Project Title: Clinical Study of Phase I/II of SARS-CoV-2 Vaccine (Vero cell), Inactivated

Protocol Title: Randomized, Double-blind, Placebo-controlled Clinical Trial, to Evaluate Safety and Immunogenicity of Inactivated SARS-CoV-2 Vaccine (Vero cell), in Healthy Adults Aged 18-59 Years

Name of Investigational Product: SARS-CoV-2 Vaccine (Vero cell), Inactivated

Sponsor: Sinovac Research & Development Co., Ltd.

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

Statistical Company: Beijing Key Tech Statistics Technology Co., Ltd.

Protocol No.: PRO-nCOV-1001

Protocol Version Date: April 14, 2020

Version No.: 1.2

Protocol Approver: Qiang GAO

Signature of the Approver:

Approval Date:

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

Signature of thePrincipal Investigator

I agree to:

- Take the responsibility to correctly guide the conduct of the clinical study in the region.
- Ensure that thisstudy can be conducted in accordance with the trial protocoland the standard operating procedures for clinical studies
- Ensure that the personnel involved in the project fully understand the information of the investigational product and other responsibilities and obligationsrelated to the study specified in the project.
- Ensure that any modificantions of the trial protocol will not be conducted without the without the review and written approval of the sponsor and the Independent Ethics Committee (IEC), unless the immediate hazard for the subjects needs to be eliminated or follow the requirements of the registration regulatory authorities (e.g., administrative management aspect of the project).
- I am completely familiar with the method to correctly use the vaccine described in the trial protocol, have fully understood other information provided by the sponsor, including but not limited to the following contents: current investigator'sbrochure (IB) or equivalent documents and supplements of the IB (if any).
- I am familiar with and will abide by *Good Clinical Practice* (GCP), *Guidances on Vaccine Clinical Trial Quality Management (Trial)* and all current regulations.

Name of the Princeple Investigator: Fengcai ZHU
Signature:
Date:

Revision Record

No.	Original Version/Date/Revised content	Current Version/Date/Revised content
1	Version 1.1 /April 14th, 2020/7.6 Test suspension and termination criteria	Version 1.2/April 14th, 2020/In "7.6 Test suspension and termination standard", add "after each vaccination, count the adverse reactions of the subjects, and implement the test suspension or termination according to the following standards." The standard should be defined as the suspension and termination standard of vaccination groups.
2	Version 1.1/April 14th, 2020/8.2 Exclusion criteria for subjects	Version 1.2/April 14th, 2020/ Delete "(7) IgG or IgM screening result is positive (phase I only);" (phase I only) "; delete" (7) throat swab or anal swab RT-PCR test result is positive (phase I only); "(phase I only)"
3	Version 1.1/April 14th, 2020/Table 7, 11,12, 15 and 16	Version 1.2/April 14th, 2020/ Add "antinuclear antibody test" in Table 7; "add" antinuclear antibody test, IgG and IgM screening, throat swab and anal swab RT-PCR test "in" table 11 and table 12 ", change the time of informed consent and demographic information collection to visit 0; add" antinuclear antibody "in table 15 and table 16
4	When Version 1.2 is approved, Version 1.1is invalid.	
5	Version 1.0/April 11th, 2020/ 2.6 Testing unit of test sample	Version 1.1/April 14th, 2020/ Increased detection of antinuclear antibodies
6	Version 1.0/April 11th, 2020/ 7.2.1 Phase ITest end point	Version 1.1/April 14th, 2020/ In the exploratory end point, "the positive rate of antinuclear antibody (emergency immune procedure) was increased on the 7th /14th /21st /28th /42nd day after the first dose of the test vaccine; the positive rate of antinuclear antibody (routine immune procedure) was increased on the 28th /35th /42nd /56th day after the first dose of the test vaccine."
7	Version 1.0/April 11th, 2020/ 8.3 Exclusion criteria for subjects	Version 1.1/April 14th, 2020/ "Self report with SARS history" added to exclusion criteria
8	Version 1.0/April 11th, 2020/ 8.3 Exclusion criteria for subjects	Version 1.1/April 14th, 2020/ Platelet count was increased in the blood routine index of laboratory screening
9	Version 1.0/April 11th, 2020/ 9.1 Visit plan	Version 1.1/April 14th, 2020/ The visit time of the 0 th visit in Table 9 and table 10 was changed from d-14-0 to d-7-0
10	Version 1.0/April 11th, 2020/ 9.5 Safety follow-up observation	Version 1.1/April 14th, 2020/ Change "the investigator visited them and collected safety observation data for 0-7 days" to "the investigator visited them (phase I is not less than 2 face-to-face interviews)".
11	Version 1.0/April 11th, 2020/ 9.6 Sample collection	Version 1.1/April 14th, 2020/ "For the detection of serum antibody (neutralizing antibody / IgG / IgM), the venous blood samples for the detection of serum inflammatory factor + antinuclear antibody should be separated from the serum in time, divided into two tubes (a set of single tube of serum phase I not less than 1ml, phase II not less than 0.5mL, b set of backup serum), and recorded." It is modified as "the blood samples used for the detection of serum antibodies (neutralizing antibody / IgG /IgM/ antinuclear antibody) shall be separated from the serum in time and packed into two tubes (a set of serum phase I is not less than 1ml, phase II is not less than 0.5mL, b set is backup serum), and record."
12	Version 1.0/April 11th, 2020/ 9.7.1 Safety observation index	Version 1.1/April 14th, 2020/ Platelet count increased in routine blood test

No.	Original Version/Date/Revised content	Current Version/Date/Revised content
13	Version 1.0/April 11th, 2020/ 9.7.6 Handling of adverse events	Version 1.1/April 14th, 2020/ During the observation period of the trial, if the subjects have fever and cough and other respiratory symptoms, they should immediately go to the designated hospital for treatment. If necessary, they should collect throat swab / sputum and anal swab, and carry out CT and other imaging examinations to analyze whether the disease is caused by new coronavirus infection. Once new coronavirus infection occurs, they should be treated according to SAE, especially whether there is ade phenomenon.

Protocol Summary

PROTOCOL TITLE	A Randomized, Double-Blinded, Placebo-Controlled, Phase I/II Clinical Trial, to Evaluate the Safety and Immunogenicity of Inactivated SARS-CoV-2 Vaccine (Vero cell) , 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 Emergency Immunization Schedule: Day 0,14 Routine Immunization Schedule: Day 0,28
ROUTE OF ADMINISTRATION	Intramuscularly, deltoid region
CHALLENGE SCHEDULE, if applicable	None
BLOOD SAMPLE COLLECTION	The blood-collection time points for different vaccination schedules are 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, 20 The schedule of day 0,14 (Phase II) Blood collection on day 0,28,42,194 The schedule of day 0,28 (Phase II) Blood collection on day 0,56,208
PARAMETERS OF SAFETY	Primary Endpoint – Incidence of adverse reactions occured from the begining of the vaccination to 28 days after the whole –schedule vaccination. Secondary Endpoints – Incidence of adverse reactions 7 days after each dose of vaccination; – Incidence of abnormal laboratory index (blood routine test, blood chemistry test, and urine routine test) on the 3th day after each dose of vaccination; – Incidence of SAEs from the beginning of the vaccination to 6 months post the whole-schedule vaccination. Exploratory Endpoints – The change of IL-6, IL-2, and TNF-α in serum 7 days after each dose of vaccination；

	– The positive rate of serum antinuclear antibody on the 7/14/21/28/42th day after each dose of vaccination (emergency schedule); – The positive rate of serum antinuclear antibody on the 28/35/42/56th day after each dose of vaccination (routine schedule).
PARAMETERS OF IMMUNOGENICITY	Primary Endpoint – The seroconversion rate of neutralizing antibodies 14 days (emergency schedule)/28 days (routine schedule) after the whole-schesule vaccination. Secondary Endpoints – The seropositive rate, GMT, and GMI of neutralizing antibodies 14 days (emergency schedule)/28 days (routine schedule) after the whole-schesule vaccination; – The seroconversion rate, seropositive rate, GMT, and GMI 7/14/21/42 days after the first dose vaccination (emergency schedule); – The seroconversion rate, seropositive rate, GMT, and GMI 28/35/42 days after the first dose vaccination (routine schedules); – The seropositive rate of IgG, IgM antibodies 7/14/21/28/42 days after the first dose vaccination (emergency schedule); – The seropositive rate of IgG,IgM antibodies 28/35/42/56 days after the first dose vaccination (routine schedule). Exploratory Endpoints – Positive rate of specific T cell response 14 days after vaccination (IFN-γ detection using Elispot); – The seropositive rate and GMT 6 months after the whole-schedule vaccination.

Glossary

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
TP	Total Protein

Abstract

SARS-CoV-2 Vaccine (Vero Cell), Inactivated developed by Sinovac Research & Development Co. and Ltd. (hereinafter referred as to "Sinovac (R&D)") can induce active immunity and prevent diseases caused by the SARS-CoV-2. According to the preliminary immunogenicity studies, the vaccine can produce good neutralizing antibody responses, and has a good effecitiveness in anmals. At the same time, comprehensive safety evaluations were carried out on animals, showing that the new vaccine is safe. This protocol is drafted on the basis of *Regulation of Drug Registration*[1], *Good Clinical Practice (GCP)* [2], *Guidance on Vaccine Clinical Trial* [3], *Guidance on Vaccine Clinical Trial Quality Management (Trial)*[4] and *Guidance on SARS-CoV-2 Vaccine (Trail)*, etc.

The main purpose of this study is to evaluate the safety and immunogenicity of the investigational vaccine. A randomized, double-blind, placebo-controlled design is adopted. In the phase I clinical trial, 144 healthy adults aged 18-59 will be selected as study subjects. After the informed consents are signed, subjects who pass the physical examination, meet the inclusion criteria and didn't meet the exclusion criteria will be enrolled into the study. Each enrolled subject will receive two doses of injection at the emergency schedule of day 0,14, or the routine schedule of day 0, 28. A total of 72 subjects will be enrolled for the trial of each immunization schedule, and the subjects will be phased enrolled, with 36 at medium dosage stage, and 36 at high dosage stage. The sujects enrolled at each dosage stage will be assigned in a 2:1 ratio to receive investigational vaccine or placebo respectively. The medium stage vaccination should be carried out firstly. The high dosage stage vaccination will start only with the condition that safety observation 0~7 days after the first dose of the medium dosage stage vaccination is finished, and the good safety profiles is confirmed by the DMC, according to the occurrence of the solicited and unsolicited adverse events, as well as the occurrence of the abnormal results of the blood routine, blood biochemical and urine routine testing. The immediate reactions occur within 30 minutes after each dose of vaccination will be observed on site. The local and systemic solicited adverse events (AEs) occur withi 0~7 days after each dose vaccination, as well as the unsolicited AEs from the beginning of the vaccination to 28 days after the whole schedule vaccination will be collected. Additionally, the SAEs from the beginning of the vaccination until 6 months after the whole schedule vaccination will be collected.

