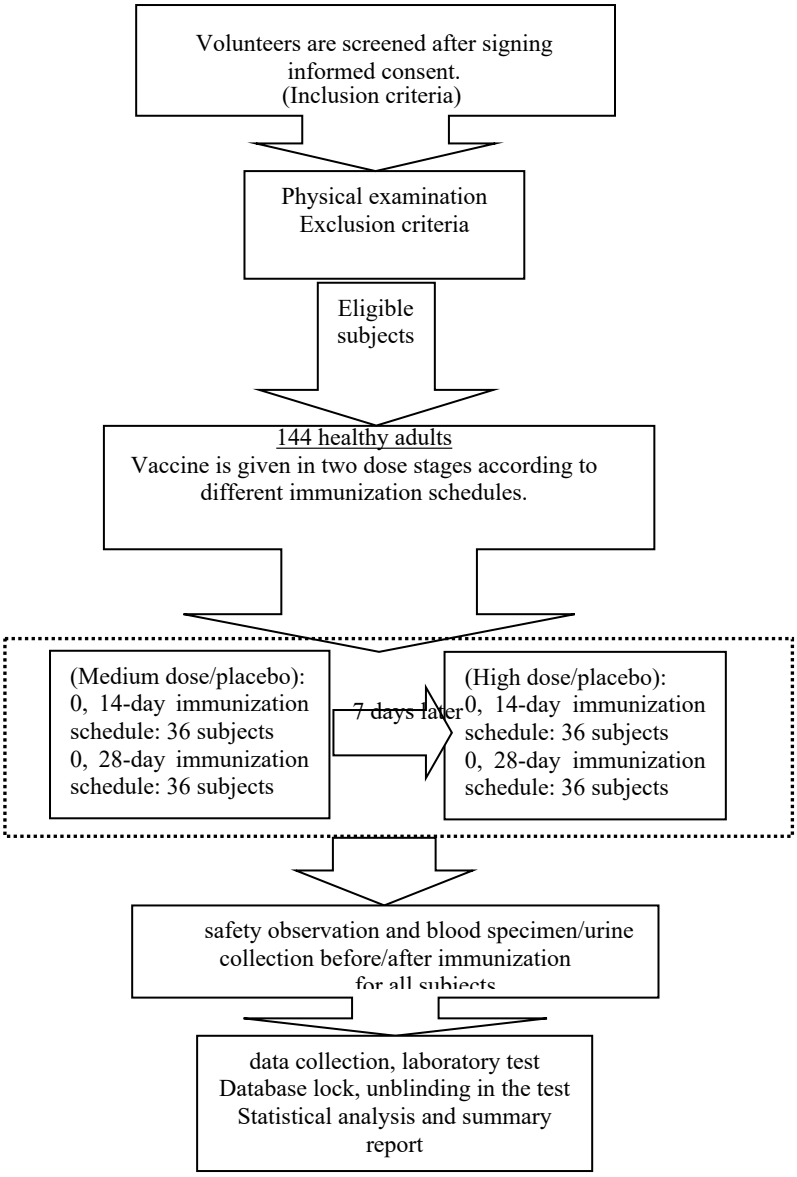
for unblinding. Only one study number can be subject to unblinding, and then it will become invalid. It is invalid for the study number that has been subject to unblinding. In this trial, 5 emergency envelopes are prepared for Phase I emergency and routine schedules, 10 emergency envelopes are prepared for Phase II emergency and routine schedules, and such envelopes shall be kept by the site personnel-in-charge. The blind review personnel shall check the opening and closing status of emergency envelopes.

During the study period, if emergency unblinding is jointly decided by the principal investigator, the Sponsor and DMC, the site personnel-in-charge shall open and read the emergency letter, log in to the online emergency unblinding system with the random unblinding password in the letter, perform emergency unblinding according to the prompt information, and make relevant records. The subjects with this study number will suspend the trial for withdrawal treatment, and the investigator will record the reasons for suspension in the CRF. The emergency letters that have been opened and read shall be kept properly and returned to the Sponsor after the trial.

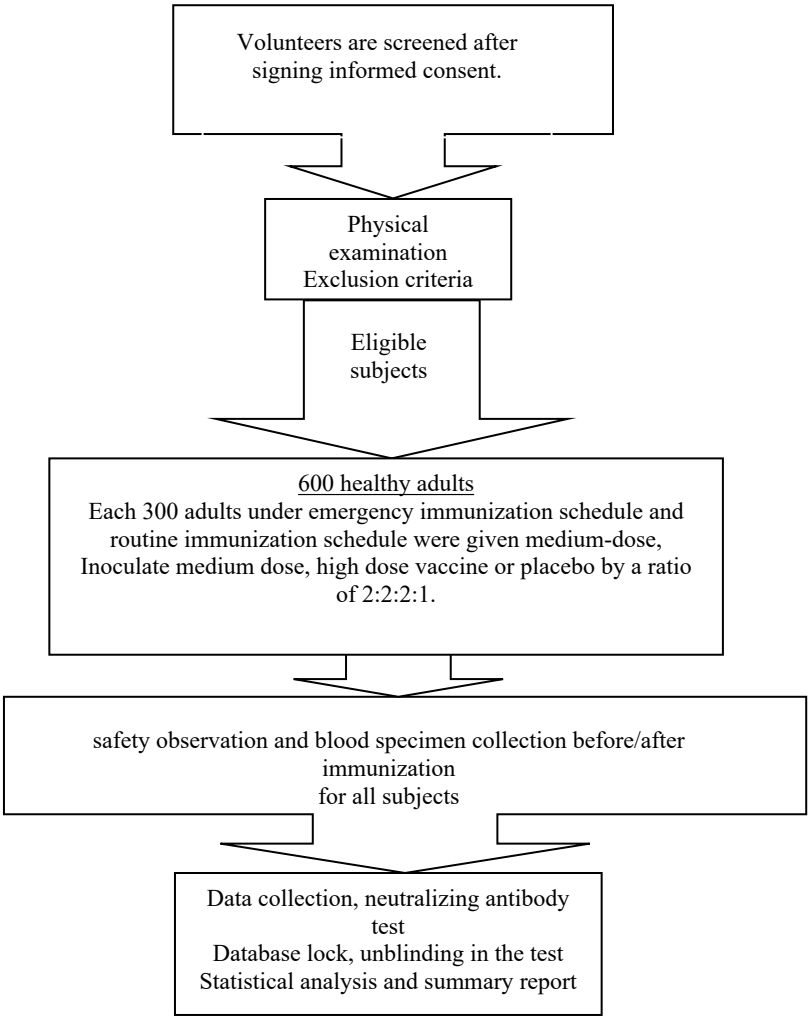
8.4.4 Unblinding regulations

The unblinding of Phase I and Phase II clinical trials shall follow the time points below: upon obtaining the serum detection results 14 days after two doses of immunization in emergency immunization schedule; upon obtaining the serum detection results 28 days after two doses of immunization in routine immunization schedule. It shall be implemented jointly by the Sponsor, the principal investigator and the statistician, and the unblinding record shall be kept. After the unblinding, the personnel responsible for observing the subjects, judging the results and validating the data shall remain blind until the final database is locked.

8.4.5 Flow chart



Flow Chart 7 Phase I clinical trial of COVID-19 Vaccine, Inactivated



Flow Chart 8 Phase II clinical trial of COVID-19 Vaccine, Inactivated

8.5 Research Duration

8.5.1 Duration of Clinical Trial

Table 12 Duration of Clinical Trial

	Immunization Procedure	Time*
Phase I	Emergency schedule (Day 0, Day 14)	7.5 months
	Routine schedule (Day 0, Day 28)	8 months
Phase II	Emergency schedule (Day 0, Day 14, Day 42)	13.5 months
	Emergency schedule (Day 0, Day 14) +6 month booster immunization	13.5 months
	Routine schedule (Day 0, Day 28, Day 56)	14 months
	Routine schedule (Day 0, Day 28) +6 month booster immunization	14 months

8.5.2 Expected duration of participation for subjects

It is expected to take up to 14 months.

8.6 Test Suspension and Early Termination

After each dose of vaccination, statistics were given on adverse reaction of the subjects, and the test was suspended or terminated according to the following criteria.

Criteria for test suspension:

- One or more Grade-4 adverse reactions (local, systemic) related to vaccination;
- Over 15% of the subjects have Grade-3 or higher adverse reactions, including local reaction, systemic reaction, and vital signs.

Criteria for early termination:

- After the clinical trial is suspended, the investigator, sponsor and DMC will discuss and decide whether to terminate the trial;
- The sponsor requests a complete termination of the test and gives reasons;
- Independent Ethics Committee requests a complete termination of the test and gives reasons;
- The competent administrative department requests a complete termination of the test and gives reasons.

8.7 Protocol Violation and Deviation

The following is regarded as protocol violation (including but not limited to):

- Subjects do not meet the inclusion criteria or meet the exclusion criteria;
- Subjects received the wrong vaccine;
- SAE is not reported within the required time.

The following is regarded as protocol deviation (including but not limited to):

- Test vaccine is given not within the window period specified in the protocol;
- Blood sampling is conducted not within the window period specified in the protocol;
- Intervals with vaccination of other vaccines did not meet protocol requirements (excluding rabies vaccination or tetanus vaccination in case of emergency).

9 Subjects

9.1 Inclusion Criteria for Subjects

(1) Healthy subjects aged 18-59;

(2) Able to understand and sign the Informed Consent Form voluntarily;

(3) Provide legal proof of identity.

9.2 Exclusion Criteria for Subjects

(1) Having traveled to or lived in Wuhan or surrounding areas or communities where confirmed cases have been reported within the previous 14 days;

(2) Having contact with patients who were infected with COVID-19 (who have tested positive for nucleic acid detection) within the previous 14 days;

(3) Having contact with patients who have fever and symptoms of respiratory infections from Wuhan or surrounding areas or communities where confirmed cases have been reported within the previous 14 days;

(4) Having been in places such as houses, offices and classrooms where over 2 cases of fever and/or symptoms of respiratory infections have been reported within the previous 14 days;

(5) SARS record in self-report;

(6) Infection with COVID-19 recorded in self-report;

(7) IgG or IgM screening results were positive;

(8) The RT-PCR test results of throat and anal swabs were positive;

(9) Women who are breastfeeding, pregnant, or planning to become pregnant during the study period (Judgment is made based on subjects' self-report and urine pregnancy test results);

(10) Body mass index (BMI) ≥35 kg/m^2;

(11) Having a history of asthma and allergy to vaccine or vaccine ingredients and having serious adverse reactions to the vaccine such as urticaria, dyspnea and angioneurotic edema;

(12) Subjects with congenital malformations or developmental disorders, genetic defects, severe malnutrition, etc.;

(13) Subjects with autoimmune diseases or immune deficiency/immune inhibition;

(14) Subjects with severe chronic diseases, severe cardiovascular diseases and hypertension, diabetes, liver and kidney diseases and malignant tumors that can not be controlled by drugs;

(15) Subjects with serious neurological diseases (epilepsy, convulsions or tic) or mental diseases;

(16) Subjects with thyropathy or having a history of thyroidectomy, subjects with an absent or dysfunctional spleen and subjects with an absent spleen or splenectomy;

(17) Subjects with coagulation disorders diagnosed by a doctor (such as deficiency of coagulation factors, coagulation diseases and blood platelet disorders) or significant bruising or coagulation disorder;

(18) Having received the immunosuppressive therapy, cytotoxic therapy, and inhale corticosteroids (excluding corticosteroid spray in treatment of allergic rhinitis and surface corticosteroid treatment of acute non-concurrent dermatitis) in the past six months;

(19) Subjects with abnormal laboratory test results such as in hematology and biochemistry which are beyond the range of reference values and of clinical significance in physical examination (applicable for Phase I clinical trial only):

1) Blood routine test: white blood cell count, hemoglobin and platelet count.

2) Blood biochemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), creatinine (CR) and creatine phosphokinase (CPK);

3) Routine urine indexes: urine protein (PRO), urine sugar and urine erythrocyte

(20) Chronic alcoholics or those having a history of drug abuse;

(21) Subjects who have received blood products within 3 months before vaccination with the test vaccine;

(22) Subjects who have received other study drugs within 30 days before vaccination with the test vaccine;

(23) Subjects who have received live attenuated vaccines within 14 days before

vaccination with the test vaccine;

(24) Subjects who have received subunit or inactivated vaccines within 7 days before vaccination with the test vaccine;

(25) Subjects having an attack of various acute or chronic diseases within 7 days;

(26) Subjects with axillary temperature >37.0℃ before vaccination with the test vaccine;

(27) Subjects who are not suitable for participating in this clinical trial according to the investigator.

9.3 Exclusion Criteria for Second and Third Doses of Vaccination

Subjects with any adverse event listed in (1) to (4) are forbidden to continue vaccination but they can finish other research based on the investigator's judgment. For subjects with any adverse event listed in (5) and (6), it is up to the investigator to decide whether or not to vaccinate. For subjects with any adverse event listed in (7) to (10), the vaccination can be delayed within the time window specified in the schedule.

(1) Vaccines of the same type other than the test vaccine are used during the study period;

(2) Any serious adverse reactions that have a causal relationship with the test vaccine;

(3) Allergic shock or hypersensitivity after vaccination (including urticaria/rash that appears within 30 minutes after vaccination);

(4) Any confirmed or suspected autoimmune diseases or immunodeficiency diseases, including human immunodeficiency virus (HIV) infection;

(5) Acute or newly developed chronic diseases after vaccination;

(6) Other reactions as determined by the investigator (including severe pain, severe swelling, severe limitation of motion, persistent high fever, severe headache, or other systemic or local reactions);

(7) With acute illness (moderate or severe illness with or without fever) at the time of vaccination;

(8) Axillary temperature >37.0℃ at the time of vaccination;

(9) Having received subunit or inactivated vaccines within 7 days and having received live attenuated vaccines within 14 days.

(10) Any other causes for which subjects are not suitable for vaccination according to the investigator.

9.4 Withdrawal and Termination Criteria for Subjects

(1) Subjects requested withdrawal from the clinical trial;

(2) An intolerable adverse event occurs whether it is relevant to the test drug or not;

(3) The health conditions of the subject make the trial not applicable to him or her;

(4) The investigator will decide whether the clinical abnormality (if any) of the subject is related to the vaccine, and whether the clinical trial shall be suspended ahead of schedule;

(5) Any other reasons considered by the investigator.

If a subject dropping out of the trial ahead of schedule has been inoculated with the test vaccine, the clinical trial data of the subject will be used for safety analysis. Subjects cannot be replaced during the study. When the subject inoculated with the vaccines used in the clinical trial withdraws or suspends the trial, the investigator shall provide necessary treatment to eliminate the clinical conditions related to the trial for the subject, and follow up until the diagnosis has been accomplished/subject is stable/subject is totally improved.

10 Method and Schedule

10.1 Visit Plan

10.1.1 Phase I Clinical Trial (0, 14-day Immunization Schedule)

Table 13 Visit Schedule for Phase I Clinical Trial (0, 14-day Immunization Schedule)

Follow-up		0	1	2	3	4	5	6	7	8	9
Follow-up period	D-21～D-1	D-7～D0	D0	D3[e]	D7[e]	D14[e]	D17[e]	D21[e]	D28[e]	D42[e]	D194[e]
Preliminary notice, subject recruitment	**X**										
Informed consent		**X**									

Demographic analysis			X									
Blood collection	Blood routine examination, blood biochemistry		X		X		X	X				
	IgG and IgM screening		X									
	Throat and anal swabs RT-PCR test		X									
	Serum antibody detection (Neutralizing antibody, IgG, IgM and anti-nuclear antibody)			X		X	X		X	X	X	X
	Inflammation factor test			X		X	X		X			
	IFN-γ secretion by T cell response			X			X			X		
Routine urine test			X		X		X	X				
Female urine pregnancy test				X			X					
General examination				X								
Screening based on inclusion/exclusion criteria[a]				X			X					
Inoculation[b]				X			X					
Subjects record the safety observation results on their daily diary/contact cards[c].				X	X	X	X	X	X	X	X	
Monitoring of adverse reactions/events (including adverse events of grade 3 and above and SAE)[cd]				X	X	X	X	X	X	X	X	X
Usage records of concomitant drugs/vaccines[cd]				X	X	X	X	X	X	X	X	X

a) Screening shall be conducted based on inclusion/exclusion criteria before vaccination of every dose.

b) Subjects will be observed in the observation room for 30 minutes to ensure no adverse events, especially acute allergic reactions, and then followed up regularly as required.

c) Safety observations include assessment of adverse reactions/events and body temperature measurements. Body temperature should be taken daily 0-7 days after inoculation and when fever is suspected. Subjects will record safety observation data in the Diary Card within 14 days after vaccination of the first dose and 28 days after vaccination of the second dose. Subjects will be interviewed regularly by the investigator to verify and record adverse events and concomitant drugs/vaccines.

d) During Day 42 to Day 194, SAE and the usage records of its concomitant drugs are only collected.

e) See "Visit Plan" for window period.

Visit plan:

Visit 0- Day -7-0, informed consent, **blood collection, urine collection, collection of throat and anal swabs**, laboratory indexes (blood routine examination, blood biochemistry, routine urine test, IgG & IgM, nucleic acid).

Visit 1- Day 0, Qualified subjects were enrolled; **blood collection, urine collection**

(only in female), vaccination of the first dose.

Visit 2- 3 days (±1 day) after 1st dose - Safety observation, drug use and other vaccination records were verified, and **blood and urine were collected.**

Visit 3- Day 7 (+3 days) after 1st dose - Safety observation, drug use and other vaccination records were verified, and **blood was collected.**

Visit 4- Day 14 (+5 days) after 1st dose - Safety observation, drug use and other vaccination records were verified, **blood and urine were collected** and the 2nd dose was given.

Visit 5- Day 3 (±1 day) after 2nddose - Safety observation, drug use and other vaccination records were verified, and **blood and urine were collected;** Examination.

Visit 6- Day 7 (±3 days) after 2nd dose - Safety observation, drug use and other vaccination records were verified, and **blood was collected.**

Visit 7- Day 14(+5 days) after 2nd dose - Safety observation, drug use and other vaccination records were verified, and **blood was collected.**

Visit 8- Day 28 (+10 days) after 2nd dose - Safety observation, drug use and other vaccination records were verified, and **blood was collected.**

Visits 8~9 - SAE observations, SAE concomitant drug use record and other special cases were verified.

Visit 9 - Day 180 (+30 days) after the 2nd dose - SAE observations, concomitant drug use record and other special cases were verified, and **blood was collected.**

10.1.2 Phase I Clinical Trial (0,28-day Immunization Schedule)

Table 14 Visit Schedule for Phase I Clinical Trial (0,28-day Immunization Schedule)

Follow-up			0	1	2	3	4	5	6	7	8	9
Follow-up period		D-21～D0	D-7～D0	D0	D3[e]	D7[e]	D28[e]	D31[e]	D35[e]	D42[e]	D56[e]	D208[e]
Preliminary notice, subject recruitment		**X**										
Informed consent			**X**									
Demographic analysis			**X**									
Blood collection	Blood routine examination, blood biochemistry		**X**		**X**		**X**	**X**				
	IgG and IgM screening		**X**									
	Throat and anal swabs RT-PCR test		**X**									

Follow-up			0	1	2	3	4	5	6	7	8	9
Follow-up period		D-21～D0	D-7～D0	D0	D3[e]	D7[e]	D28[e]	D31[e]	D35[e]	D42[e]	D56[e]	D208[e]
	Serum antibody detection (Neutralizing antibody, IgG, IgM and anti-nuclear antibody)			**X**			**X**		**X**	**X**	**X**	**X**
	Inflammation factor test			**X**		**X**	**X**		**X**			
	IFN-γ secretion by T cell response			**X**			**X**			**X**		
Routine urine test			**X**		**X**		**X**	**X**				
Female urine pregnancy test				**X**			**X**					
General examination				**X**								
Screening based on inclusion/exclusion criteria[a]				**X**			**X**					
Inoculation[b]				**X**			**X**					
Subjects record the safety observation results on their daily diary/contact cards[c].				**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Monitoring of adverse reactions/events (including adverse events of grade 3 and above and SAE)[cd]				**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Usage records of concomitant drugs/vaccines[cd]				**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

a) Screening shall be conducted based on inclusion/exclusion criteria before vaccination of every dose.

b) Subjects will be observed in the observation room for 30 minutes to ensure no adverse events, especially acute allergic reactions, and then followed up regularly as required.

c) Safety observations include assessment of adverse reactions/events and body temperature measurements. Body temperature should be taken daily 0-7 days after inoculation and when fever is suspected. Subjects will record safety observation data in the Diary Card within 28 days after vaccination of every dose. Subjects will be interviewed regularly by the investigator to verify and record adverse events and concomitant drugs/vaccines.

d) During Day 56 to Day 208, SAE and the usage records of its concomitant drugs are only collected.

e) See "Visit Plan" for window period.

Visit plan:

Visit 0- Day -7-0, informed consent, **blood collection, urine collection, collection of throat and anal swabs**, laboratory indexes (blood routine examination, blood biochemistry, routine urine test, IgG & IgM, nucleic acid).

Visit 1- Day 0, Qualified subjects were enrolled; **blood collection, urine collection (only in female),** vaccination of the first dose.

Visit 2- 3 days (±1 day) after 1st dose - Safety observation, drug use and other

vaccination records were verified, and **blood and urine were collected.**

Visit 3- Day 7 (+3 days) after 1st dose - Safety observation, drug use and other vaccination records were verified, and **blood was collected.**

Visit 4- Day 28 (+10 days) after 1st dose - Safety observation, drug use and other vaccination records were verified, **blood and urine were collected** and the 2nd dose was given.

Visit 5- Day 3 (±1 day) after 2nddose - Safety observation, drug use and other vaccination records were verified, and **blood and urine were collected;** Examination.

Visit 6- Day 7 (±3 days) after 2nd dose - Safety observation, drug use and other vaccination records were verified, and **blood was collected.**

Visit 7- Day 14 (+5 days) after 2nd dose - Safety observation, drug use and other vaccination records were verified, and **blood was collected.**

Visit 8- Day 28 (+10 days) after 2nd dose - Safety observation, drug use and other vaccination records were verified, and **blood was collected.**

Visits 8~9 - SAE observations, SAE concomitant drug use record and other special cases were verified.

Visit 9 - Day 180 (+30 days) after the second dose of vaccination - SAE observations, SAE concomitant drug use record and other special cases were verified, and blood was collected.

10.1.3 Phase II clinical trial (emergency immunization schedule)

Table 15 Visit Schedule for Phase II Clinical Trial (0, 14, 42-day Immunization Schedule)

Follow-up		0	1	2	3	4	5	6	7	8	9	10	11	12
Follow-up period	D-21～D0	D-7～D0	D0	D7[e]	D14[e]	D21[e]	D28[e]	D42[e]	D42[e]	D45[e]	D49[e]	D70[e]	D222[e]	D402[e]
Preliminary notice, subject recruitment	**X**													
Informed consent		**X**												
Demographic analysis		**X**												
Blood routine examination, blood biochemistry									**X**	**X**				
Neutralizing antibody test & anti-nuclear			**X**				**X**	**X**				**X**	**X†**	**X†**

antibody test														
Throat and anal swabs RT-PCR test		**X**												
IgG and IgM screening		**X**												
General examination			**X**											
Female urine pregnancy test			**X**		**X**				**X**					
Screening based on inclusion/exclusion criteria[a]			**X**		**X**				**X**					
Inoculation[b]			**X**		**X**				**X**					
Subjects record the safety observation results on their daily diary/contact cards[c].			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		
Monitoring of adverse reactions/events (including adverse events of grade 3 and above and SAE)[cd]			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Usage records of concomitant drugs/vaccines[cd]			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	

† Only neutralizing antibody was tested.

a) Screening shall be conducted based on inclusion/exclusion criteria before vaccination of every dose.

b) Subjects will be observed in the observation room for 30 minutes to ensure no adverse events, especially acute allergic reactions, and then followed up regularly as required.

c) Safety observations include assessment of adverse reactions/events and body temperature measurements. Body temperature should be taken daily 0-7 days after inoculation and when fever is suspected. Subjects will record safety observation data in the Diary Card within 14 days after vaccination of the first dose and 28 days after vaccination of the second and third dose. Subjects will be interviewed regularly by the investigator to verify and record adverse events and concomitant drugs/vaccines.

d) During Day 70 to Day 222, SAE and the usage records of its concomitant drugs are only collected.

e) See “Visit Plan” for window period.

Visit plan:

Visit 0 - Day -7~0 - IgG/IgM antibodies and nucleic acid were screened upon informed consent.

Visit 1- Day 0, Qualified subjects were enrolled; **blood collection,** vaccination of the first dose.

Visit 2- 7 days (+3 days) after 1st dose - Safety observation, drug use and other vaccination records were verified.