Venous blood and urine sample will be collected from all subjects at different time points before and after vaccination for the blood routine, blood chemistry, urine routine testing, and the testing of serum inflammatory factor and antinuclear antibody, to evaluate the safety; as well as testin of serum neutralizing antibody, IgG and IgM antibody, and specific T cell response (IFN-γ detection using Elispot), to evaluate the immunogenicity and immune persistence of the vaccine.

The phase II will be started only with the condition that the safety observation 0~7 days after the first dose of the high dosage stage vaccination is finished, and the good safety profiles is confirmed the DMC, according to the occurrence of the solicited and unsolicited adverse event, as well as the occurrence of the abnormal results of the blood routine, blood biochemical and urine routine testing. A total of 600 healthy adults aged 18-59 will be selected in the phase II clinical trial. On the premise that informed consents are signed, subjects who pass the physical examination, meet the inclusion criteria and didn't meet the exclusion criteria will be enrolled. Each enrolled subjects will receive two doses of injection at the emergencey schedule of day 0,14 or the routine schedule of day 0,28, with 300 subjects for trial of each vaccination schedule. The subjects for each vaccination schedule will be assigned in a ratio of 2:2:1 to receive the medium dosage, high dosage vaccine, or placebo.

The immediate reactions occur 30 minutes after each dose of vaccination will be observed on site. The local and systemic solicited AEs occurred 0~7 days after each dose vaccination, as well as the

unsolicited AEs occurred from the beginning of the vaccination to 28 days after the whole schedule vaccination will be collected. Additionally, the SAEs occurred from the beginning of the vaccination untill 6 months after the whole schedule vaccination will be collected. Venous blood will be collected from all subjects at different time points before and after vaccination, for the neutralizing antibody assay, to evaluate immunogenicity and immune persistence of the investigational vaccine.

The clinical protocol will be independently undertaken by the investigator after being approved by independent ethics committee (IEC). The clinical research associates designated by the sponsor will monitor the whole process of the study, and data monitoring committee (DMC) will be established to assess the risk of clinical trials, so as to ensure the safety of the trial.

Contents

1 Introduction

Inactivated SARS-CoV-2 Vaccine (Vero cell), developed by Sinovac Research & Development Co., Ltd (hereinafter referred to as "Sinovac (R&D)"). can induce the body to produce active immunity and prevent the diseases caused by SARS-CoV-2. Preliminary immunogenicity studies showed the SAR-Cov-2 vaccine can induce good neutralizing antibody responses, and have a good effectiveness in animals. Comprehensive safety evaluations showed the SARS-CoV-2 vaccine was safety in animals. This clinical trial is designed to evaluate the safety and immunogenicity of the investigational vaccine.

2 Participanting Institutions and Responsibilities

2.1 Institution in charge of clinical trial

2.1.1 Responsibilities

The Institution in charge of clinical trials is Jiangsu Provincial Center for Disease Control and Prevention (Public Health Research Institute of Jiangsu Province). Its responsibilities are:
-Participate in making the clinical trial protocol and required forms and cards;
-Participate in the drafting of informed consent form for vaccination, preparation of SOP for clinical trial on-site operation, and application for approval of Ethics Committee; be responsible for organizing and implementing the selection of clinical trial site that meets the requirements of GCP, organizing the evaluation of the trial site, and filing in the "Drug clinical trial organization filing management information platform" of the State Drug Administration;
-Organize the implementation of clinical trials, and control the quality of the implementation process of clinical trials;
-To be responsible for guiding the site to report the serious adverse events (SAEs) occurred during the clinical trial to the provincial drug administration, as well as the sponsor and the ethics committee in a timely manner, and to carry out investigation and disposal of SAEs;
-Participate in database locking and save the locked database backup for inspection;
-Responsible for reporting the progress of clinical trial implementation to relevant administrative departments, and writing the clinical trial summary report.

2.1.2 Profile

Jiangsu Provincial Center for Disease Control and Prevention (Jiangsu CDC, i.e. Public Health Research Institute of Jiangsu Province) is a public welfare institution directly under the leadership of Jiangsu Provincial Health Committee, which is mainly engaged in disease prevention and control. As a first class provincial disease prevention and control organization, it is jointly established by the former Jiangsu Provincial Health and epidemic prevention station (Provincial tuberculosis prevention and Control Institute), Jiangsu Provincial Institute of occupational disease prevention (Provincial Institute of occupational disease prevention and control), Jiangsu Provincial Institute of health publicity and education and Jiangsu Provincial Institute of Dermatology prevention and control (Provincial STD monitoring center), and was designated as Jiangsu Provincial Health Testing and Inspection Center and Jiangsu Public Health Research Institute subsequnently joined. The Jiangsu CDC currently has 31 institutes (Departments and Offices), covering acute infectious disease control, STD and AIDS control, chronic non infectious disease control, occupational disease control, food safety and evaluation, toxicology and function evaluation, physical and chemical testing, pathogenic microorganism research, health education and health promotion, public health information and other professional disciplines. It has a strong ability in scientific research, monitoring, testing, prevention and control. In recent years, Jiangsu CDC has made great

achievements in dealing with various public health emergencies, emerging infectious diseases outbreak and the follow-up scientific research. The center has successively presided over and participated in the more than 100 clinical projects of vaccines, e.g. influenza, epidemic hemorrhagic fever, rabies, varicella, leprosy gill, meninges, hepatitis B, tuberculosis vaccine, typhoid, diphtheria combined vaccine, Haemophilus influenzae vaccine and other common vaccines or biological products, as well as the world leading vaccine such as Ebola vaccine, enterovirus type 71 vaccine, hepatitis E vaccine, Human papillomavirus vaccine (HPV), pandemic influenza vaccine, Staphylococcus aureus vaccine and H1N1 influenza vaccine. Vaccine clinical Evaluation Institute has 8 personnel with senior titles, 3 with intermediate titles, 2 with junior titles, 11 physician and 2 testing technicians.

2.2 Study Site Institution

2.2.1 Responsibilities

The clinical study site is Suining County and the study site institute is Suining CDC.Its responsibilities are:

-Cooperate in the evaluation and filing of the test site;

-Organize the personnel with corresponding professional technology and clinical research experience to participate in the work of the research site, and all participants should thoroughly read and understand the contents of the study protocol, and strictly follow the protocol to ensure that there is sufficient time to complete the clinical study within the protocol-specified period;

-Organize on-site implementation, including the organization and selection of the subjects, obtaining the informed consent signed by the subjects, screening and enrollment, vaccination, safety visit, sample collection, serum separation, sample freezing and submission, etc;

-Be responsible for data input to ensure that all the collected data are true, accurate, complete and legal;

-Accept the supervision and audit of the CRA or inspector designated by the sponsor and the inspection of drug regulatory anthorities to ensure the quality of clinical research;

-Ensure that the subjects get proper treatment in case of adverse reactions / events during the study period. In case of serious adverse reactions/events, take appropriate treatment measures for the subjects immediately, and report to the sponsor, ethics committee as well as provincial drug administration;

-Be responsible for the storage of relevant clinical trial data during the clinical trial.

2.2.2 Profile

Suining County CDC is located 200 meters north of the intersection of suihebei road and Yongchang Road in Suining County, with 54 authorized personnel and 48 actual staff. Among them, 42 are health professionals; 28 with university degree or above , 9 with college degree, 5 with technical secondary school degree;10 with senior title and 7 with intermediate title. The center consists of 10 departments, including comprehensive department, health education department, disease control department, quality control department, emergency response office, prevention and Control Department of local diseases and parasitic diseases, health department, health inspection department, prevention and Control Department of chronic non infectious diseases, and outpatient department. It has won many honors, such as advanced collective of disease prevention and control in Xuzhou, Progress award of CDC in Xuzhou, etc. The central laboratory has passed the "laboratory qualification" and "food inspection qualification" organized by the Provincial Bureau of quality supervision.

For a long time, Suining County CDC has paid attention to the laboratory construction. Now it has advanced detection instruments and equipment such as gas-mass spectrometry, atomic absorption,

ion chromatography, atomic fluorescence, PCR detector, etc. The government invested more than 2 million RMB to add flow injection analyzer, full-automatic biochemical analyzer, five classification blood cell counter and other instruments and equipment for the center, in 2017.
The laboratory of the County CDC successfully passed the qualification certification of provincial laboratory in the same year, and perform excellent in 9 external proficiency tests and laboratory comparison. At present, Suining CDC has passed 143 items of qualification certification or accreditation, and the laboratory certifying coverage rate is 80%.
Suining County CDC has been responsible for the following projects for many years: surveillance of measles, rubella, mumps immune level and etiology, the fifth round of global fund malaria project, global fund AIDS project, national pilot project, Jiangsu mosquito vector comprehensive monitoring project, China adult Tobacco epidemiological survey, national health literacy monitoring project etc.
Suining County CDC has successively undertaken phase I clinical trial of typhoid a paratyphoid combined vaccine of Luoyi (Wuxi) biopharmaceutical Co., Ltd., phase III clinical trial of quadrivalent influenza virus split vaccine of Shanghai Institute of Biological Products Co., Ltd., and phase Ib clinical trial of recombinant Staphylococcus aureus vaccine (E.coli) of Olymvax Biopharmaceuticals. The Suining County CDC has accepted the GCP on-site inspection of the former Audit and Inspection Center of China Food and Drug Administration.

2.3 Sponsor

2.3.1 Responsibilities

The sponsor is Sinovac Research & Development Co., Ltd..Its responsibilities are:
-Provide the preliminary clinical trial plan, sign and seal to approve the final plan.
-Provide clinical study approval documents, investigator brochure (pre clinical safety information of products), product implementation standards and other field application documents.
- Provide trial vaccine, and issue vaccine qualified report.
- Evaluate and select the institution in charge of the clinical trial and the study site, appoint the CRA to assess the study site and preform the monitor responsibilities according the requirements of GCP; take ultimate responsibility for the quality of the clinical trial.
-Participate in the investigation and treatment of cases of abnormal reactions to the vaccine, and provide the medical treatment and related compensation costs for the confirmed vaccine-related abnormal reactions; disposal of other conditions specified in the work agreement.
-Provide clinical study funds.