Visit 3- 14 days (+5 days) after 1st dose - Safety observation, drug use and other vaccination records were verified, and the 2nd dose was given.

Visit 4- 7 days (+3 days) after 2nd dose - Safety observation, drug use and other vaccination records were verified.

Visit 5- Day 14 (+5 days) after 2nd dose - Safety observation, drug use and other vaccination records were verified, and **blood was collected.**

Visit 6- Day 28 (+10 days) after 2nd dose - Safety observation, drug use and other vaccination records were verified, and **blood was collected.**

Visit 7 - Day 28 (+30 days) after second dose of vaccination - Subjects numbered C001~C030 were required to have blood collected, and those whose blood routine and blood biochemical indexes met the vaccination conditions would be given the third dose of vaccine; subjects numbered C031~C150 were not required to have blood collected and were directly given the third dose of vaccine.

Visit 8- Day 3 (±2 days) after the third dose of vaccination- only subjects numbered C001~C030 received this visit to verify safety observation, drug use and other vaccination records, and blood was collected.

Visit 8- Day 7 (+3 days) after the 3rd dose - Safety observation, drug use and other vaccination records were verified.

Visit 10- 28 days (+10 days) after 3rd dose - Safety observation, drug use and other vaccination records were verified, and **blood was collected.**

Visits 10~11 - SAE observations, SAE concomitant drug use record and other special cases were verified. **Visit 11** - Day 180 (+30 days) after the third dose of vaccination- SAE observations, SAE concomitant drug use record and other special cases were verified, and blood was collected.

Visit 12 - Day 360 (+30 days) after the third dose of vaccination - blood collection.

Table 16 Visit Schedule for Phase II Clinical Trial (Day 0, Day 14 Immunization Schedule + 6-month booster immunization)

Follow-up	Primary immunization									Booster immunization				
		0	1	2	3	4	5	6	7	8	9	10	11	12
Follow-up period	D-21～D0	D-7～D0	D0	D7[e]	D14[e]	D21[e]	D28[e]	D42[e]	D194[e]	D194[e]	D201[e]	D208[e]	D222[e]	D374[e]
Preliminary notice, subject recruitment	**X**													
Informed consent		**X**												
Demographic analysis		**X**												
Neutralizing antibody test & anti-nuclear antibody test			**X**				**X**	**X**	**X**			**X†**		**X†**
Pharyngeal and anal swabs RT-PCR test		**X**												
IgG and IgM screening		**X**												
General examination			**X**											
Female urine pregnancy test			**X**		**X**					**X**				
Screening based on inclusion/exclusion criteria[a]			**X**		**X**					**X**				
Inoculation[b]			**X**		**X**					**X**				
Subjects record the safety observation results on their daily diary/contact cards[c].			**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	
Adverse reaction/event monitoring (including level 3 or higher adverse events and SAEs)[cd]			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Usage records of concomitant drugs/vaccines[cd]			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

† Only neutralizing antibody was tested.

a) Screening shall be conducted based on inclusion/exclusion criteria before vaccination of every dose.

b) Subjects will be observed in the observation room for 30 minutes to ensure no adverse events, especially acute allergic reactions, and then followed up regularly as required.

c) Safety observations include assessment of adverse reactions/events and body temperature measurements. Body temperature should be taken daily 0-7 days after inoculation and when fever is suspected. Subjects recorded safety observation data in the Diary Card on Day 14

after first dose of vaccination and on Day 28 after the second dose of vaccination and booster inoculation, and were interviewed regularly by the investigator to verify and record adverse events and concomitant drugs/vaccines.

d) Only records of SAE and SAE concomitant drug use were collected from the end of visit 6 to visit 8 and from the end of visit 11 to visit 12.

e) See "Visit Plan" for window period.

Visit plan:

Visit 0 - Day -7~0 - IgG/IgM antibodies and nucleic acid were screened upon informed consent.

Visit 1- Day 0, Qualified subjects were enrolled; **blood collection,** vaccination of the first dose.

Visit 2- 7 days (+3 days) after 1st dose - Safety observation, drug use and other vaccination records were verified.

Visit 3- 14 days (+5 days) after 1st dose - Safety observation, drug use and other vaccination records were verified, and the 2nd dose was given.

Visit 4- 7 days (+3 days) after 2nd dose - Safety observation, drug use and other vaccination records were verified.

Visit 8- Day 14 (+5 days) after 2nd dose - Safety observation, drug use and other vaccination records were verified, and **blood was collected.**

Visit 6- Day 28 (+10 days) after 2nd dose - Safety observation, drug use and other vaccination records were verified, and **blood was collected.**

Visits 6~7 - SAE observations, SAE concomitant drug use record and other special cases were verified.

Visit 7 - Day 180 (+30 days) after the second dose of vaccination - SAE observations, SAE concomitant drug use record and other special cases were verified, and blood was collected.

Visit 8 - Day 180 (+60 days) after the second dose of vaccination - SAE observations, SAE concomitant drug use record and other special cases were verified, and booster immunization were given.

Visit 9 - Day 7 (+3 days) after booster immunization -safety observation, drug use and other vaccination records were verified.

Visit 10 - Day 14 (+5 days) after booster immunization -safety observation, drug use and other vaccination records were verified, and blood was collected.

Visit 11 - Day 28 (+10 days) after booster immunization -safety observation, drug use and other vaccination records were verified.

Visits 11~12 - SAE observations, SAE concomitant drug use record and other special cases were verified.

Visit 12 - Day 180 (+30 days) after booster immunization - SAE observations, SAE concomitant drug use record and other special cases were verified, and blood was collected.

10.1.4 Phase II clinical trial (routine immunization schedule)

Table 17 Visit Schedule for Phase II Clinical Trial (0, 28, 56-day Immunization Schedule)

Follow-up		0	1	2	3	4	5	6	7	8	9	10	11
Follow-up period	D-21～D0	D-7～D0	D0	D7[e]	D28[e]	D35[e]	D56[e]	D56[e]	D59[e]	D63[e]	D84[e]	D236[e]	D416[e]
Preliminary notice, subject recruitment	**X**												
Informed consent		**X**											
Demographic analysis		**X**											
Blood routine examination, blood biochemistry								**X**	**X**				
Neutralizing antibody test/ anti-nuclear antibody test			**X**				**X**				**X**	**X†**	**X†**
Throat and anal swabs RT-PCR test		**X**											
IgG and IgM screening		**X**											
General examination			**X**										
Female urine pregnancy test			**X**		**X**			**X**					
Screening based on inclusion/exclusion criteria[a]			**X**		**X**			**X**					
Inoculation[b]			**X**		**X**			**X**					
Subjects record the safety observation results on their daily			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		

diary/contact cards[e].													
Monitoring of adverse reactions/events (including adverse events of grade 3 and above and SAE)[cd]			X	X	X	X	X	X	X	X	X	X	
Usage records of concomitant drugs/vaccines[cd]			X	X	X	X	X	X	X	X	X	X	

† Only neutralizing antibody was tested.

a) Screening shall be conducted based on inclusion/exclusion criteria before vaccination of every dose.

b) Subjects will be observed in the observation room for 30 minutes to ensure no adverse events, especially acute allergic reactions, and then followed up regularly as required.

c) Safety observations include assessment of adverse reactions/events and body temperature measurements. Body temperature should be taken daily 0-7 days after inoculation and when fever is suspected. Subjects will record safety observation data in the Diary Card within 28 days after vaccination of every dose. Subjects will be interviewed regularly by the investigator to verify and record adverse events and concomitant drugs/vaccines.

d) During Day 84 to Day 236, SAE and the usage records of its concomitant drugs are only collected.

e) See "Visit Plan" for window period.

Visit plan:

Visit 0 - Day -7~0 - IgG/IgM antibodies and nucleic acid were screened upon informed consent.

Visit 1- Day 0, Qualified subjects were enrolled; **blood collection,** vaccination of the first dose.

Visit 2- 7 days (+3 days) after 1st dose - Safety observation, drug use and other vaccination records were verified.

Visit 3- 28 days (+10 days) after 1st dose - Safety observation, drug use and other vaccination records were verified, and the 2nd dose was given.

Visit 4- 7 days (+3 days) after 2nd dose - Safety observation, drug use and other vaccination records were verified.

Visit 5- Day 28 (+10 days) after 2nd dose - Safety observation, drug use and other vaccination records were verified, and **blood was collected.**

Visit 6 - Day 28 (+30 days) after second dose of vaccination - Subjects numbered

D001~D030 were required to have blood collected, and those whose blood routine and blood biochemical indexes met the vaccination conditions would be given the third dose of vaccine; subjects numbered D031~D150 were not required to have blood collected and were directly given the third dose of vaccine.

Visit 7- Day 3 (±2 days) after the third dose of vaccination - only subjects numbered D001~D030 received this visit to verify safety observation, drug use and other vaccination records, and blood was collected.

Visit 8- Day 7 (+3 days) after the 3rd dose - Safety observation, drug use and other vaccination records were verified.

Visit 8- Day 28 (+10 days) after the 3rd dose - Safety observation, drug use and other vaccination records were verified, and **blood was collected.**

Visits 9 ~10 - SAE observations, SAE concomitant drug use record and other special cases of the subjects were verified.

Visit 10 - Day 180 (+30 days) after the third dose of vaccination - SAE observations, SAE concomitant drug use record and other special cases were verified, and blood was collected.

Visit 11 - Day 360 (+30 days) after the third dose of vaccination - blood collection.

Table 18 Visit Schedule for Phase II Clinical Trial (Day 0, 28 Immunization Schedule + 6-month booster immunization)

	Primary immunization								Booster immunization			
Follow-up		0	1	2	3	4	5	6	7	8	9	10
Follow-up period	D-21～D0	D-7～D0	D0	D7[e]	D28[e]	D35[e]	D56[e]	D208[e]	D208[e]	D215[e]	D236[e]	D388[e]
Preliminary notice, subject recruitment	**X**											
Informed consent		**X**										
Demographic analysis		**X**										
Neutralizing antibody test & anti-nuclear antibody test			**X**				**X**	**X**			**X†**	**X†**
Throat and anal swabs RT-PCR test		**X**										
IgG and IgM screening		**X**										
General examination			**X**									
Female urine pregnancy test			**X**		**X**				**X**			

Screening based on inclusion/exclusion criteria[a]			X		X				X			
Inoculation[b]			X		X				X			
Subjects record the safety observation results on their daily diary/contact cards[c].			X	X	X	X	X		X	X	X	
Monitoring of adverse reactions/events (including adverse events of grade 3 and above and SAE)[cd]			X	X	X	X	X	X	X	X	X	X
Usage records of concomitant drugs/vaccines[cd]			X	X	X	X	X	X	X	X	X	X

† Only neutralizing antibody was tested.

a) Screening shall be conducted based on inclusion/exclusion criteria before vaccination of every dose.

b) Subjects will be observed in the observation room for 30 minutes to ensure no adverse events, especially acute allergic reactions, and then followed up regularly as required.

c) Safety observations include assessment of adverse reactions/events and body temperature measurements. Body temperature should be taken daily 0-7 days after inoculation and when fever is suspected. Subjects will record safety observation data in the Diary Card within 28 days after vaccination of every dose. Subjects will be interviewed regularly by the investigator to verify and record adverse events and concomitant drugs/vaccines.

d) Only records of SAE and SAE concomitant drug use were collected from the end of visit 5 to visit 7 and from the end of visit 9 to visit 10.

e) See "Visit Plan" for window period.

Visit plan:

Visit 0 - Day -7~0 - IgG/IgM antibodies and nucleic acid were screened upon informed consent.

Visit 1- Day 0, Qualified subjects were enrolled; **blood collection,** vaccination of the first dose.

Visit 2- 7 days (+3 days) after 1st dose - Safety observation, drug use and other vaccination records were verified.

Visit 3- 28 days (+10 days) after 1st dose - Safety observation, drug use and other vaccination records were verified, and the 2nd dose was given.

Visit 4- 7 days (+3 days) after 2nd dose - Safety observation, drug use and other vaccination records were verified.

Visit 5- Day 28 (+10 days) after 2nd dose - Safety observation, drug use and other

vaccination records were verified, and **blood was collected.**

Visits 5 & 6 - SAE observations, SAE concomitant drug use record and other special cases of the subjects were verified.

Visit 6- Day 180 (+ 30 days) after second dose of vaccination - safety observation, drug use and other vaccination records were verified, and blood was collected.

Visit 7- Day 180 (+ 60 days) after second dose of vaccination- safety observation, drug use and other vaccination records were verified, and blood was collected.