2.3.2 Profile

Sinovac Research & Development Co., Ltd., formerly known as the R & D center of Sinovac Biotech Co., Ltd., is a biological high-tech enterprise wholly owned by Sinovac (Hong Kong) Co., Ltd. and registered in 2009 with a registered capital of 9.6 million US dollars. The company is Zhongguancun high-tech enterprise and Zhongguancun gold seed enterprise.
Sinovac (R&D) specializes in the research, development and technical services of human vaccines and related products, providing technical support for the prevention and control of major infectious diseases. Relying on the advantages of the group in vaccine R & D and industrialization for many years, the company has gradually formed a R & D mode with the enterprise as the main body and the combination of production, learning and research. It has constructed a virus separation and identification technology platform, a cell factory platform, a micro carrier fermentation technology platform, a virus pure chemical technology platform, a bacterial fermentation and purification platform, a polysaccharide protein combination technology platform, and a freeze-drying technology platform, animal evaluation platform, quality control platform, diagnostic reagent raw

material development platform, each platform's professional and technical advantages complement each other, cross penetrate, and promote the company's research and development to move forward steadily and efficiently.
Sinovac (R&D) has undertaken 2 national major new drug development projects and 1 Beijing Science and technology plan, and has obtained 12 Chinese invention patents. The 23 valent pneumonia polysaccharide vaccine developed by the company has successfully completed clinical studies and industrialization in Sinovac (Beijing). At present, the company is developing Poliomyelitis Hib series combined vaccine, 13 valent pneumococcal combined vaccine, Recombinant hepatitis B vaccine, etc.

2.4 Sample Testing Institute 1

2.4.1 Responsibilities

Suining County Hospital of Traditional Chinese Medicine. Its responsibilities are:

-Be responsible for blood routine, blood biochemistry and urine routine tests.

2.4.2 Profile

Suining County Hospital of traditional Chinese medicine is a tertiary comprehensive hospital of traditional Chinese medicine, which integrates medical treatment, first aid, teaching, scientific research, prevention, health care and rehabilitation, with advanced equipment, strong technology, complete specialties and orderly management. It is named "Baby Friendly Hospital" by the Ministry of health, teaching hospital of Nanjing University of traditional Chinese medicine, safety Hospital of Jiangsu Province, demonstration unit of "assured consumption" in Jiangsu Province, Jiangsu Province Member of "Nanjing metropolitan area TCM Hospital Cooperative Development Consortium" and "Jiangsu TCM hospital technical cooperation hospital". In recent years, it has been awarded the honorary titles of "people's satisfaction hospital" and "civilized unit" in Xuzhou City.
The hospital is divided into two districts, the south district covers an area of 36.4 mu, with a building area of 48000 square meters, 28 clinical departments, 10 medical technology departments, 14 wards, 400 nuclear beds and 715 actual open beds. At present, there are 1177 employees, 283 with middle and senior professional titles, 2 doctoral students and 11 postgraduate students. The hospital has a complete range of modern diagnosis and treatment equipment, with 510 modern diagnosis and treatment equipment of more than 10000 yuan. North hospital area of traditional chinese medicine hospital is an important livelihood project in Suining County. According to the requirements and construction standards of the tertiary hospital, it is expected to be put into use in 2020. The completion of the branch hospital will make the hospital become the largest and most complete green garden, ecological and environmental protection, low-carbon and energy-saving modern hospital in Suining County, and provide reliable guarantee for the construction of the leading tertiary hospital of traditional Chinese medicine leading in Northern Jiangsu.

2.5 Sample Testing Institute 2

2.5.1 Responsibilities

Suining county CDC, its responsibilities are:
-Be responsible for the pre-screening of IgG and IgM of volunteers;
-Be responsible for the PT-PCR nucleic acid of throat and anal swab.

2.5.2 Profile

See 2.2.2 section.

2.6 Sample TestingInstitute 3

2.6.1 Responsibilities

National Institute of Food and Drug Control (NIFDC), its repsonsibities are:

-Be responsible for the detection of serum neutralizing antibody, IgG, IgM antibody and antinuclear antibody.

2.6.2 Profile

NIFDC is an institution directly under the National Medical Products Administration. It is the legal institution and the highest technical arbitration institution for the quality inspect of pharmaceutical biological products. It is also the designated "World Health Organization (WHO) drug quality assurance cooperation center". According to the regulatory requirements, the NIFDC perform the inspection for registration, import, supervision, safety evaluation, and batch release of biological products of multi-field products including drugs, biological products, medical devices, foods, health foods, cosmetics, laboratory animals, packaging materials, etc. Additionally, the NIFDC is responsible for the national research, distribution and management of the drug, medical device standard substances and the bacterial strains for production verification, and carry out relevant technical research work.

2.7 Sample Testing Institute 4

2.7.1 Responsibilities

Jiangsu Huatai Vaccine Engineering Technology Research Co., Ltd. is mainly responsible for:

-Testing of specific T cell response by IFN – γ detection.

-Testing of serum inflammatory factors.

2.7.2 Profile

Jiangsu Huatai vaccine Engineering Technology Research Co., Ltd., as a wholly-owned state-owned holding company in Taizhou pharmaceutical high tech Industrial Development Zone, has a registered capital of 50 million RMB, mainly engaged in vaccine engineering technology R&D, biological product R&D, clinical evaluation, technology transfer and consultation. The company has 22 professional service personnel, including 2 with doctorate degree and 10 with master degree. Relying on the Management Committee of Taizhou pharmaceutical high tech Industrial Development Zone, the company has established cooperative relations with Chinese Academy of Medical Sciences, China food and drug testing and Research Institute, Nanjing University, Jiangsu Provincial Center for Disease Control and prevention, Taiwan Institute of health vaccine research and development center and other units, and has many experts and consultants. The laboratory covers an area of 13,000 square meters, including inspection and testing laboratory, large-scale instrument sharing laboratory, R&D laboratory, phase I clinical evaluation base, vaccine production pilot line, original liquid filling workshop, etc., as well as 6,000 square meters of office service site. Vaccine Engineering Center has built vaccine R&D technology center, biological products pilot production base, vaccine clinical evaluation center and biological products inspection and testing center, with the qualification and ability to independently carry out technical services.

There are 20 companies in R&D of biological products, mainly including Tsuen Shin pharmaceutical, Zhonghui Yuantong, Ruike biology, Saihua biology, etc., with a total number of 420 R&D personnel. The main instruments and equipment include ultra-high performance liquid chromatograph, separation flow cytometer, molecular interaction instrument, purifier,

ultracentrifuge, fluorescence quantitative PCR, biochemical analyzer, etc., totaling more than 350 sets, worth more than 40 million yuan.
The company's cooperative unit's research projects mainly include Rabies vaccine (Vero cell), VLP HPV vaccine, tetravalent influenza vaccine, monoclonal antibody, biosimilar products and many other products, including 4 innovative drugs, 8 new drug clinical trial approvals have been obtained in recent years, and the phase I clinical evaluation experiment of Ebola, anthrax and cholera vaccine project has been completed at the same time.

2.8 Monotroing Institution

2.8.1 Responsibilities

The Clinical Research Department of Sinovac Biotech Co., Ltd. is responsible for the supervision of clinical trials.
-Carry out clinical trial supervision according to GCP, protocol and SOP;
-Assist the sponsor to undertake the screening, training of the study institution, and hold the kick-off meeting;
-Check the trial process and progress;
-Check the signing of informed consent;
-Check the qualification of investigators and effectiveness of the implementation equipment;
-Check the transportation, storage, distribution, use, return and treatment of clinical trial vaccine;
-Check the collection, storage and transportation of biological samples;
-Check the handling of adverse events;
-Check the logicality of original records and report documents;
-Complete the monitoring work after the study completion, etc.

2.8.2 Profile

Since its establishment in 2002, Clinical Research Department of Sinovac Biotech Co., Ltd. has independently conducted the organization, implementation, monitoring, data management and statistical analysis of multiple studies such as inactivated hepatitis A vaccine, combined hepatitis A and hepatitis B vaccine, SARS vaccine, influenza A vaccine, H5N1 vaccine, EV71 vaccine, 23 valent pneumococcal vaccine, varicella vaccine, inactivated polio vaccine and quardrivalent influenza vaccine, and has rich experiences in clinical trial organization, implementation and management.

2.9 Data Management

2.9.1 Responsibilities

Meta Clinical Technology Co., Ltd. is responsible for data management of this clinical trial.
-Develop data management plan and data verification plan according to the requirements of the protocol;
-Provide EDC and other related online services;
-Carry out data management in accordance with the *technical guidelines for clinical trial data management* during the trial, and confirm that all data reports and records are correct and complete;
-Clean up the data, raise questions about the research data, and assist the investigators to verify and clarify;
-Write data management report.

2.9.2 Profile

Meta Clinical Technology Co., Ltd. is a contract research organization (CRO) which mainly

undertakes data related service outsourcing business in clinical trials of domestic and foreign pharmaceutical enterprises. It was founded in September 2014. Now, there are offices in Shanghai, Beijing, Xi'an and Shenyang etc. The company has a strategic partnership with Colin Likang, which is a CRO providing comprehensive service. Meta Clinical Technology Co., Ltd.has provided data management, statistical analysis and drug pharmacovigilance services for phase I~IV and bioequivalence clinical trial of 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, and other international or domestic requirements of clinical trial;

-Personnel who have experiences in clinical trial design, implementation, data management and statistical analysis in China, United States, European Union, Japan, South Korea, etc., and familiar with relevant drug management regulations and implementation rules;

-A complete education and training system.

2.10 Statistics Analysis

2.10.1 Responsibilities

Beijing Key Tech Statistics Technology Co., Ltd. is responsible for statistical analysis of clinical trials.

- Writing the section of randomization, sample size and statistical analysis section if the clinical trial protocol;
- Prepare statistical analysis plan according to clinical trial protocol;
- Impletation of randomization and blinding;
- Carry out statistical analysis according to the proposed statistical analysis plan and write statistical analysis report.

2.10.2 Profile

Beijing Key Tech Statistics Technology Co., Ltd. (hereinafter referred to as "Key Tech") was registered and established in Beijing in August 2017. It is a domestic funded company specializing in clinical trial data management and statistical analysis services. It takes the biostatistics service of clinical research as the core, mainly for the registration of clinical trials, and provides the statistical strategy consultation, statistical design and statistical analysis throughout the whole clinical trial process. At present, Key Tech has established offices in Beijing, Xi'an and Nanning, with 43 employees, mainly graduated from the Fourth Military Medical University, Peking University, Sichuan University and other domestic first-class universities. Among them, at present, there are 21 statisticians / statistical programmers, 18 data managers, 1 quality control personnel and 3 other non business personnel in the on-the-job employees; according to the education background distribution, there are 3 doctors, 6 masters and 34 undergraduates.

Since its establishment, Key Tech has assisted the applicants to obtain 8 clinical trial approvals, completed 18 new drug applications, including 5 new biological products of class I, and 5 products already approved for marketing, including the first 13 valent pneumonia vaccine, first nasal spray influenza vaccine, the second adamutumab product, the third quadrivalen influenza vaccine and varicella vaccine in China.In 2019, Key Tech signed an agreement with Abbott on statistical consulting services in the Asia Pacific region, and established a long-term partnership with domestic and foreign major innovative pharmaceutical enterprises.

2.11 Data Monitoring Committee

The data monitoring committee is composed of experts in clinical medicine, epidemiology and statistics. Its main responsibilities are:
- be responsible for reviewing safety data and conducting risk assessment of clinical trials to ensure the safety of the trials.

3 Background and Principle

3.1 Summary

Since December 8, 2019, Hubei Province has reported several cases of unexplained pneumonia, most of whom work or live in the South China seafood market where live animal sales exist. The early stage of pneumonia presents severe symptoms of acute respiratory infection, and some patients develop rapidly into acute respiratory distress syndrome (ARDS). The pneumonia was confirmed to be human to human transmission, and the epidemic escalated rapidly in early January. There were cases in all provinces of China, Japan, Singapore, the United States and more than 20 countries. A novel coronavirus was detected in the throat swab samples of patients in January 7, 2020 by the China Center for Disease Control and Prevention (CDC). The novel coronavirus pneumonia epidemic was declared as a public health emergency in January 31, 2020 by WHO. In March 12, 2020, WHO declared the epidemic entered the international pandemic stage.

The novel coronavirus gene sequences are most closely related to the two SARS like coronavirus (bat-SL-CoVZC45 and bat-SL-CoVZXC21) [6] derived from bat. The International Committee on Taxonomy of Viruses (ICTV) announced that the official classification name of this noval coronavirus was Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in February 12, 2020, and the World Health Organization announced on the samen day that the official name of the disease caused by the virus was COVID-19.

3.2 Virology

Coronavirus (COV) is an important pathogen of human and vertebrate. It can infect respiratory tract, gastrointestinal tract, liver and central nervous system of human, livestock, birds, bats, mice and many other wild animals. Since the outbreak of severe acute respiratory syndrome (SARS) in 2003 and the outbreak of Middle East respiratory syndrome (MERS) in 2012, the possibility of CoVs spreading from animals to humans has been proved. CoVs belong to the coronavirinae family of Nidovirales coronavirus family, which includes four genera: α-coronavirus, β- oronavirus, γ-coronavirus and δ-coronavirus [7].

SARS-CoV-2, enveloped, with a diameter of 60-140nm, harbors a linear single-stranded positive sense RNA genome, encoding 4 structural proteins. The genetic characteristics of SARSr-COV and MERSr-COV are significantly different. At present, the homology with bat-SL-COVZC45 is more than 85%. In vitro, the virus could be detected in respiratory epithelial cells in 96 hours, while in Vero E6 and Hun-7 cell lines, it takes about 6 days.

So far, the whole genome sequences of virus are comparable, showing that there is no obvious mutation in the virus. Close monitoring on novel coronavirus also indicated no significant variation existed, from virus isolated from the environment or from early-stage patients or from recent patients [8]. However, novel coronavirus is a positive-strand RNA, hence, mutation and recombination are still possible in the future which would increase or decrease the virulent.

The understanding of the physical and chemical characteristics of coronavirus mostly comes from the literatures of SARS-CoV and MERS-COV. It is sensitive to UV and heat, and it could be

inactivated under the condition ether of 56 ℃ for 30 minutes or 75% ethanol, chlorine containing disinfectant, etc. While chlorhexidine cannot effectively inactivate the virus [9].

3.3 Clinical Manifestations

Based on the current epidemiological survey, the latent period of the COVID-19 is from 1 to 14 days, mostly 3 to 7 days. Fever, fatigue and cough are the main manifestations. A small number of patients with nasal obstruction, runny nose, sore throat, myalgia and diarrhoea. Severe patients arise with dyspnoea and/ or hypoxemia one week after the onset of the disease, among which could rapidly progress to acute respiratory distress syndrome, septic shock, metabolic acidosis and coagulation dysfunction. What is noteworthy is that patients with severe or critical condition may be accompany with moderate to low fever, or even without fever.

Atypical symptoms, such as vomiting, diarrhoea, weakness and short breath arise in children and new-borns, moreover, patients with mild manifestation were accompany with symptoms of fever, slight fatigue, without pneumonia. Most patients have a good prognosis, while few of them are in a critical condition. Patient were elderly or with chronic diseases have poor prognosis. The clinical manifestations between pregnant women and non-pregnant were similar[9].

3.4 Epidemiologic Feature

Transmission route and Susceptible population

COVID-19 patients are the main source of infection, and asymptomatic patients may also be contagious. Respiratory secretions through droplets and intimate contact contributed to person-to-person transmission. The virus is transmitted through the droplets produced by patients' coughing, sneezing and talking. The susceptible people are generally susceptible to infection after inhalation. Aerosol transmission is possible if under a relatively closed environment for long time.

The fecal-oral route remains to be determined. Recently, novel coronavirus was detected in faces of patients diagnosed in Wuhan, Shenzhen and even the United States. It indicated that the virus could be duplicated and existed in the digestive tract, suggesting the possibility of fecal-oral route transmission [10] However, the possibility of transmission through intake food contaminated by virus is still undetermined. Others pointed out that aerosol transmission is possible through feces droplets, while further investigation still needed.

It's reported that new-borns, whose delivered by positive pregnant patients, were diagnosed as positive 30 hours after birth, which indicated possibility of maternal-neonatal transmission [11].

Epidemic situation of COVID-19 in China

AS of 10:00 (CEST) on March 31st, 2020, there have been 82,631 cases and 3321 deaths in China[12]. *China-WHO Novel Coronavirus Pneumonia (COVID-19) Joint Investigation Report* [13] pointed out that of 55,924 confirmed patients, the median age is 51 years (2 days to 100 years), and the interquartile spacing is 39 to 63 years old. 77.8% of patients are aged between 30 and 69 years old. Among them, 51.1% are male, 77% are from Hubei Province, 21.6% are farmers or manual workers.

In China, person-to-person transmission of novel coronavirus pneumonia occurs mainly in families according to the cluster case investigation and some family transmission studies in several provinces. A total of 1836 reported cases from Guangdong Province and Sichuan Province, of them1,308 patients were reported in 344 clusters, 78%-85% of which occurred in family members. The research for family internal transmission is in progress, but the preliminary results in Guangdong Province estimate that the second attack rate of family members is about 3%-10%. As the epidemic continues, although familial cluster infection dominates, community cluster infection also increases within

hospital[13].

Global Epidemic situation of COVID-19

As of 10:00 (CEST) on on March 31st, 2020, there have been 750,890 cases and 36,405 deaths were reported globally [12]. The countries with high incidence are the United States (140640 confirmed cases in total), Italy (101,739 confirmed cases in total), Spain (85,195 confirmed cases in total), Germany (61,913 confirmed cases in total), France (43,977 confirmed cases in total), Iran (41,495 confirmed cases in total) and the United Kingdom (22,145 confirmed cases in total) etc. The outbreak has influenced 203 countrie all around the world, and has caused global COVID-19 pandemic.

3.5 R&D of Vaccines

At present, there is no approved treatment or vaccine for COVID-19 in the world. Only two candidate vaccines have entered the clinical trial stage, i.e. the RNA vaccines developed by Moderna and NIAID in the United States, and the virus vector vaccines developed by CanSino BIO and the Military Medical Research Institute.

On March 13th, 2020, WHO released information on the SARS-COV-2 vaccine R&D of 41 enterprises in the world, most of which are from United States (20), and 5 of them are from China. The majority of candidate vaccine types are virus vector vaccine and protein vaccine.

4 Preclinical Study and Laboratory Evaluation of Vaccines

4.1 Safety Study

The single dose toxicity study in rats, active systemic anaphylaxis study in guinea pigs, repeated dose toxicity study on rats, repeated dose toxicity study on cynomolgus monkey and reproductive development toxicity study in rats were carried out for the experimental vaccine. The results are as follows:

4.1.1 Single Dose Toxicity Study on Rats

Objective: To evaluate the acute toxicity of SARS-CoV-2 Vaccine on Sprague-Dawley (SD) rats within 14 days after a single dose, so as to provide toxic data for acute poisoning.

Design: 20 quarantined SD rats with equal gender and weight, were selected and randomized into vaccine group and control group to receive intramuscularly high dosage vaccine (0.5mL/1200SU/rat) or saline/0.5mL for one dose. Acute toxicity was observed for 14 days after injection, then perform anatomical observation.

Results: No death or near death rats was observed in two groups, and also no clinical abnormal reaction was observed. The body weight in each group showed a normal increasing trend, and compared with the negative control animals of the same gender in the same period, there was no statistical difference in the body weight of the animals in the sample group, and there was no significant effect of the drug on the food intake of the animals. Gross anatomical observation shows no abnormality in the main organs and tissues of animals in each group.

Conclusion: when the SD rats were injected with the vaccine in high dose intended for clinical use, no abnormal changes related to drug administration were observed, and the maximum tolerated dose (MTD) of SD rats was greater than or equal to 1200SU/dose.

4.1.2 Active Systemic Anaphylaxis Test in Guinea Pigs

Objective: Observed the rapid active systemic anaphylaxis of guinea pig by sensitization via

intramuscular injection of SARS-CoV-2 vaccine (once every two days for three times) and booster at D19/D26 via intravenous injection, provide animal data for the clinical trials of the tested product.