Visit 8 - Day 7 (+3 days) after booster immunization -safety observation, drug use and other vaccination records were verified.

Visit 9 - Day 28 (+10 days) after booster immunization -safety observation, drug use and other vaccination records were verified, and blood was collected.

Visits 9 ~10 - SAE observations, SAE concomitant drug use record and other special cases of the subjects were verified.

Visit 10 - Day 180 (+30 days) after booster immunization - SAE observations, SAE concomitant drug use record and other special cases were verified, and blood was collected.

10.2 Recruitment and Informed Consent

Recruitment notices will be issued to volunteers who meet the enrollment criteria. The informed consent will be explained to the volunteers in detail. Under the condition of voluntary participation, the volunteers and the study doctors sign the informed consent which is in duplicate, and the copy is reserved by the volunteer.

10.3 Screening and Random Enrollment

Subjects who are normal in physical examination (Women undergo a urine pregnancy test to rule out pregnancy.) and screened qualified as per other inclusion/exclusion criteria (Screening No. consists of S and screening order, such as “S0001”.) will be enrolled and given Research Number based on enrollment order. The study numbers of the subjects under the emergency immunization schedule and routine immunization schedule in Phase I are A001-A072 and B001-B072 respectively. The study numbers of the subjects under the emergency immunization schedule and routine immunization schedule in Phase II are C001-C300 and D001-D300 respectively.

10.4 Vaccination

According to the Research Numbers of the subjects, the vaccinator takes the vaccine with the corresponding number, open it and check the numbers on the label of the vaccine bottle, on the movable label in the packaging box and on the label outside the vaccine package. After confirmation, the vaccinator performs vaccination. Then, he tears off the movable label in the packaging box, paste it in the corresponding position of the original record sheet, and fill in the vaccination information in the original record book.

See “8.3 Study Plan” for immunization schedules.

10.5 Safety Follow-up and Observation

Diary Card was issued to subjects after vaccination of each dose. Subjects were required to record the solicited (systemic, local) adverse events 0 to 7 days after vaccination and the non-solicited adverse events 0 to 28 days (0 to 14 days for the first dose under emergency immunization schedule) after vaccination. Subjects were required to record any clinical symptoms, drugs and usage of other vaccines in detail on their diary cards 0 to 28 days (0 to 14 days for the first dose under emergency immunization schedule) after vaccination. The investigators verified the adverse events reported by subjects.

Systematic observation was conducted on Day 7 after vaccination. Subjects observed their own symptoms and signs and filled in the Diary Card on a daily basis; meanwhile, the investigator paid a visit (no less than 2 face-to-face visits in Phase I), and collected safety observation data on Day 0 ~ 7; the occurrence of adverse events was recorded on Day 8 ~ 28 (Day 8 ~ 14 for the first dose of the emergency immunization schedule) by combining active reporting by subjects with investigator regular follow-up. Safety follow-up was observed until the 28th day after vaccination.

Subjects were informed that any adverse events should be recorded at any time and that acute allergic reaction, grade 3 or higher adverse events, and SAE should be reported to the investigator at any time. The investigator should conduct investigation for verification and follow-up until those problems are resolved, and finally complete

detailed investigation and follow-up records which should include the following contents:

- Description of adverse events
- Start time and end time of adverse events
- Severity of adverse events
- Correlation with vaccination
- Laboratory test results
- Processing measures

If subjects develop acute allergic reaction and grade 3 or higher adverse events after vaccination, treatment should be provided in time to relieve the pain of the subjects as soon as possible; If subjects develop SAE after vaccination, a medical green passage should be initiated for immediate medical treatment. Medication and medical treatment at each follow-up should be recorded in detail.

10.6 Sampling

- **Sampling plan**

Sampling before/after immunization should be conducted according to "10.1 Visit Plan" for subjects. The sampling plan is as follows:

Table 19 Sampling Plan for Phase I Clinical Trial (0, 14-day Immunization Schedule)

Sample type	No. of follow-up	0	1	2	3	4	5	6	7	8	9
Venous blood (ml)	Follow-up period	D-7～D0	D0	D3[e]	D7[e]	D14[e]	D17[e]	D21[e]	D28[e]	D42[e]	D194[e]
	Blood routine	**3**		**3**		**3**	**3**				
	Blood biochemistry	**5**		**5**		**5**	**5**				
	Inflammatory factor		**5**		**5**	**5**		**5**			
	Neutralizing antibody, IgG antibody, IgM and antinuclear antibody		**5**		**5**	**5**		**5**	**5**	**5**	**5**
	T cell reaction		**10**			**10**			**10**		
	Total	**8**	**20**	**8**	**10**	**28**	**8**	**10**	**15**	**5**	**5**
Fingertip blood (ml)	IgG and IgM screening	**Proper dose**									
Urine (ml)	Urine routine test	**5~10**		**5~10**		**5~10**	**5~10**				
	Urine pregnancy test (female)		**5~10**			**5~10**					

Throat and anal swabs	RT-PCR test	**Proper dose**									

e: See "10.1 Visit Plan" for window period.

Table 20 Sampling Plan for Phase I Clinical Trial (0,28-day Immunization Schedule)

Sample type	No. of follow-up	0	1	2	3	4	5	6	7	8	9
Venous blood (ml)	Follow-up period	D-7～D0	D0	D3[e]	D7[e]	D28[e]	D31[e]	D35[e]	D42[e]	D56[e]	D208[e]
	Blood routine	**3**		**3**		**3**	**3**				
	Blood biochemistry	**5**		**5**		**5**	**5**				
	Inflammatory factor		**5**		**5**	**5**		**5**			
	Neutralizing antibody, IgG antibody, IgM and antinuclear antibody		**5**			**5**		**5**	**5**	**5**	**5**
	T cell reaction		**10**			**10**			**10**		
	Total	**8**	**20**	**8**	**5**	**28**	**8**	**10**	**15**	**5**	**5**
Fingertip blood (ml)	IgG and IgM screening	**Proper dose**									
Urine (ml)	Urine routine test	**5~10**		**5~10**		**5~10**	**5~10**				
	Urine pregnancy test (female)		**5~10**			**5~10**					
Throat and anal swabs	RT-PCR test	**Proper dose**									

e: See "10.1 Visit Plan" for window period.

Table 21 Sampling Plan for Phase II Clinical Trial (0, 14, 42-day Immunization Schedule)

Sample type	No. of follow-up	0	1	2	3	4	5	6	7	8	9	10	11	12
	Follow-up period	D-7～D0	D0	D7[e]	D14[e]	D21[e]	D28[e]	D42[e]	D42[e]	D45[e]	D49[e]	D70[e]	D222[e]	D402[e]
Fingertip blood (ml)	IgG and IgM screening	**Proper dose**												
Throat and anal swabs	RT-PCR test	**Proper dose**												
Venous blood (ml)	Blood routine examination*								**3**	**3**				
	blood biochemistry #								**5**	**5**				
	Neutralizing antibody & antinuclear antibody		**3**				**3**	**3**				**3**	**3†**	**3†**
	Total		**3**				**3**	**3**	**8**	**8**		**3**	**3**	**3**
Urine (ml)	Urine pregnancy test		**5~10**		**5~10**				**5~10**					

	(female)													

† Only neutralizing antibody was tested; e: See "10.1 Visit Plan" for window period.

* Only the subjects numbered as C001~C030 underwent blood routine test;

* Only the subjects numbered as C001~C030 underwent blood biochemistry test;

Table 22 Sampling Plan for Phase II Clinical Trial (Day 0, Day 14 Immunization Schedule +6-month Booster Immunization)

Sample type	No. of follow-up	Primary immunization								Booster immunization				
		0	1	2	3	4	5	6	7	8	9	10	11	12
	Follow-up period	D-7～D0	D0	D7[e]	D14[e]	D21[e]	D28[e]	D42[e]	D194[e]	D194[e]	D201[e]	D208[e]	D222[e]	D374[e]
Fingertip blood (ml)	IgG and IgM screening	**Proper dose**												
Throat swab + anal swab	RT-PCR test	**Proper dose**												
Venous blood (ml)	Neutralizing antibody & antinuclear antibody		**3**				**3**	**3**	**3**			**3†**		**3†**
Urine (ml)	Urine pregnancy test (female)		**5~10**		**5~10**					**5~10**				

† Only neutralizing antibody was tested; e: See "10.1 Visit Plan" for window period.

Table 23 Sampling Plan for Phase II Clinical Trial (0, 28, 56-day Immunization Schedule)

Sample type	No. of follow-up	0	1	2	3	4	5	6	7	8	9	10	11
	Follow-up period	D-7～D0	D0	D7[e]	D28[e]	D35[e]	D56[e]	D56[e]	D59[e]	D63[e]	D84[e]	D236[e]	D416[e]
Fingertip blood (ml)	IgG and IgM screening	**Proper dose**											
Throat and anal swabs	RT-PCR test	**Proper dose**											
Venous blood (ml)	Blood routine examination*							**3**	**3**				
	blood biochemistry #							**5**	**5**				
	Neutralizing antibody & antinuclear		**3**				**3**				**3**	**3†**	**3†**

	antibody												
	Total		**3**				**3**	**8**	**8**		**3**	**3**	**3**
Urine (ml)	Urine pregnancy test (female)		**5~10**		**5~10**			**5~10**					

† Only neutralizing antibody was tested; e: See “10.1 Visit Plan” for window period.

* Only the subjects numbered as D001~D030 underwent blood routine test;

* Only the subjects numbered as D001~D030 underwent blood biochemistry test;

Table 24 Sampling Plan for Phase II Clinical Trial (Day 0, Day 28 Immunization Schedule +6-month Booster Immunization)

Sample type	No. of follow-up	Primary immunization							Booster immunization			
		0	1	2	3	4	5	6	7	8	9	10
	Follow-up period	D-7～D0	D0	D7[e]	D28[e]	D35[e]	D56[e]	D208[e]	D208[e]	D215[e]	D236[e]	D388[e]
Fingertip blood (ml)	IgG and IgM screening	**Proper dose**										
Throat and anal swabs	RT-PCR test	**Proper dose**										
Venous blood (ml)	Neutralizing antibody & antinuclear antibody		**3**				**3**	**3**			**3†**	**3†**
Urine (ml)	Urine pregnancy test (female)		**5~10**		**5~10**				**5~10**			

† Only neutralizing antibody was tested; e: See "10.1 Visit Plan" for window period.

- **Sample numbering principle**

During screening, samples are numbered as "screening No. + serial number of sampling" and the samples of enrolled subjects are numbered as "study number + serial number of sampling".

- **Sample management**

All samples collected on site should be sent to the laboratory in time to complete the handover with laboratory personnel.

Serum shall be separated from blood samples for serum antibody (neutralizing antibody/IgG/IgM) test, placed into 2 tubes (no less than 1ml for serum tube A in phase I and no less than 0.5ml in phase II, and tube B for backup serum), and recorded. After separation, serum should be kept below -20 ºC. Blood samples used for IFN-γ secretory reaction of specific T cells should be kept below -20 ºC. Record should be kept for sample handover, serum separation and sample preservation.

For all submitted samples, specimen submission record should be made and temperature control record during submission should be kept.

10.7 Safety Evaluation

10.7.1 Safety Observation Indexes

Solicited local adverse events: pain, induration, swelling, vaccinal areola, skin rash and pruritus.

Solicited systemic adverse events (including vital signs): fever (axillary temperature), acute allergic reaction, abnormal skin and mucosa, diarrhea, anorexia, vomiting, nausea, muscle pain, headache, cough and fatigue.

Phase I laboratory test:

Blood routine examination: white blood count, hemoglobin and platelet count;

Blood biochemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), creatinine (CR) and creatine phosphokinase (CPK).

Routine urine test: urine protein (PRO), urine sugar and urine erythrocyte.

Phase II laboratory test (only subjects numbered C001～C030 and D001～D030 were given the third dose):

Blood routine examination: white blood count, hemoglobin and platelet count;

Blood biochemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), creatinine (CR), creatine phosphokinase (CPK), and glucose.

10.7.2 Definition of adverse event/reaction

The safety of the vaccine will be evaluated based on the range, intensity and severity of local adverse events, systemic adverse events, vital signs and adverse events for laboratory test indicators and on correlation of adverse events with vaccination.

All adverse medical events occurring during the trial (i.e., from the signing of the informed consent) will be collected, recorded, and reported by the investigator to the sponsor and the inspector.

(1) Adverse event (AE): any untoward medical occurrence in subjects after vaccination with the test vaccine in a clinical trial, which does not necessarily associated with the test vaccine.