Design: According to the weight of the animal before administration, choose 36 Hartley guinea pigs of similar weight and randomly divide them into 4 groups, the low dosage group, high dosage group, negative control and positive control group, sensitized by vaccine of 0.5mL/1200SU/dose, saline and human hemoglobin. On D1, D3 and D5, the animals were intramuscularly sensitized, on D19 and D26, booster the animals via intravenous injection. The first three animals in each group received booster vaccination via foot vein, the booster dosage is twice of the sensitization dosage. Perform clinical observation after administration, the design of the study is shown in the following table:

Table 1 Design of Active Systemic Anaphylaxis Study in Guinea Pigs

Group	Sample/ Control	Number of animal	Sensitization (i.m) D1, D3, D5		Booster (i.v) D19, D26	
			Dosage	Volume (mL/GP)	Dosage	Volume (mL/GP)
1	Negative control	4	0	0.5	0	1
2	Positive control	4	20 mg/animal	0.5	40 mg/ animal	1
3	Low dose of test sample	4	0.1dose/ animal	0.05	0.2 dose / animal	0.1
4	High dose of test sample	4	1dose/ animal	0.5	2 dose / animal	1

Results: No abnormal reaction observed in regular clinical observation, the weight of animals was weighted before grouping, before last sensitization and before administration on the day of booster, the increase of weight in each group was normal. The anaphylaxis reaction in low dosage group, high dosage group and negative control group were all negative. The positive control showed positive in anaphylaxis after booster on D19 and D26.

Conclusion: No allergic reaction was observed when the guinea pigs was injected with the vaccine in high dose intended for clinical use.

4.1.3 Repeated Dose Toxicity Test in Rats

Objective: Evaluate the possible toxicity reaction and target organ after repeat dosing SD rats for 4 weeks via intramuscular injection of SARS-CoV-2 vaccine and the recovery of the toxicity reaction for 4 weeks after vaccination, provide animal data for clinical trials.

Design: According to the animal weight measured before grouping, 150 animals with qualified quarantine and similar body weight were selected and randomly divided into 7 groups according to the gender section, which were used in the main test group (1-4 groups, low-dose group of test sample, high-dose group of test sample, negative control group and adjuvant control group) and satellite group (5-7 groups, low-dose group of test sample, high-dose group of test sample and negative control group). There were 15 animals of each sex in the main experimental group, 15 animals of each sex in the satellite group and 5 animals of each sex in the satellite group. The low-dose group, high-dose group, negative control group and adjuvant control group were treated with 0.5mL/300SU/dose, 0.5mL/1200SU/dose of test samples, 0.5mL/dose of normal saline, 0.5mL/dose of adjuvant respectively.

The safety of the drug was observed by intramuscular injection on the 1st, 8th and 15th day until 4 weeks after the last administration. The test indexes include: clinical observation of allergicreaction, injection local reaction, body weight/body temperature/food/ophthalmic examination, clinical

pathological indexes (blood cell count, coagulation function, blood biochemistry, urinalysis), immunological indexes (T-lymphocyte subsets, cytokines, antibodies) and pathological examination (gross anatomy observation, histopathology examination).

Test results: At present, it is found that after three times of administration, there is no abnormal reaction in clinical observation of each group of animals, no abnormal temperature rise after administration, body weight fluctuates in a small range, and there is no drug-related change, neither fibrinogen measured on the 2nd and 4th day nor blood cell count measured on the 4th day has any definite abnormal change related to administration.

4.1.4 Repeated Dose Toxicity Test on Cynomolgus Monkey

Objective: Evaluate the possible toxicity reaction and target organ after repeat dosing in cynomolgus monkeys for 4 weeks via intramuscular injection of SARS-CoV-2 vaccine and the recovery of the toxicity reaction for 4 weeks after vaccination, providing animal data for clinical trials.

Design: According to the weight of animal before grouping, 40 quarantined animals with similar weight were selected and randomized according to gender into 4 groups, which are low dosage, high dosage, negative control and adjuvant control groups. 10 Macaca fascicularis each, half male and half female. The animals in low dosage group, high dosage group, negative control and adjuvant control groups were administered by 0.5mL/300SU/dose vaccine, 0.5mL/1200SU/dose vaccine, 0.5mL/dose saline and 0.5mL adjuvant solution on D0, D7 and D14 intramuscularly. The safety observation is conducted until 14 days after the last administration. The indicators including: clinical observation including allergenic reaction and local irritation, etc., weight/temperature/food consumption/ophthalmic testing, clinicopathologic indicator (blood cell count, coagulation function, bloodchem, urine analysis), immunology indicators (T-lymphocyte subsets, cell factors, C-reaction protein, alexin, antibodies), pathology testing (gross anatomical observation, histopathological examination).

Results: the first dose of immunization was completed on March 3rd, the first batch of euthanasia was completed on March 20th, and all the tests were completed on March 31st. Test data were obtained on April 6th. At present, it was found that on the 12th day, one female animal in the adjuvant control group had mild oral wall paleness, while 1/10, 2/10, 1/10 and 3/10 of the animals in the negative, adjuvant, low and high dose groups had yellow stools respectively, and no other abnormal reactions were found in each group; after administration, there was no significant increase in body temperature and CRP in the acute phase, and the body weight was in a small range. No drug-related changes were found in the internal fluctuation, and no definite abnormal changes were found in the blood cell count, blood coagulation and blood biochemistry measured on the 4th day.

4.1.5 Reproductive and Development Toxicity Study in Rats

Objective: To evaluate the effect of the SARS-COV-2 vaccine on the fertility of male and female rats, the development of pregnant / lactating female rats, embryos and fetuses, to understand the effect of the vaccine on teratogenesis and offspring development of rats, and to investigate the antibody level in the blood of embryo or offspring and to provide reference for safe drug use in different population.

Design: According to the weight of the animal before administration, the animals were randomized into 4 groups according to gender. 28 male rats and 56 female rats were randomized in low dosage group, high dosage group, negative control group and adjuvant group and administered with 0.5mL/300SU/dose vaccine, 0.5mL/1200SU/dose vaccine, 0.5mL/dose saline and 0.5mL adjuvant solution. The male rats were administered three times before mating on D1, D8, D15 and D29 while

females were administered three times before mating on D1, D8 and D15. 1 week after last administration of male rates, the males and females are mated. The female rats are administered on GD6 and PND7. ON GD20, 1/2 pregnant mice in each group were caesarean for inspection of the foetus (appearance, viscera, skeleton), the other 1/2 of the pregnant rats had a normal labor and feed until the end of lactation.

Results: the male rats had been given drugs for 3 times, no abnormal symptoms were found, and the male rats were weighed once, no abnormality was found. The first administration was completed in femaile rats on March 19th, 2020.

4.2 Immunogenicity Study

In order to evaluate inactivated SARS-CoV-2 Vaccine (Vero cell), mice and rats were immunized intraperitoneally and intramuscularly with vaccine of different dosage, and different adsorption methods at different immunization schedules. Blood samples were collected at different time points for the testing of serum neutralizing antibody titer and IgG antibody titer after immunization, to determine the immunogenicity of the vaccine. The formulation, dosage and immune schedule of the vaccine are determined according to the immunogenicity results.

Study Design:

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

Two different processes were employed to prepare aluminium-containing SARS-CoV-2 vaccines of 1200 SU/0.5 ml, 600 SU/0.5 ml, 300 SU/0.5 ml and 150 SU/0.5 ml, and aluminium-free SARS-CoV-2 vaccines of 1200 SU/0.5 ml, 600 SU/0.5 ml and 300 SU/0.5 ml. Mice were intraperitoneally immunized by the above vaccines, 10 mice per group, 0.5 ml per mouse. For the mice immunized with one injection, serum was collected on Day 7, Day 14 and Day 21 after immunization; for the mice immunized with two injections on Day 0, 7 and Day 0, 14, serum was collected on Day 14, Day 21 and Day 28, and serum IgG antibody titer was determined separately. Negative animal control was set. Immunogenicity of vaccines prepared by two different processes was compared via a comparison of the antibody titers, the specific study design is shown in the table below:

Table2 Study design of the comparison between immunogenicity of aluminium-adsorbed and non-aluminium adsorbed SARS-CoV-2 vaccine

Dosage (SU/0.5 ml)	Inactivated SARS-CoV-2 vaccine				Inactivated non-aluminium adsorbed SARS-CoV-2 vaccine			
	Batch No.	One injection	Two injections on D0, 7	Two injections on D0, 14	Batch No.	One injection	Two injections on D0, 7	Two injections on D0, 14
1200 SU	20200303-1	10	10	10	20200303-5	10	10	10
600 SU	20200303-2	10	10	10	20200303-6	10	10	10
300 SU	20200303-3	10	10	10	20200303-7	10	10	10
150 SU	20200303-4	10	10	10	/	/	/	/

- Determination of Immunization Dosage and Immunization Schedule

Mice group: Fifty mice were randomized into five groups to intraperitoneally receive three kinds of emergency schedule and two kinds of routine schedule using four antigen content vaccine of 300SU/0.5mL, 600SU/0.5mL, 1200SU/0.5mL and 2400SU/0.5mL, respectively.

Rats group: Twenty-five rats were randomized into five groups to intraperitoneally receive three kinds of emergency schedule and two kinds of routine schedule using four antigen content vaccine

of 300SU/0.5mL, 600SU/0.5mL, 1200SU/0.5mL and 2400SU/0.5mL, respectively.
Details of immunization and blood sample collection are shown below.

Table 3 StudyDesign of the Immunization Dosage and Immunization Schedule of SARS-COV-2 vaccine

Immunization Schedule	Immunization Schedule	Date of blood sampling	Amount
Emergency schedule	Day 0	Day 7, 14, 21, 28, 35, 42	10 Mice, 5 Rat
	Day 0, Day7	Day 14, 21, 28, 35, 42	10 Mice,5 Rat
	Day 0, Day 3, Day 7	Day 7, 14, 21, 28, 35, 42	10 Mice,5 Rat
Routine Schedule	Day 0, Day 14	Day 21, 28, 35, 42	10 Mice,5 Rat
	Day 0, Day 14, Day 28	Day 35, 42	10 Mice,5 Rat

Study result:

- Determination of Aluminum adsorption and non aluminum adsorption

The vaccines containing aluminum adjuvant and the vaccine free from aluminum in mice are able to produce a certain level of novel coronavirus antibody on the 7th day after initial immunization. The vaccine of 1200SU/0.5mL free from aluminium adjuvant with was the same as that of 300SU/0.5mL with aluminum adjuvant. The immunogenicity of the vaccine containing aluminum is better than that of the vaccine without aluminum.

- Determination of Immunization dosage and Immunzation schedule

(1) For the same species of animals immunized by different doses via the same procedure, the neutralizing antibody titer was determined at the same blood sampling time point. The results showed that the immunization doses and produced neutralizing antibody titers showed a good dose-response relationship.

(2) For the same species of animals immunized by the same dose via different procedures (one-injection, two-injection and three-injection), the enzyme-labelled antibody titer was determined at the same blood sampling time point. The results showed that the immunization effect of two-injection and three-injection procedures were both not inferior to that of one-injection procedure in mice, and the immunization effect of two-injection and three-injection procedures were both superior to that of one-injection procedure in rats. Because of the short interval between three injections, the immunization effect of two-injection procedure was comparable to that of the three-injection procedure.

(3) For the two-injection immunization procedure of the same dose at different time points (Day 0, 7 and Day 0, 14), the enzyme-labelled antibody level of Day 0, 14 immunization procedure was an order of magnitude higher than that of Day 0, 7 immunization procedure on Day 21, indicating that the interval between two injections should be more than 14 days in clinical trials.

(4) For two-injection immunization by different doses via the same immunization procedure, the neutralizing antibody titers of 1200 SU and 2400 SU are almost the same.

Conclusion: the formulation containing aluminium adjuvant was selected, the expected doses in clinical trials were determined to be 300 SU/dose, 600 SU/dose and 1200 SU/dose, and the immunization procedure was determined to be two injections.

4.3 Study of Virus Challenge

Objective: To evaluate the protective effect of the SARS-COV-2 vaccine on animals and whether there is Antibody-Dependent Enhancement (ADE) , and provide animal study data for clinical

research and use.

Design: the rhesus monkeys were immunized with the vaccine with different immunization schedules and dosage. The animals are attacked with SARS-COV-2 at 21-42 days after the first dose vaccination. The protective effect of the vaccine is evaluated according to the observation of clinical symptoms, the detection of serum and viral load, and the results of histopathological examination. Additionally, the presence of ADE with different antibody level is observed. The overall design is as follows:

Table 4 Study design of Virus Challenge Study

No	Group	Immunization schedule (day)	Dosage	The day of virus chanllenge after initial immunization	The Day of Euthanasia (after attack)	Amout of animals
1	3 doses- vaccine	0,7,14	High dosage (1200SU/0.5ml)	23	7	4
			Medium dosage (600SU/0.5ml)	22	7	4
2	3 doses- vaccine	0,7,14	/	21	7	2
3	Model	/	/	21	7	2
4	2 doses- vaccine	0,21	High dosage (1200SU/0.5ml)	47	7	4
			Medium dosage (600SU/0.5ml)	43	7	4
5	2 doses- vaccine	0,14	High dosage (1200SU/0.5ml)	23	7	4
			Medium dosage (600SU/0.5ml)	22	7	4
7	2 doses- adjuvant	0,21	/	22	7	2

Result:

- 3 doses schedule

For the study of the three doses schedule on day 0,7,14, all groups have finished the vaccination on on March 4th, March 11th and March 18th , and then were attacked with virus on March 25-27 and euthanasia was performed on April 1-3. The current study results are as follows:

a. Clinical observation

Animals were given close clinical observation for 1 hour after virus attack, and then observed at least twice a day in the morning and afternoon until the end of the study. At present, monkeys in the model group and the adjuvant group have already appeared fever symptoms, and there was no abnormal situation in the medium dose group.

b. Serum testing

Blood sample was collected before the vaccination, every 7 days after the vaccination, and 3,5,7 days for the neutralizing antibody (Nab), the results showing that all groups were negative in NAb (<8) on the day 0 and day 7. All the high dosage group converted to seropositive with the model group and the adjuvant group remained seronegative on the day 14. All the high dosage groups and medium dosage groups produced a high level antibody titer on the day 21 (before the virus challenge). Abnormality of WBC count and lymphocyte percentage is not found at present. Detection of virus by RT-PCR method, biochemical indicators (ALT, LDH, CK, TP and ALB), and

cytokines etc. are in progress.
c. Virus load detection
Pharyngeal and anal swabs were collected before and 3, 5 and 7 days after the virus attack for RT-PCR detection, which is currently in progress.

- 2 doses schedule

For the two dose schedule of day 0,14, all groups have finished the vaccination on March 9th and March 23th, the day 21 blood sample after the vaccination was collected on March 30th, the virus attack of the medium dosage groups was finished on March 31th, and the virus attack of the high dosage group was finished on April 1th. The euthanasia is planned on April 7-8th.

4.4 Study of Cross Neutralization

The cross neutralization tests of different viruses were carried out on the serum of patients of acute stage and convalescent stage. The preliminary results showed that the general neutralization antibody level in the acute stage serum was not high, with a certain proportion of acute stage was seronegative; the overall serum neutralization antibody level was higher in the convalescent stage than the acute stage patients, with the fact that 100% of the convalescent stage was seropositive and the high titer antibody have a good protection effect in the recovery process.
The antibody test was also conducted on the immune serum of monkeys, the results showed that the immune serum has a good cross neutralization reaction with the non-vaccine strains demontrasting a good dose-response relationship.
Cross neutralization tests will be continued.

5 Product Features

5.1 Preparation Process and Formula of Vaccine

Inactivated SARS-CoV-2 Vaccine (Vero Cell), is prepared from novel coronavirus (CN02 Strain), which is inoculated on African green monkey kidney cells (Vero Cells), then cultured, harvested, inactivated, concentrated, purified and finally aluminium absorbed. The finished vaccine is a milky white suspension liquid, which can be layered due to precipitation and easily dispersed. The main component of the vaccine is the inactivated noval coronavirus (SARS-COV-2), with the excipients of aluminum hydroxide, disodium hydrogen phosphate, sodium dihydrogen phosphate, sodium chloride, etc., and the vaccine is preservative-free. The vaccine is packaged with prefilled syringes or vials, 0.5ml for each container. The vaccine can induce the immunity against the SARS-COV-2, which can prevent the disease caused by the SARS-COV-2 infection.

The investigational vaccine is manufactuted by Sinovac Research & Development Co., Ltd. and tested eligible by National Institute for Food and Drug Control according to *Manufacturing and Quality Control Requirements of Inactivated SARS-CoV-2 Vaccine（Vero Cell) (Draft Version)*. The vaccine is injectable with the specificantion of 0.5mL/container. The antigen content of low, medium and high dosage vaccine is 300SU, 600SU, and 1200SU/0.5mL respectively.

5.2 Stability

The stability study plan of the Bulk and Final product of SARS-CoV-2 Vaccine (Vero Cell), is drafted and being implemented accrodingly.

5.3 Control Vaccine

In this study, placebo produced by Sinovac Research & Development Co., Ltd. was adpopted as the control. The placebo is aluminum hydroxide diluent with trace of milkly white precipitation. The appearance is consistent with the investigational vaccine.

It is tested eligible by National Institute for Food and Drug Control according to the *Manufacturing and Quality Control Requirements of Inactivated SARS-CoV-2 Vaccine（Vero Cell）(Draft Version)*. The vaccine is injectable with the specification of 0.5mL/container. It contains no SARS-CoV-2 antigen.

5.4 Storage and Transportation

Vaccines should be stored and transported at 2~8℃, preventing from light.

5.5 Administration Route and Schedule

Eligible subjects are intramuscularly injected at the lateral deltoid muscle of the upper arm, with a single dose of 0.5ml investigational vaccine or control vaccine, at the two doses schedule of day 0,14 and day 0,28. The vaccine should be shaken well before inoculation. The schedule of day 0,14 and 0,28 are the proposed emergency vaccination schedule and routine vaccination schedule respectively.

5.6 Information of Investigational Vaccine

The information of Investigational vaccine is as below:

Table 5 Information of Investigational Vaccine

Group	Name	Pacakge	Antigen content	Manufacturer	Phase	Batch number	Expiration date
Medium dosage vaccine	Inactivated SARS-CoV-2 Vaccine(Vero Cell)	Pre-filled syringe	600SU/ 0.5mL	Sinovac (R&D)	Phase I	20200304	2023.02.28
					Phase II	20200308	2023.03.20
High dosage vaccine	Inactivated SARS-CoV-2 Vaccine (Vero Cell)	Pre-filled syringe	1200SU/ 0.5mL	Sinovac (R&D)	Phase I	20200310	2023.03.25
					Phase II	20200309	2023.03.21
Placebo	Aluminum hydroxide diluent	Pre-filled syringe	0SU/ 0.5mL	Sinovac (R&D)	Phase I	2020022801	2023.02.27
					Phase II	2020022801	2023.02.27

5.7 Package

The vaccine will be packed in a box with a label. The label of the vaccine is shown below. See "7.4 randomization and blinding" for the vaccine numbering rules on the label.

Phase I/II of Clinical Trial of SARS-CoV-2 Vaccine
(Vero Cell), Inactivated
PRO-nCOV-1001
A001
Only for clinical study, stored at 2-8℃
Expiration date:

The box diagram is as below:

Phase I/II of Clinical Trial of SARS-CoV-2 Vaccine
(Vero Cell), Inactivated
PRO-nCOV-1001
Serial No.:
Only for clinical study, stored at 2-8℃
Expiration date:

6 Purpose

To evaluate the safety and immunogenicity of inactivated SARS-CoV-2 Vaccine (Vero cell) in adults.

6.1 Clinical Trial Phase I

To evaluate the safety, tolerance and preliminary immunogenicity of different dosage vaccine administered at different immunization schedules in adults.

6.2 Clinical Trial Phase II

To evaluate the safety and preliminary immunogenicity of different dosage vaccine administered at different immunization schedules in adults so as to determine the appropriate dosage and immunization schedule for further clinical evalution.

7 Design

7.1.1 Overall Design

Randomized, double blind and placebo control clincal trial

7.1.2 Sample Size Considerations

Clinical trial phase I: according to the requirements of the *Good Clincial Practic* and *Provisions for Drug Registration*, phase I clinical trial is a small size study aims to safety evaluation. The total sample sizeof phase I are 144 subjects, with a total of 72 subjects for each immunization schedule, and 48 sujects receive medium or high dosage investigational vaccine for each immunization schedule. The sample size meets the requirements of phase I clinical trial.