(2) Adverse reaction: adverse events related to vaccination with the test vaccine that occur during vaccination at prescribed doses and schedules.

(3) Serious adverse events (SAE): events arising during the clinical trial which lead to hospitalization or prolonged hospitalization, injury/disability, working ability damage, life-threat conditions, death and congenital malformation or other events.

(4) Solicited/non-solicited adverse events: the solicitation period (within 0-7 days after vaccination with each dose) and non-solicitation period (8-28 days after vaccination with each dose). The solicited symptoms occurring during the solicitation period are referred to as solicited adverse events, and other symptoms occurring during the solicitation period and all symptoms occurring during the non-solicitation period are referred to as non-solicited adverse events.

10.7.3 Outcome of Adverse Events

The outcomes of adverse events include: (1) recovery, (2) not recovered, (3) recovered with sequela, (4) death, (5) loss to follow-up/unknown.

10.7.4 Judgment on Clinical Significance of Laboratory Indexes

Judgment on clinical significance includes: (1) within the range of reference values; (2) There was no clinical significance if not within the range of reference values; (3) There was clinical significance if not within the range of reference values.

10.7.5 Correlation Between Adverse Events and Vaccines

Investigators should try their best to explain AE and assess the possible causal links, i.e., the causal link with the inoculation of the research vaccine and the superseding causes (such as the medical history and combined treatment of underlying diseases). It is applicable to all AEs, including the severe and non-severe ones.

The causal link assessment will be determined by the degree of the reasonable explanation of events obtained in the following one or more aspects:

As for the preparations of such kind, reactions of similar properties had been observed previously;

For preparations of similar kinds, similar events had been reported on literature;

From the perspective of time, the events occur with the inoculation of the research vaccine and re-occur after the re-inoculation of the research vaccine.

According to the definition, all solicited AEs (i.e., local adverse reactions in solicited reports) occurred at the vaccination site will be deemed as related to vaccination.

The causal links of AE shall be assessed by investigators according to the

following questions, and whether there are reasonable probabilities that the AE is caused by vaccination:

(1) Definitely irrelevant: Adverse events may be caused by other factors, such as subjects' clinical conditions, other treatment or concomitant medication.

(2) Possibly irrelevant: Adverse events may be caused by other factors, such as subjects' clinical conditions, other treatment or concomitant medication; inconsistent with the known information of the test vaccine.

(3) Possibly relevant: Adverse events are consistent with the known information of the test vaccine. They are related causally to the test vaccine and may be related to other factors.

(4) Probably relevant: Adverse events are consistent with the known information of the test vaccine. They are related causally to the test vaccine and cannot be interpreted by other factors, such as subjects' clinical conditions, other treatment or concomitant drugs.

(5) Definitely relevant: Adverse events are consistent with the known information of the test vaccine. They are related causally to the test vaccine and cannot be interpreted by other factors, such as subjects' clinical conditions, other treatment or concomitant drugs. In addition, adverse events are repeated when the test vaccine is administered to subjects again.

10.7.6 Handling of Adverse Events

Reactions below grade 2 such as vaccinal areola, swelling, pain, or (and) fever and general malaise after vaccination can generally disappear spontaneously without special treatment.

The investigator should make investigation and medical follow-up on the adverse reactions/events of grade 3 and above that occur in subjects from the start of immunization to 28 days after immunization, including medical history, physical examination and necessary laboratory examination, treatment and tracking until the event is solved, and detailed investigation records should be completed. Investigation records should include symptoms, signs, diagnosis, and laboratory results.

In the event of a serious adverse event, the investigator should promptly take the necessary actions and report it within 24 hours. If any of the female subjects became pregnant during the study period, they will be treated as those with SAE. During test observation, subjects who developed fever, with cough and other respiratory symptoms should be seen immediately at the designated hospitals, throat swabs/sputum and anal swabs should be collected if necessary. Besides, imaging examinations such as CT should be performed to analyze and determine if the disease was caused by novel coronavirus infection. In case of COVID-19 infection, it shall be treated according to SAE, and the presence of ADE phenomenon was especially analyzed.

10.7.7 Report on Serious Adverse Events

(1) The responsible organization established an emergency plan for SAE. After the investigator was informed of the SAE, appropriate action should be taken for the subject and documented immediately. He should report the SAE to the sponsor within 24 hours after being informed, and immediately provide a detailed and written follow-up report. SAE reports and follow-up reports should indicate the subject identification code in the clinical trial, rather than the real name, citizenship number, address, and other identity information of the subjects.

For reports on death events, the investigator should report to the sponsor and the ethics committee in written form and timely provide other necessary materials, such as autopsy report and final medical report.

Upon the reception of safety information related to the clinical trial from the sponsor, the investigator should sign for confirming the reception and read the information within 24 hours, consider whether corresponding adjustment is necessary to the treatment of subjects, and promptly report to the ethics committee the suspicious and unexpected serious adverse reactions provided by the sponsor.

(2) The sponsor should analyze and assess vaccine safety information received from any source, including the severity, correlation with the test vaccine, and whether it is an unexpected event.

During drug clinical trial, the sponsor should report the suspected unexpected

serious adverse reaction (SUSAR) rapidly to all the investigators participating in the clinical trial and to the clinical trial institution and ethics committee; the sponsor should report SUSAR rapidly to the national drug regulatory department and health authority in the form of individual case safety report in accordance with the *Standards and Procedures for Rapid Reporting of Safety Data during Drug Clinical Trials*.

For suspicious and unexpected serious adverse reactions (SUSAR) resulting in death or threatening the life, the sponsor shall soon report them upon being first informed within 7 nature days and report related follow-up information in next 8 nature days (The day on which the applicant is first informed is Day 0). For SUSAR not resulting in death or threatening the life, the sponsor shall soon report them upon being first informed within 15 nature days. For information on other potentially serious safety risks, the sponsor should also report to the national drug evaluation agency as soon as possible, while a medical and scientific judgment should be made for each case. After the initial report, the sponsor shall continue to track SAE and report related new information or change information to the previous report in the form of follow-up reports within 15 days after receiving new information. The sponsor is not allowed to change the investigator's judgment of the correlation between SAE and the vaccine. In case of disagreement between the sponsor and the investigator, the opinions of the sponsor and the investigator should be showed in detail in the report, and reported according to the higher management requirements.

In exceptional cases, the investigator and sponsor should timely provide SAE related information and safety reports as required by regulatory authorities and the independent ethics committee.

(3) The contacts and contact information of the sponsor, the ethics committee and Jiangsu Medical Products Administration are as follows:

24h contact of Sinovac Life Sciences Co., Ltd.:

Wang Jiayi, Mobile: 18518337983；Fax: 010-82890408.

Contact of Jiangsu Provincial Center for Disease Control and Prevention:

Ba Lu, Mobile: 025-83759406；Fax: 025-83759406.

Jiangsu Medical Products Administration

Mobile: 025-83273714； Fax: 025-83273714.

10.7.8 Safety Evaluation Criteria

Solicited local adverse events, systemic adverse events and vital signs: the grading of solicited adverse events mainly refers to the Guidelines of the National Medical Products Administration for Adverse Event Classification Standards for Clinical Trials of Preventive Vaccines (2019)[14], as shown in the following table. Solicited adverse events and non-solicited adverse events of the same symptom are graded according to the following criteria.

Table 25 Grading of (Local) Adverse Events at Inoculation Site

	Grade 1	Grade 2	Grade 3	Grade 4
Pain	Having no or marginal effect on limb activity	Having an effect on limb activity	Having an effect on daily life	Loss of basic living skills or hospitalization
Induration * #	Diameter 2.5-＜5 cm or area 6.25-＜ 25 cm^2 and having no or marginal effect on daily life	Diameter 5-＜10 cm or area 25-＜ 100 cm^2 or having an effect on daily life	Diameter ≥10 cm or area ≥100 cm^2 or fester or secondary infection or phlebitis or sterile abscesses or wound drainage or having serious effect on daily life	Abscess, exfoliative dermatitis, dermal or deep tissue necrosis
Swelling #	Diameter 2.5-＜5 cm or area 6.25-＜ 25 cm^2 and having no or marginal effect on daily life	Diameter 5-＜10 cm or area 25-＜ 100 cm^2 or having an effect on daily life	Diameter ≥10 cm or area ≥100 cm^2 or fester or secondary infection or phlebitis or sterile abscesses or wound drainage or having serious effect on daily life	Abscess, exfoliative dermatitis, dermal or deep tissue necrosis
Vaccinal areola#	Diameter 2.5-＜5 cm or area 6.25-＜ 25 cm^2 and having no or marginal effect on daily life	Diameter 5-＜10 cm or area 25-＜ 100 cm^2 or having an effect on daily life	Diameter ≥10 cm or area ≥100 cm^2 or fester or secondary infection or phlebitis or sterile abscesses or wound drainage or having serious effect on daily life	Abscess, exfoliative dermatitis, dermal or deep tissue necrosis
Rash* #	Diameter 2.5-＜5 cm or area 6.25-＜25 cm^2 and having no or marginal effect on daily life	Diameter 5-＜10 cm or area 25-＜ 100 cm^2 or having an effect on daily life	Diameter ≥10 cm or area ≥100 cm^2 or fester or secondary infection or phlebitis or sterile abscesses or wound drainage or having serious effect on daily life	Abscess, exfoliative dermatitis, dermal or deep tissue necrosis
Pruritus	Pruritus at inoculation site, mitigated spontaneously or within 48 hours after treatment	Pruritus at inoculation site, not mitigated within 48 hours after treatment	Having an effect on daily life	NA

*Induration and rash: In addition to the grading and evaluation by measuring the diameter directly, the change of measurements should also be recorded.

#Induration and swelling, rash and vaccinal areola: The maximum measured diameter or area should be used; The grading and evaluation should be based on the function grade and actual measurements and indicators with a higher grade should be chosen.

Table 26 Grading of (Systemic) Adverse Events and Vital Signs Not at Inoculation Site

	Grade 1	Grade 2	Grade 3	Grade 4
Acute allergic reaction*	Local urticaria (blister), no treatment required	Local urticaria, requiring for treatment or mild angioedema, no treatment required	Extensive urticaria or angioedema requiring for treatment or mild bronchospasm	Allergic shock or life-threatening bronchospasm or laryngeal edema
Abnormal skin & mucous	Erythema/pruritus/ color change	Diffuse rash/maculopapule/xerosis cutis/desquamation	Herpes zoster/exudation/desquamation/ulceration	Exfoliative dermatitis (involving mucosa) or erythema multiforme or suspected Stevens-Johnsons syndrome
Diarrhoea	Mild or transient, 3 or 4 times per day, abnormal poop or mild diarrhea lasting less than a week	Moderate or persistent, 5 to 7 times per day, abnormal poop, or diarrhea lasting over 1 week	Over 7 times per day, abnormal poop, or bloody diarrhea, orthostatic hypotension, electrolyte imbalance, venous transfusion >2L indicated	Hypotensive shock, hospitalization indicated
Anorexia	Loss of appetite, but normal food intake	Loss of appetite, decreased food intake, but no significant weight loss	Loss of appetite, and significant weight loss	Need for intervention (such as tube feeding and parenteral nutrition)
Vomiting	1 - 2 times /24 hours and daily activities not affected	3 to 5 times /24 hours or limited activity	Over 6 times within 24 hours or requiring intravenous infusion	Hospitalization or other nutrition channels indicated due to hypotensive shock
Nausea	Transient (<24 hours) or intermittent, and basically normal food intake	Persistent nausea leads to reduced food intake (24-48 hours)	Persistent nausea leads to almost no food intake (>48 hours) or requiring intravenous infusion	Life-threatening (such as hypotensive shock)
Muscular pain (not at the inoculation site)	Daily activities not affected	Daily activities marginally affected	Severe muscle pain, and daily activities severely affected	Urgent intervention or hospitalization indicated
Headache	Daily activities not affected, and treatment not required	Transient, daily activities marginally affected, treatment or intervention probably required	Daily activities severely affected, treatment or intervention required	Refractory, urgent intervention or hospitalization required

	Grade 1	Grade 2	Grade 3	Grade 4
Cough	Transient, no treatment required	Continuous cough which can be treated effectively	Paroxysmal cough which can not be controlled by treatment	Urgent intervention or hospitalization indicated
Fatigue and weakness	Hypoergia <48 hours, no impact on activity	Hypoergia for 20% to 50% >48 hours, with slight impact on activity	Hypoergia for >50%, with heavy impact on activity	Incapable of taking care of oneself, and emergency treatment or hospitalization
Vital signs				
Fever (axillary temperature)	37.3～＜38.0	38.0～＜38.5	≥38.5	≥39.5, lasting over 3 days

The sign * indicates type I hypersensitivity

Laboratory indexes: The first step is to determine the clinical significance. When there are "abnormality and clinical significance", the grading mainly refers to the Guidelines of the National Medical Products Administration for Adverse Event Classification Standards for Clinical Trials of Preventive Vaccines (2019)[14], the Guidelines for Adverse Event Classification Standards for Clinical Trials of Preventive Vaccines (2005) (Only Creatinine) [15] and the Grading Criteria of the National Institute of Allergy and Infectious Diseases (NIAID) under the National Institutes of Health (NIH) for Clinical Assessment (Only Platelets)[16], as shown in the following table:

Table 27 Grading of Blood Routine Indexes

Indicators/grading	Grade 1	Grade 2	Grade 3	Grade 4
Leukocyte increase (WBC, 10^9/L)	11~＜13	13～＜15	15～＜30	≥30
Leukocyte decrease (WBC, 10^9/L)	2.000～2.499	1.500～1.999	1.000～1.499	＜1.000
Low hemoglobin (g/dL)-male	10.0～10.9	9.0～＜10.0	7.0～＜9.0	＜7.0
Low hemoglobin (g/dL)-female	9.5～10.4	8.5～＜9.5	6.5～＜8.5	＜6.5
Platelet (10^9/L)	75-99.999	50-74.999	20-49.999	<20

Table 28 Grading of Blood Biochemical Indexes

Indicators/grading	Grade 1	Grade 2	Grade 3	Grade 4
Liver function (ALT,AST)	1.25～＜2.5 ×ULN	2.5～＜5.0×ULN	5.0～＜10×ULN	≥10×ULN
Increase of total bilirubin (mg/dL; μmol/L)	1.1～＜1.6×ULN	1.6～＜2.6×ULN	2.6～5.0×ULN	≥5.0×ULN

Creatinine (CR)	1.1～1.5×ULN	1.6～3.0×ULN	3.1～6×ULN	>6×ULN
Creatine phosphokinase (CPK)	1.25～＜1.5×ULN	1.5～＜3.0×ULN	3.0～＜10×ULN	≥10×ULN
Glu (mmol/L)	6.11～＜6.95	6.95～＜13.89	13.89～＜27.75	≥27.75

Note: The ULN refers to the upper limit of normal; blood glucose shall be measured on an empty stomach.

Table 29 Grading of Routine Urine Test Indexes

Indicators/grading	Grade 1	Grade 2	Grade 3	Grade 4
Urine protein (PRO) (Urine test strip)	1+	2+	3+ orhigher	NA
Urine glucose (Urine test strip)	Little - 1+ or ≤250mg	2+ or >250 - ≤500mg	＞2+ or >500mg	NA
RBC (microscopy) [Red blood cells /high power field (rbc/hpf) (excluding women's periods)]	6～＜10	≥10	gross hematuria, with or without blood coagulum; or barrel-type urinary erythrocyte; or treatment required	Urgent intervention or hospitalization indicated

Adverse events not included in above grading table should be graded and evaluated according to the following standards:

Grade 1 mild: short time (<48h) or slight discomfort; daily activities not affected, and treatment not required;

Grade 2 moderate: mild or moderate limited activity, medical attention probably required, treatment not required or mild treatment required;

Grade 3 severe: obvious limited activity, treatment required, hospitalization probably required;

Grade 4 critical: probably deadly, severe limited activity, monitoring and treatment required.

Grade 5: death

10.8 Concomitant Medication and Vaccination

10.8.1 Concomitant Medication

- If any adverse event (AE) occurs during the trial, the drug therapy and medical treatment should be allowed if necessary.
- In case of severe allergic reaction or life threatening events, first aid measures should be taken immediately.
- The investigator should record any concomitant medication information,

including name, dosage form, dosage, and duration of use.

10.8.2 Concomitant Vaccination

- Other vaccines can be administered at least 7 days after the test vaccine is administered.
- During the trial, subjects can be vaccinated with such vaccines as rabies vaccine and tetanus vaccine in case of emergency.
- Detailed information should be recorded, including the name of the vaccine, the use of the vaccine and the time of vaccination if concomitant vaccination.

10.9 Immunogenicity evaluation

Humoral immunity: Blood samples collected at different time points should be subject to neutralizing antibody test, IgG test and IgM test (IgG and IgM tests are only applicable to Phase I clinical trial.) The positive conversion rate and positive rate of neutralizing antibody, GMT, GMI, and the positive rate of IgG and IgM antibodies should be calculated.

Cellular immunity (applicable to Phase I clinical trial): Blood samples collected at different time points should be subject to IFN-γ secretory reaction test of specific T cells to calculate the positive rate.

10.9.1 Evaluation Standards

- Evaluation standards for serum neutralizing antibody

  The evaluation standards for positive serum antibody are as follows:

  - If antibody titer≥1:8, it is positive.

  The evaluation standards for the positive conversion of serum antibody are as follows:

  - If neutralizing antibody titer is less than 1:8 before immunization and no less than 1:8 after immunization, the positive conversion of antibody is considered. Or if neutralizing antibody is no less than 1:8 before immunization and neutralizing antibody titer increases 4 times after immunization, the positive conversion of antibody is considered.
- Evaluation standards for IgG and IgM

See kit instructions.

10.9.2 Laboratory Test Methods

- Serum antibody test:
  - Neutralizing antibody test - micro neutralization test;
  - IgG/IgM test - Enzyme-Linked Immune-sorbent Assay (ELISA)
- IFN-γ secretory reaction test of specific T cells: Enzyme-Linked Immune Absorbent Spot (ELISPOT) (mononuclear cell)

10.10 Data Management

10.10.1 Original Data

The original data should include the informed consent form, diary cards and original record books. The following basic data should be recorded.

- Test name and subject's code
- Demographic data
- Inclusion/exclusion criteria
- Vaccination record
- Follow-up date and date when the subject stops the test
- Adverse event/reaction and its processing and outcome
- Accompanying medical treatment and other vaccinations

All data should be recorded in the original form, and stored in a special room properly by the investigator. The original data will be filed in the research center, because it can prove that the subject has participated in the clinical trial and the data is true and complete.

The investigator should make original records in an earnest, accurate and timely manner, and all collected original data shall be recorded on the day when the original data are acquired. A black sign pen should be used. In case of any writing error, cross out the wrong words and write correct ones next to the wrong words while signing and giving the date.

10.10.2 Case Report Form (CRF)

In this trial, "Electronic Data Capture (EDC)" is used to establish the electronic

CRF. As an important component of the clinical trials and research reports, the electronic CRF is used to record clinical trial data. Information should be inputted with standard language according to the EDC instructions and CRF filling instructions.

The data on the electronic CRF should be derived from and consistent with the original data. The input, verification, modification, cleanup and quality control of any electronic CRF data will be recorded in the EDC system. Upon completion of the data cleanup, the investigator should confirm the data in each electronic CRF and create an electronic signature for each electronic CRF.

Only the investigator and authorized staff will be allowed to access the EDC system during the trial.

10.10.3 Data Locking

After input, verification and cleanup of all data, the final data verification is carried out. According to the evaluation criteria, the analyzed population should be determined, and the situations that deviate from the schedule as well as their impact on data group analysis should be confirmed. Then, the database should be locked.

10.10.4 Privacy Protection for Subjects and Data Utilization Range

Any information regarding the identity of the subject will be confidential and the name will not appear in any publication or report of the study. Study records will be made available to the sponsor‘s representatives in the presence of the investigator for the purpose of medical data collection. Besides, the monitor and inspector of the study and the representatives from Vaccine Clinical Trial Ethics Committee, Jiangsu Provincial Center for Disease Control and Prevention and National Medical Products Administration (NMPA) can, as required, review the subjects’ original data related to the study to confirm the accuracy of the data collected in the study. The original data obtained in this study will only be used for publication of papers or results related to this project.

10.11 Statistical Analysis

10.11.1 Analysis Set

10.11.1.1 Phase I clinical trial

(1) Full Analysis Set, FAS

The Intent to Treat (ITT) principle is followed, including all subjects who were randomized to groups, are given at least 1 dose, have the blood collected at least once before and after immunization and have effective antibody titer values. Among them, the subjects who were incorrectly vaccinated were evaluated for immunogenicity according to ITT principle and the original random grouping.

(2) Per protocol set (PPS) on Day 14 after second dose of immunization

It is a subset of FAS, including all subjects who follow the inclusion/exclusion criteria, are randomized into groups, are given the first and second doses of vaccination within the time window period according to the protocol, have the blood collected on Day 14 before immunization and after the second dose of immunization, and have effective antibody titer values. Among them, subjects who meet the following conditions cannot enter PPS:

- Violate the trial protocol;
- The wrong vaccination number;
- subjects that are given the second dose of vaccination or have the blood collected on Day 14 after the second dose of immunization out of visit window.
- Use vaccines or drugs prohibited by the protocol:

  ①Other research or unregistered products (drugs or vaccines) that are not research vaccine

  ②Long-term use (lasting for more than 14 days) of immunosuppressants or other immunomodulatory drugs (inhaled or topical steroids are allowed);

  ③Immunoglobulin and/or blood preparations;
- Newly diagnosed autoimmune diseases, including human immunodeficiency virus (HIV) infection;
- Other conditions affecting the evaluation of vaccine immunogenicity on Day 14 after second dose of immunization.

(3) Per protocol set 2B (PPS–2B) on Day 28 after second dose of immunization

It is a subset of FAS, including all subjects who follow the inclusion/exclusion criteria, are randomized into groups, are given the first and second doses of vaccination within the time window period according to the protocol, have the blood collected on Day 28 before immunization and after the second dose of immunization, and have effective antibody titer values. Among them, subjects who meet the following conditions cannot enter PPS:

- Violate the trial protocol;
- The wrong vaccination number;
- subjects that are given the second dose of vaccination or have the blood collected on Day 14 after the second dose of immunization out of visit window.
- Use vaccines or drugs prohibited by the protocol:

  ①Other research or unregistered products (drugs or vaccines) that are not research vaccine

  ②Long-term use (lasting for more than 14 days) of immunosuppressants or other immunomodulatory drugs (inhaled or topical steroids are allowed);

③Immunoglobulin and/or blood preparations;

- Newly diagnosed autoimmune diseases, including human immunodeficiency virus (HIV) infection;
- Other conditions affecting the evaluation of vaccine immunogenicity on Day 14 after second dose of immunization.

(4) Immune persistence set (IPS-6)

Include all subjects who have received full-course vaccination and have blood collected 6 months after full-course immunization and have effective antibody titer values.

(5) Safety set (SS)

Include all subjects randomized in groups and given at least one dose of vaccine. Among them, according to ASaT (All Subjects As Treated) principle, the safety evaluation of subjects with wrong vaccination is carried out according to the actual vaccination group of subjects.

The safety dataset is divided into total safety dataset, first dose safety set and second dose safety set. The safety of each dose is analyzed based on the actual number of people vaccinated each time. The first dose safety set includes all subjects who have given the first dose of vaccination, which is recorded as SS1; the second dose safety set includes subjects who have given the second dose of vaccination, which is recorded as SS2.

10.11.1.2 Phase II clinical trial

Immunogenicity and persistence analysis set

Day 0, Day 14, Day 42 immunization schedule

(1) Full Analysis Set, FAS

The Intent to Treat (ITT) principle is followed, including all subjects who were randomized to groups, are given at least 1 dose, have the blood collected at least once before and after immunization and have effective antibody titer values. Among them, the subjects who were incorrectly vaccinated were evaluated for immunogenicity according to ITT principle and the original random grouping.

(2) Per protocol set (PPS) on Day 14 after second dose of immunization

It is a subset of FAS, including all subjects who follow the inclusion/exclusion criteria, are randomized into groups, are given the first and second doses of vaccination within the time window period according to the protocol, have the blood collected on Day 14 before immunization and after the second dose of immunization, and have effective antibody titer values. Among them, subjects who meet the following conditions cannot enter PPS:

- Violate the trial protocol;
- The wrong vaccination number;
- subjects that are given the second dose of vaccination or have the blood collected on Day 14 after the second dose of immunization out of visit window.
- Use vaccines or drugs prohibited by the protocol:

①Other research or unregistered products (drugs or vaccines) that are not

research vaccine

②Long-term use (lasting for more than 14 days) of immunosuppressants or other immunomodulatory drugs (inhaled or topical steroids are allowed);

③Immunoglobulin and/or blood preparations;

- Newly diagnosed autoimmune diseases, including human immunodeficiency virus (HIV) infection;
- Other conditions affecting the evaluation of vaccine immunogenicity on Day 14 after second dose of immunization.