Clincal trial phase II: according to the requirments of the *Good Clincial Practic* and *Provisions for Drug Registration*, the phase II clincal trial mainly evaluates the immunogenicity and safety of different dosage vaccine in the targeted population and the samplesize is more than 300.
The total number of sujects in phase II is 600, with that of subjects receive medium, high dosage vaccine and placebo os 240, 240, and 120 respectively. Thus, the subjects in trial group is 480. The sample size meets the requirement of l phase II clinical trial.

7.2 Clinical Trial Endpoint

7.2.1 Endpoint of Phase I

7.2.1.1 Primary Endpoint

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

7.2.1.2 Secondary Endpoint

- Incidence of adverse reactions within 7 days after each dose of vaccination；
- Incidence of abnormal laboratory index (blood routine test, blood chemistry test, and urine routine test) on the 7 th day after each dose of vaccination;
- Incidence of SAEs from the beginning of the vaccination to 6 months after the whole schedule vaccination;
- Seroconversion rate, seropositive rate, GMT and GMI of neutralizing antibody on the 7,14,21,28, and 42th day after the first dose vaccination (for the emergency immunization schedule)；

- Seropositive rate of IgG and IgM antibody on the 7,14,21,28, and 42th day after the first dose vaccination (for the emergency immunization schedule);
- Seroconversion rate, seropositive rate, GMT and GMI of neutralizing antibody on the 28,35,42, and 56 th day after the first dose vaccination (for the routine vaccination schedule);
- Seropositive rate of IgG and IgM antibodyon the 28, 35, 42, and 56th day after the first dose vaccination (routine immunization schedule).

7.2.1.3 Exploratory Endpoint

- Positive rate of specific T cell response 14 days after the whole schedule vaccination (IFN-γ detection using Elispot);
- Serpositive rate and GMT 6 months after the whole schedule vaccination；
- Change of IL-6, IL-2 and TNF-α in serum on the 7th day after each dose vaccination；
- Seropositive rate of anti-nuclear anbidy on the 7,14,21,28, and 42th day after the first dose vaccination (for the emergency immunization schedule) ；
- Seropositive rate of anti-nuclear anbidy on the 28,35, 42, and 56 days after the first dose vaccination (for the routine immunization schedule).

7.2.2 Phase II Endpoint

7.2.2.1 Primary Endpoint

- Seroconversion rate of neutralizing antibody on the 14th (for the emergency immunization schedule) or 28th (for the routine immunization schedule) day after the whole schedule vaccination;
- Incidence of adverse reactions occur from the beginning of the vaccination to 28 days after the whole schedule vaccination.

7.2.2.2 Secondary Endpoint

- Seropositive rate, GMT, and GMI of the neutralizing antibody on the 14th (for the emergency immunization schedule) or 28th (for the routine immunization schedule) day after the whole schedule vaccination;
- Seroconversion rate, seropositive rate, GMT, and GMI of the neutralizing antibody on the 28th day after the whole course vaccination at the emergency immunization schedule;
- Incidence of adverse reactions within 7 days after each dose vaccination；
- Incidence of SAEs from the beginning of the vaccination to 6 months afterthe whole schedule vaccination.

7.2.2.3 Exploratory Endpoint

- Seropositive rate and GMT of neutralizing antibody 6 months after the whole schedule vaccination;
- Seropositive rate of anti-nuclear antibody on the 28th and 42th day after the first dose vaccination (for the emergency immunization schedule);
- Seropositive rate of anti-nuclear antibody on the 56th day after the first dose vaccination (routine immunization schedule).

7.3 Study Plan

7.3.1 Study Plan of Phase I Clinical Trial

Single centered, randimized, double blinded and placebo controlled clinical trial design is adopted. A total of 144 healthy adults aged 18~59 years old are selected as subjects. After informed consent,

subjects who pass the physical examination, meet the inclusion criteria and did not meet the exclusion criteria will be enrolled into the study. Enrolled subjects receive different dosage vaccine or placebo at different immunization schedules, simutanoeouly, the method of sequential vaccination medium dosage to high dosage is adopted. The purpose of the study is to evaluate the safety, tolerability, and preliminary immunogenicity of the investigational vaccine.

The subjects for the emergency immuniation schedule (day 0,14) and routine immunization schedule (day 0,28) respectively, with 72 subjects for each immunization schedule. Simutaneously, subjects are phased enrolled, with 36 at medium dosage stage which will run-in first, following by 36 at high dosage stage. The subjects enrolled in each dosage stage will be randomly assigned in a 2:1 ratio to receive vaccine or placebo. The high dosage stage vaccination will start only with the condition that safety observation 0~7 days after the first dose of the medium dosage stage vaccination is finished, and the good safety profiles is confirmed by the DMC, according to the occurrence of the solicited and unsolicited adverse events, as well as the occurrence of the abnormal results of the blood routine, blood biochemistry, and urine routine testing.

The immediate reactions occur within 30 minutes after each dose of vaccination will be observed on site. The local and systemic solicited adverse events (AEs) occur withi 0~7 days after each dose vaccination, as well as the unsolicited AEs from the beginning of the vaccination to 28 days after the whole schedule vaccination will be collected. Additionally, the SAEs from the beginning of the vaccination until 6 months after the whole schedule vaccination will be collected.

Venous blood and urine sample will be collected from all subjects at different time points before and after vaccination for the blood routine, blood chemistry, urine routine testing, and the testing of serum inflammatory factor and antinuclear antibody, to evaluate the safety; as well as testin of serum neutralizing antibody, IgG and IgM antibody, and specific T cell response (IFN-γ detection using Elispot), to evaluate the immunogenicity and immune persistence of the vaccine.

The detailed study plan of phase I clinical trial is shown in the table 6

Table 6 Study Plan of Clinical Trial Phase I

Schedule (day)	Miedum dosag	High dosage	Placebo	Total	Blood sampling time (day)	Antibody test / T cell response test (day)	blood routine, blood biochemistry, urine routine 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
In total	**48**	**48**	**48**	**144**				

Remark：*time points of specific T cell response (IFN-γ detection using Elispot).

7.3.2 Study Plan of Phase II Clinical Trial

Single centered, randomized, double blinded and placebo controlled clinical trial design is adopted. The phase II clinical trial will start only with the condition that safety observation 0~7 days after the first dose of the high dosage stage vaccination is finished, and the good safety profiles is confirmed by the DMC, according to the occurrence of the solicited and unsolicited adverse events, as well as the occurrence of the abnormal results of the blood routine, blood chemistry, and urine

routine testing.

A total of 600 healthy adults aged 18~59 years old are selected as subjects. After informed consent, subjects who pass the physical examination, meet the inclusion criteria and didn't meet the exclusion criteria will be enrolled into the study. Subjects will receive two doses of injection at the emergency immunization schedule of day 0,14 or routine immunization schedule of day 0,28, with 300 subjects for each immunization shcdule. The subjects for each schedule will be randomly assigned in a 2:2:1 ratio to receive the medium dosage, high dosage vaccine or placebo.

The immediate reactions occur within 30 minutes after each dose of vaccination will be observed on site. The local and systemic solicited adverse events (AEs) occur withi 0~7 days after each dose vaccination, as well as the unsolicited AEs from the beginning of the vaccination to 28 days after the whole schedule vaccination will be collected. Additionally, the SAEs from the beginning of the vaccination until 6 months after the whole schedule vaccination will be collected. Venous blood is collected at different time points before and after the vaccination for the neutralizing antibody assay, to evaluate the immunogenicity and immune persistence of the vaccine.

The detailed study plan of phase II clinical trial is shown in the table 7.

Table 7 Research plan of Phase II

Schedule (day)	Medium dosage	High dosage	Placebo	Total	Netralizing antibody test & Anti-nuclear antibody test (day)
0,14	120	120	60	300	0,28,42,194
0,28	120	120	60	300	0,56,208
In total	**240**	**240**	**120**	**600**	

7.4 Randomization and Double Blinding

7.4.1 Randomization

In phase I and phase II clinical trial, the blinding code of emergency and routine immunization schedule should be generated separately by the randomization statistitian by the method of block randomization using SAS software (version 9.4). The blinding code refers to the list of the correspondence between the random number and the trial products (i.e., vaccine or placebo), which is prepared in duplicate and should be sealed after the completion of the blind coding. The original copy should be kept by the investigator for unblinding of the trial, and the duplicate copy should be kept by the sponsor. In the phase I clinical trial, the vaccine (or placebo) numbers for the emergency immunization schedule and that for the routine immunization schedule are A001-A072 and B001-B072 respectively. In the phase II clinical trial, the vaccine (or placebo) number numbers for the emergency immunization schedule and that for the routine immunization schedule are C001-C300 and D001 and D300.

The blinding code of the backup vaccine (or placebo) is also generated by the randomization statistian using SAS software (version 9.4). In the phase I clinical trial, the backup vaccine (or placebo) is prepared in a 1:1:1 ratio of medium dosage, high dosage vaccine, and placebo, and the backup vaccine (or placebo) numbers are X01-X036. In phase II clinical trial, the backup vaccine (or placebo) is prepared in a 2:2:1 ratio of medium dosage, high dosage vaccine, and placebo. In case of the circumstances such as color change and damage of the trial products, the inoculation personnel should report to the person in charge of the site and principle investigator, the initiation procedure of the backup vaccine should be started up, a backup vaccine (or placebo) number should be obtained through the online backup vaccine acquisition system, and the corresponding backup vaccine should be used instead of the problem vaccine.

All trial vaccines and placebos will be pasted with blind labels. See "5.7 vaccine packaging" for label style. The subjects should be inoculated with the vaccine labelled with the number which is in accordance with their study number assigned at the enrolment.

7.4.2 Double Blinding

In this study, a double-blind design is adopted, in which the randomization statistician and other personnel who do not participate in the trial will engaged in vaccine (or placebo) blinding, i.e. pasting the printed number label to the specified location of the vaccine (or placebo), according to the generated blinding code. The whole process of vaccine (or placebo) blinding will be supervised by the randomization statistician. The blinding code should be sealed after the completion of the blind coding.