(3) Per protocol set 2B (PPS–2B) on Day 28 after second dose of immunization

It is a subset of FAS, including all subjects who follow the inclusion/exclusion criteria, are randomized into groups, are given the first and second doses of vaccination within the time window period according to the protocol, have the blood collected on Day 28 before immunization and after the second dose of immunization, and have effective antibody titer values. Among them, subjects who meet the following conditions cannot enter PPS:

- Violate the trial protocol;
- The wrong vaccination number;
- Subjects that are given the second dose of vaccination or have the blood collected on Day 28 after the second dose of immunization out of visit window.
- Use vaccines or drugs prohibited by the protocol:

  ①Other research or unregistered products (drugs or vaccines) that are not research vaccine

  ②Long-term use (lasting for more than 14 days) of immunosuppressants or other immunomodulatory drugs (inhaled or topical steroids are allowed);

  ③Immunoglobulin and/or blood preparations;

- Newly diagnosed autoimmune diseases, including human immunodeficiency virus (HIV) infection;
- Other conditions affecting the evaluation of vaccine immunogenicity on Day 28 after second dose of immunization.

(4) Per protocol set (PPS3) on Day 28 after third dose of immunization

It is a subset of FAS, including all subjects who follow the inclusion/exclusion criteria, are randomized into groups, are given the third dose of vaccination within the time window period according to the protocol, have the blood collected after immunization, and have effective antibody titer values. Among them, subjects who meet the following conditions cannot enter PPS:

- Violate the trial protocol;
- The wrong vaccination number;
- Subjects that are given the second and third doses of vaccination or have the blood collected on Day 28 after the third dose of immunization out of visit window.
- Use vaccines or drugs prohibited by the protocol:

  ①Other research or unregistered products (drugs or vaccines) that are not research vaccine

②Long-term use (lasting for more than 14 days) of immunosuppressants or other immunomodulatory drugs (inhaled or topical steroids are allowed);

③Immunoglobulin and/or blood preparations;

- Newly diagnosed autoimmune diseases, including human immunodeficiency virus (HIV) infection;
- Other conditions affecting the evaluation of vaccine immunogenicity on Day 28 after third dose of immunization.

(5) Immune persistence set 6B (IPS-6B)

Include all subjects who have completed the full-course vaccination according to Day 0, Day 14, Day 42 immunization schedule, have blood collected 6 months after full-course immunization, and have effective antibody titer values.

(6) Immune persistence set 12 (IPS-12)

Include all subjects who have completed the full-course vaccination according to Day 0, Day 14, Day 42 immunization schedule, have blood collected 12 months after full-course immunization, and have effective antibody titer values.

Day 0, Day 14 immunization schedule (+6-moth booster immunization)

(1) Full Analysis Set, FAS

The Intent to Treat (ITT) principle is followed, including all subjects who were randomized to groups, are given at least 1 dose, have the blood collected at least once before and after immunization and have effective antibody titer values. Among them, the subjects who were incorrectly vaccinated were evaluated for immunogenicity according to ITT principle and the original random grouping.

(2) Per protocol set (PPS) on Day 14 after the second dose of immunization at the primary immunization stage

It is a subset of FAS, including all subjects who follow the inclusion/exclusion criteria, are randomized into groups, are given the first and second doses of vaccination within the time window period according to the protocol, have the blood collected on Day 14 before immunization and after the second dose of immunization, and have effective antibody titer values. Among them, subjects who meet the following conditions cannot enter PPS:

- Violate the trial protocol;
- The wrong vaccination number;
- subjects that are given the second dose of vaccination or have the blood collected on Day 14 after the second dose of immunization out of visit window.
- Use vaccines or drugs prohibited by the protocol:

  ①Other research or unregistered products (drugs or vaccines) that are not research vaccine

  ②Long-term use (lasting for more than 14 days) of immunosuppressants or other immunomodulatory drugs (inhaled or topical steroids are allowed);

  ③Immunoglobulin and/or blood preparations;

- Newly diagnosed autoimmune diseases, including human immunodeficiency virus (HIV) infection;
- Other conditions affecting the evaluation of vaccine immunogenicity on Day

14 after second dose of immunization.

(3) Per protocol set 2B (PPS-2B) on Day 28 after the second dose of immunization at the primary immunization stage

It is a subset of FAS, including all subjects who follow the inclusion/exclusion criteria, are randomized into groups, are given the first and second doses of vaccination within the time window period according to the protocol, have the blood collected on Day 28 before immunization and after the second dose of immunization, and have effective antibody titer values. Among them, subjects who meet the following conditions cannot enter PPS:

- Violate the trial protocol;
- The wrong vaccination number;
- Subjects that are given the second dose of vaccination or have the blood collected on Day 28 after the second dose of immunization out of visit window.
- Use vaccines or drugs prohibited by the protocol:

  ①Other research or unregistered products (drugs or vaccines) that are not research vaccine

  ②Long-term use (lasting for more than 14 days) of immunosuppressants or other immunomodulatory drugs (inhaled or topical steroids are allowed);

  ③Immunoglobulin and/or blood preparations;
- Newly diagnosed autoimmune diseases, including human immunodeficiency virus (HIV) infection;
- Other conditions affecting the evaluation of vaccine immunogenicity on Day 28 after second dose of immunization.

(4) Immune persistence set 6A (IPS-6A) for primary immunization

Include all subjects who have received primary vaccination according to Day 0, Day 14 immunization schedule, have blood sampling 6 months after primary immunization, and have effective antibody titer values.

(5) Full analysis set for booster (bFAS)

The Intent to Treat (ITT) principle is followed, including all subjects who are randomized to groups, receive booster immunization after primary immunization, are given booster vaccine, have blood collected at least once before and after booster immunization and have effective antibody titer values. Among them, the subjects who were incorrectly vaccinated were evaluated for immunogenicity according to ITT principle and the original random grouping.

(6) Per Protocol Set (bPPS) on Day 14 after booster immunization

It is a subset of FAS, including all subjects who follow the inclusion/exclusion criteria, are randomized into groups, have received primary immunization and 6-month booster immunization during the time window period according to the protocol, have the blood collected on Day 14 before and after booster immunization, and have effective antibody titer values. Among them, subjects who meet the following conditions cannot enter PPS:

- Violate the trial protocol;
- The wrong vaccination number;
- Subjects that receive booster immunization or have the blood collected on Day 14 after booster immunization out of visit window.

- Use vaccines or drugs prohibited by the protocol:

  ①Other research or unregistered products (drugs or vaccines) that are not research vaccine

  ②Long-term use (lasting for more than 14 days) of immunosuppressants or other immunomodulatory drugs (inhaled or topical steroids are allowed);

  ③Immunoglobulin and/or blood preparations;
- Newly diagnosed autoimmune diseases, including human immunodeficiency virus (HIV) infection;
- Other conditions affecting the evaluation of vaccine immunogenicity on Day 14 after booster immunization.

(7) Immune persistence set 6 for booster (bIPS-6)

Include all subjects who have received primary vaccination according to Day 0, Day 14 immunization schedule, received booster immunization 6 months after primary immunization, have blood collected 6 months after booster immunization, and have effective antibody titer values.

Day 0, Day 28, Day 56 immunization schedule

(1) Full Analysis Set, FAS

The Intent to Treat (ITT) principle is followed, including all subjects who were randomized to groups, are given at least 1 dose, have the blood collected at least once before and after immunization and have effective antibody titer values. Among them, the subjects who were incorrectly vaccinated were evaluated for immunogenicity according to ITT principle and the original random grouping.

(2) Per protocol set 2B (PPS-2B) on Day 28 after second dose of immunization

It is a subset of FAS, including all subjects who follow the inclusion/exclusion criteria, are randomized into groups, are given the first and second doses of vaccination within the time window period according to the protocol, have the blood collected on Day 28 before immunization and after the second dose of immunization, and have effective antibody titer values. Among them, subjects who meet the following conditions cannot enter PPS:

- Violate the trial protocol;
- The wrong vaccination number;
- Subjects that are given the second dose of vaccination or have the blood collected on Day 28 after the second dose of immunization out of visit window.
- Use vaccines or drugs prohibited by the protocol:

  ①Other research or unregistered products (drugs or vaccines) that are not research vaccine

  ②Long-term use (lasting for more than 14 days) of immunosuppressants or other immunomodulatory drugs (inhaled or topical steroids are allowed);

  ③Immunoglobulin and/or blood preparations;
- Newly diagnosed autoimmune diseases, including human immunodeficiency virus (HIV) infection;

- Other conditions affecting the evaluation of vaccine immunogenicity on Day 28 after second dose of immunization.

(3) Per protocol set 3 (PPS3) on Day 28 after third dose of immunization

It is a subset of FAS, including all subjects who follow the inclusion/exclusion criteria, are randomized into groups, are given the third dose of vaccination within the time window period according to the protocol, have the blood collected on Day 28 after immunization, and have effective antibody titer values. Among them, subjects who meet the following conditions cannot enter PPS:

- Violate the trial protocol;
- The wrong vaccination number;
- Subjects that are given the second and third doses of vaccination or have the blood collected on Day 28 after immunization out of visit window.
- Use vaccines or drugs prohibited by the protocol:

  ①Other research or unregistered products (drugs or vaccines) that are not research vaccine

  ②Long-term use (lasting for more than 14 days) of immunosuppressants or other immunomodulatory drugs (inhaled or topical steroids are allowed);

  ③Immunoglobulin and/or blood preparations;
- Newly diagnosed autoimmune diseases, including human immunodeficiency virus (HIV) infection;
- Other conditions affecting the evaluation of vaccine immunogenicity on Day 28 after third dose of immunization.

(4) Immune persistence set 6B (IPS-6B)

Include all subjects who have completed the full-course vaccination according to Day 0, Day 28, Day 56 immunization schedule, have blood collected 6 months after full-course immunization, and have effective antibody titer values.

(5) Immune persistence set 12 (IPS-12)

Include all subjects who have completed the full-course vaccination according to Day 0, Day 28, Day 56 immunization schedule, have blood collected 12 months after full-course immunization, and have effective antibody titer values.

Day 0, Day 28 immunization schedule (+6-moth booster immunization)

(1) Full Analysis Set, FAS

The Intent to Treat (ITT) principle is followed, including all subjects who were randomized to groups, are given at least 1 dose, have the blood collected at least once before and after immunization and have effective antibody titer values. Among them, the subjects who were incorrectly vaccinated were evaluated for immunogenicity according to ITT principle and the original random grouping.

(2) Per protocol set 2B (PPS-2B) on Day 28 after the second dose of immunization at the primary immunization stage

It is a subset of FAS, including all subjects who follow the inclusion/exclusion criteria,

are randomized into groups, are given the first and second doses of vaccination within the time window period according to the protocol, have the blood collected on Day 28 before immunization and after the second dose of immunization, and have effective antibody titer values. Among them, subjects who meet the following conditions cannot enter PPS:

- Violate the trial protocol;
- The wrong vaccination number;
- Subjects that are given the second dose of vaccination or have the blood collected on Day 28 after the second dose of immunization out of visit window.
- Use vaccines or drugs prohibited by the protocol:

  ①Other research or unregistered products (drugs or vaccines) that are not research vaccine

  ②Long-term use (lasting for more than 14 days) of immunosuppressants or other immunomodulatory drugs (inhaled or topical steroids are allowed);

  ③Immunoglobulin and/or blood preparations;
- Newly diagnosed autoimmune diseases, including human immunodeficiency virus (HIV) infection;
- Other conditions affecting the evaluation of vaccine immunogenicity on Day 28 after second dose of immunization.

(3) Immune persistence set 6A (IPS-6A) for primary immunization

Include all subjects who have received primary vaccination according to Day 0, Day 28 immunization schedule, have blood collected 6 months after primary immunization, and have effective antibody titer values.

(4) Full analysis set for booster (bFAS)

The Intent to Treat (ITT) principle is followed, including all subjects who are randomized to groups, receive booster immunization after primary immunization, are given booster vaccine, have blood collected at least once before and after booster immunization and have effective antibody titer values. Among them, the subjects who were incorrectly vaccinated were evaluated for immunogenicity according to ITT principle and the original random grouping.

(5) Per Protocol Set (bPPS) on Day 28 after booster immunization

It is a subset of FAS, including all subjects who follow the inclusion/exclusion criteria, are randomized into groups, have received primary immunization and 6-month booster immunization during the time window period according to the protocol, have the blood collected on Day 28 before and after booster immunization, and have effective antibody titer values. Among them, subjects who meet the following conditions cannot enter PPS:

- Violate the trial protocol;
- The wrong vaccination number;
- Subjects that receive booster immunization or have the blood collected on Day 28 after booster immunization out of visit window.
- Use vaccines or drugs prohibited by the protocol:

  ①Other research or unregistered products (drugs or vaccines) that are not research vaccine

②Long-term use (lasting for more than 14 days) of immunosuppressants or other immunomodulatory drugs (inhaled or topical steroids are allowed);

③Immunoglobulin and/or blood preparations;

- Newly diagnosed autoimmune diseases, including human immunodeficiency virus (HIV) infection;
- Other conditions affecting the evaluation of vaccine immunogenicity on Day 28 after booster immunization.

(6) Immune persistence set 6 for booster (bIPS-6)

Include all subjects who have received primary vaccination according to Day 0, Day 28 immunization schedule, received booster immunization 6 months after primary immunization, have blood collected 6 months after booster immunization, and have effective antibody titer values.

Safety Set

Include all subjects randomized in groups and given at least one dose of vaccine. Among them, according to ASaT (All Subjects As Treated) principle, the safety of subjects with wrong vaccination was evaluated according to the actual vaccination group of subjects. The safety dataset is divided into total safety dataset and safety sets for doses. The safety of each dose is analyzed based on the actual number of people vaccinated each time.

10.11.2 Statistical Analysis Method

10.11.2. General principles

The measurement data are statistically described with average, standard deviation, median, maximum and minimum; the enumeration data or ranked data are presented by frequency and relative frequency.

All statistical analysis will be completed with the help of the statistical software SAS 9.4.

10.11.2.2 Characteristics of Subjects

The number of subjects who are screened and enrolled into each group and complete the test and the number of subjects in each analysis set are summarized; and the reasons for subjects' drop-out are analyzed. The list of subjects who fail in screening, the list of withdrawal subjects and the list of subjects who do not enter each analysis set are listed respectively.

10.11.2.3 Immunogenicity evaluation

The positive conversion rate and positive rate of antibodies after immunization in

medium-dose group, high-dose group and placebo group are calculated respectively. The bilateral 95% confidence interval is calculated by Clopper-Pearson. Chi-square test/Fisher exact probability test is used to statistically test the differences between groups.

The GMT and GMI of antibodies after immunization in the test group and control group are calculated by geometric mean and 95% confidence interval, and logarithmic analysis of variance is used to statistically test the differences between groups.

The positive rates of IgG and IgM antibodies and IFN-γ secretion by specific T cells after immunization are analyzed by the same statistical method as the positive rate of neutralizing antibodies.

10.11.2.4 Safety Evaluation

Adverse events are medically coded by MedDRA. In this trial, the treatment emergent adverse events are statistically analyzed, and the adverse events occurring before inoculation are listed in the form of a list.

The times, number and incidence of all adverse events, adverse events related to the research vaccine and adverse events unrelated to the research vaccine are calculated for each group. Fisher exact probability test is used to statistically compare the differences between the groups. The severity, dose and occurrence time of adverse events and adverse events related to vaccine are subject to statistical analysis. Make a list of adverse events related to research vaccine and a list of adverse events unrelated to research vaccine. The adverse events after vaccination with each dose are statistically analyzed. Adverse events for each dose will be analyzed based on the safety set for each dose.

The times, number and incidence of all serious adverse events, serious adverse events related to research vaccine, and serious adverse events unrelated to research vaccine are calculated for each group respectively. Fisher exact probability test should be used to statistically compare the differences between the groups. Make a list of serious adverse events.

The changes of blood routine, blood biochemical and urine routine indexes before

and after inoculation are described statistically. The changes in the clinical significance of blood routine, blood biochemical and urine routine indexes are statistically described in the form of cross table before and after inoculation.

10.11.2.5 Processing of missing data

In the statistical analysis of the full analysis set, for those with missing serum test results after immunization, the method of last observation carried forward (LOCF) is used to fill the data. For those with missing serum results before immunization but after immunization, the maximum value of the serum antibody before immunization is used to fill the value of antibody after immunization of all subjects and the corresponding immunogenicity endpoint is further derived and calculated. Missing data in exploratory endpoints and safety endpoints are not processed in this trial.

11 Clinical Trial Monitoring

11.1 Sponsor's Responsibility

The sponsor should execute and maintain the quality assurance and control system and prepare quality management documents to make sure that the test is executed according to regulations. Meanwhile, data, record and report should meet the requirements of GCP and other regulations.

11.2 Investigator's Responsibility

The main investigator should manage and clearly divide the roles of all participants in the clinical trial. The investigator should keep the subject's individual data secret. The document provided to the sponsor should be identified only with the subject identification code and subject number. The investigator keeps a list of subjects' identifications in the investigator's file. In accordance with GCP principle, each subject's original data is allowed to be monitored, audited, and reviewed.

11.3 Personnel Training

Before the start of the test, the sponsor and the principal investigator should conduct training to the participants in the form of a meeting. The training should include: clinical trial protocol, trial procedures, time arrangement, operational precautions,

filling of trial data, etc. If new monitors or investigators participate in the trial, they should be trained separately. Retraining can be conducted if the sponsor or principal investigator deems it necessary. Records should be made for each training.

11.4 Compliance Guaranteeing of Subjects

According to the clinical trial protocol, a concise and well-organized volunteer recruitment letter and an informed consent form are prepared.

Responsible physicians should be told to communicate with volunteers in plain language so as to make subjects fully informed.

Subjects are screened strictly according to the criteria for inclusion and exclusion.

Follow-up personnel should have a high sense of responsibility and professionalism. Training is required to improve their communication skills and affinity. In the process of safety follow-up, measures should be taken to ensure effective contact between subjects and investigators and timely deal with adverse reactions found. Subjects should be provided with relevant health consultation.

11.5 Reported on Protocol Deviations/Violations

The on-site investigator authorized by the principal investigator should immediately report to the principal investigator after finding any deviations/violations of the clinical trial protocol or receiving any report on deviations/violations of the clinical trial protocol. Stop the current protocol deviations/violations (excluding beyond-period inoculation/sample collection); for the protocol deviations/violations that have occurred, wait for the written/e-mail reply from the sponsor and the principal investigator.

11.6 Management of Test Vaccine

11.6.1 Definition and Treatment of Cold Chain Damage

Once the refrigerator storing vaccine shows the temperature of <2°C or >8°C, it should be recorded as cold chain damage. Upon the cold chain damage, the investigator should transfer the vaccine to a dark place at the temperature of 2-8°C as soon as possible, timely report it to the sponsor, and then decide to stop or continue using vaccine in accordance with the written opinions of /e-mail reply by the sponsor.

11.6.2 Acceptance of Test Vaccine

The sponsor sends the vaccines used in clinical trial to the test site. The investigator must sign the vaccine acceptance receipt which should briefly show information about the received vaccine (completeness of the package and normal indication of the cold chain system).

When the investigator finds that the vaccine package is damaged, that the vaccine goes bad or that there is any blocky substance that cannot be shaken, the vaccine cannot be used and should be returned to the sponsor. If the cold chain system is damaged during transportation and storage or the vaccine is frozen, the vaccine cannot be used, and should be stored separately, marked with "×" on the outer package, managed by the designated person, and returned to the sponsor.

11.6.3 Management of Test Vaccine

The test vaccine should be managed by the designated person and monitored by the monitor. The Warehouse Standing Book for Vaccines should include the amount of vaccines received, the amount of vaccines given to subjects, the amount of vaccines left, or the amount of vaccines lost. The investigators will count all the test vaccines at the end of the trial. When research is finished, the remaining test vaccines are counted and returned to the sponsor.

11.7 Sample Management in Clinical Trials

Specimens for routine blood, blood biochemistry, urine routine, inflammatory factors, anti-nuclear antibody and T-cell reaction tests are disposed of by the testing organization as medical waste after test. The backup serum should be temporarily kept by the test organization on site until the test organization issues the immunogenicity test report which should be verified correct. The backup serum can be stored or processed by the sponsor after the project is over. If backup serum is required, the approval from the independent ethics committee and the consent from the subject should be obtained.

11.8 Storage of Data on Clinical Test

Data in the clinical trial must be stored as per the requirements in GCP Appendix

2. The investigator should retain the clinical trial data for at least 5 years after the clinical trial ends. The sponsor should maintain clinical trial data for at least 5 years after the marketing of the drug.

11.9 Finished Criteria for Clinical Trial

- The test samples are sent to the corresponding test organization, and the test report should be issued;
- All subjects complete the required visits, and the original data and documents of the clinical trial are handed over to the archivist for archiving and preservation;
- The remaining number of test vaccines is accurate and the remaining test vaccines are handed over to the sponsor;
- The statistical analysis report and summary report meet the requirements of the sponsor.

12 Ethical Approval

12.1 Review and Approval

The clinical trial protocol should be approved by the local independent ethics committee. The principal investigator submits the clinical protocol and all necessary additional documentation to the independent ethics committee, After the approval of the committee, the investigator provides the sponsor with a certificate of approval from the committee.

12.2 Field Supervision

Throughout the trial, the independent ethics committee should supervise if there's any ethical damage to the subjects and if the subjects obtain treatment or compensation and corresponding medical insurance measures when they are badly influenced by the study. What's more, the independent ethics committee should evaluate the risks borne by the subjects.

12.2.1 Informed Consent and Informed Consent Form

Ensure that the subject enrollment method and the relevant data provided to

subjects are comprehensive and understandable, and that the method of obtaining informed consent is appropriate. Throughout the trial, the independent ethics committee should periodically review the progress of the trial and assess the risks and benefits of the subjects.

12.2.2 Potential Risks and Risk Minimization

If an adverse reaction is identified as associated with the vaccination (abscess at vaccination site and rash after vaccination), treatment will be provided timely for subjects in accordance with relevant provisions. In case of life-threatening event, the subject will be escorted to the hospital for treatment immediately and report should be made.

Under strict supervision, the trained, experienced medical personnel could carry out vaccination and collect venous blood in accordance with the rules and procedures, so as to minimize the pain of the subject suffering from vaccination and blood collection (including pain and rare local infection in vein puncture site).

12.2.3 Protection Measures for Subjects

The clinical trial should be performed in centers for disease control and prevention with vaccination qualification at county or municipal level. The sponsor should assess the study site in strict accordance with the GCP requirements prior to the start of the trial. The environmental and facilities of the test site should meet the requirements stipulated in Guidelines for Quality Management in Clinical Trial of Vaccines (Trial). An emergency plan for prevention and handling of damages and emergencies of subjects should be made on test site. In physical examination room and blood collection room, qualified and experienced doctors and nurses should be in place to strictly follow the inclusion/exclusion criteria and to collect blood smoothly. Proper first-aid facilities, equipment and medicines should be available in the emergency room and emergency physicians should be qualified and competent. After adverse events occur at test site, subjects should be treated immediately in an emergency room on the site and sent to contracting hospitals by ambulances on site after the condition is stable if emergency hospitalization is required. Ambulances should be equipped with the necessary first aid

facilities and drugs. The trial site should sign a Green Channel Agreement with local county-level or higher general hospitals. During the enrollment of subjects, contracting hospitals should be notified for timely treatment. Staff responsibilities should be clarified. Contact numbers and rescue routes should be available to ensure the timely treatment of sudden adverse events and the effective contact between the subject and investigator so that any adverse events are promptly reported and dealt with. When subjects experience serious adverse events and need to be hospitalized for emergency treatment, contracting hospitals can provide green channel services including medical treatment, hospitalization and medical security to ensure that subjects can be treated in time. The investigator follows the progress of the events and completes the investigation records until the end of the serious adverse events.

12.3 Confidentiality

The subjects' privacy should be kept during the study and the collection of biological samples, as well as during the reporting and publication of the study. Only subject code, sample number, collection time and test index are recorded for the test sample. It is strictly restricted that only principal test personnel can obtain electronic and printed copies.

13 Modification of Clinical Trial Protocol

After the sponsor and investigator have signed the clinical trial protocol, if there are any modifications to the protocol, all protocols modified should be re-signed and dated by the principal investigator and sponsor, with the protocols not modified attached.

All modified protocols should be reported to the independent ethics committee and approved by the independent ethics committee before being executed. When a protocol is modified, it should be pointed out whether it is necessary to modify the informed consent and electronic CRF form.

14 Disclosure and Publication of Data

After the completion of this clinical trial, if the results of the trial need to be

disclosed and/or published, the positive results will be disclosed and/or published together with the negative results.

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