The whole process of blinding must be recorded in writting. Personnel who conduct blinding are forbidden to participate in other relevant work of this clinical trial, and should not disclose the blinding code to any person participating in this clinical trial.

7.4.3 Emergency Unblinding

Except for the blinding, the statistician should prepare emergency envelopes reserved for the potential emergency unblinding. In each envelope, there is a random password which can correspond to any study number, and the actual group of this study number can be disclosed through the online unblinding system. Each random password represents a chance of unblinding, that is to say, only one study number can be unblinded using a certain password, and then it will be invalid, and it is also invalid for the already unblended study number. In this study, 5 emergency envelopes are prepared for each immunization schedule in the phase I clinical trial, and 10 emergency envelopes are prepared for each immunization schedule for the phase II clinical trial. All the emergency envelopes are kept by the personnel in charge of the study site. Sealed status of the emergency envelopes should be checked during the blind audit process.

During the study, if the principle investigator, the sponsor and DMC jointly decide it is necessary to unblind in an emergency, the person in charge of the site shall open the emergency letter, log in to the online emergency unblinding system with the random code of unblinding in the envelope and conduct the emergency unblinding following the operation prompts, and make relevant records. Subjects with this study number will discontinue the trial and be treated as dropout, and the principle investigator will record the reason for discontinuation in the case report form (CRF). The opened emergency envelope should be properly kept and returned to the sponsor after the study is completed.

7.4.4 Unblinding Regulations

The phase I and phase II clinical trials will be unblinded according to the following time points: the unblinding of the emergency immunization schedule will be conducted after the serum antibody test results of the 14th day after the whole schedule vaccination are obtained; that of the routine immunization schedule will be conducted after the serum antibody test results of the 28th day after the whole schedule vaccination are obtained. The unblinding will be jointly implemented by the sponsor, the principle investigator and the statistical party, and a record of unblinding should be kept.

7.4.5 Flow Chart

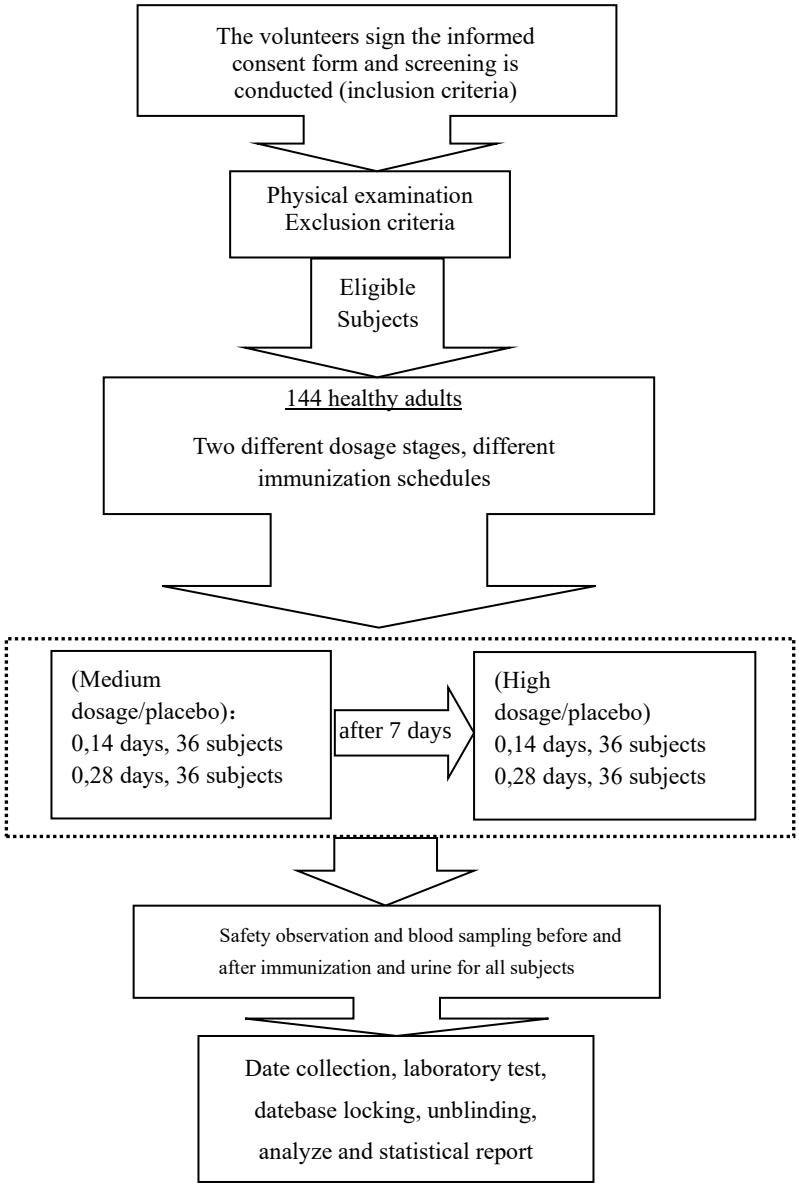


Figure 1 Flow Chart of Clinical Trial Phase I of Inactivated SARS-COV-2 Vaccine (Vero cell)

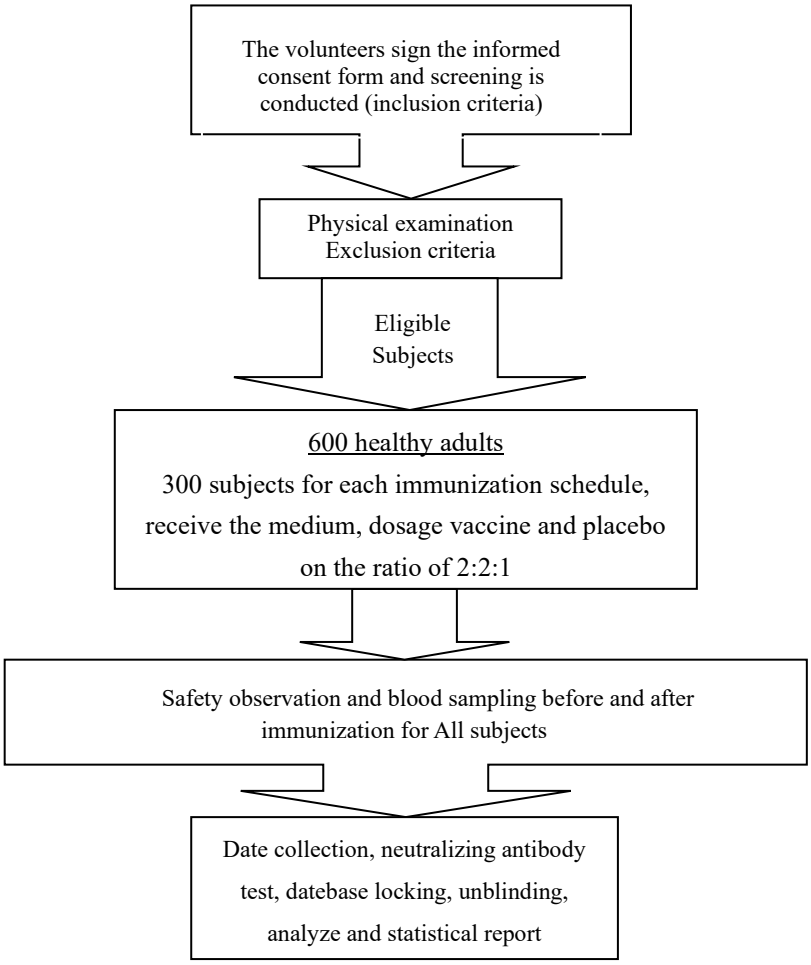


Figure 2 Flow chart of clinical trial phase II of Inactivated SARS-COV-2 vaccine (Vero cell),

7.5 Study Time

7.5.1 Duration of Clinical Trial

Table 8 Duration of Clinical Trial

Immunization Schedule	Time*
Emergence immunization schedule	2.5 months
Routine immunization schedule	4 months

*The time in table do not contain the duration of immune persistence.

7.5.2 Estimated Time for Subjects to Participate in the Trial

It is estimated that the maximum study duration is 8 months

7.6 Trial Suspension and Early Termination

After each dose vaccination, the adverse reactions of the subjects should be analyzed, and the trial was suspended or terminated according to the following standards.

Criteria of trial suspension:

- One or more than one case of the grade 4 adverse events related to vaccination (local, systmic) related to vaccination occur;

- More than 15% of the subjects have grade 3 and above adverse events related to vaccination , including local reaction, systemic reaction and vital signs

Early Termination Criteria of the Trial:

- After the clinical trial is suspended, the principle investigator, sponsor and DMC will jointly discuss and decide whether to early terminate the trial；
- The sponsor requests to fully terminate the trial and has explained reasons;
- The ethics committee requests to fully terminate the trial and has explained reasons;
- The administrative departments require to the fully terminate the trial and has explained reasons.

7.7 Protocal Violation and Deviation

Conditions of protocal violation are listed as follows (including but not limited to):

- Subjects do not meet the inclusion criteria or meet exclusion criteria；
- Subjects are vaccinated with wrong vaccine;
- SAE is not reported within the specified time。

Conditions of protocal deviation are listed as follows (including but not limited to):

- Not receiving the investigational vaccine within the protocol-required time window;
- Not receiving the blood sampling within the protocol-required time window;
- The interval time with other vaccines can not meet the requirement of protocal (Except for rabies or tetanus vaccination in case of emergency).

8 Study Population

8.1 Inclusion Criteria

(1) Healthy subjects aged 18-59 years old;
(2) Be able to understand and sign the informed consent voluntarily;
(3) Provide legal identification.

8.2 Exclusion Criteria

(1) Travel / residence history of Wuhan city and surrounding areas or other communities with case reports within 14 days prior to the entry;
(2) Contact with SARS-CoV-2 infected persons (positive for nucleic acid detection) within 14 days prior to the netry;
(3) Contact patients with fever or respiratory symptoms from Wuhan city and surrounding areas, or from communities with case reports within 14 days prior to the entry;
(4) Two or more cases of fever and / or respiratory symptoms in a small cantact area of subjects, such as family, office, school class or other places within 14 days prior to the entry;
(5) History of SARS;
(6) History of SARS-CoV-2 infection;
(7) IgG or IgM screening result is positive;
(8) The result of RT-PCR of swab or anal swab is positive;
(9) Women in lactation, pregnancy or planned pregnancy during the study (based on self-report of subjects and results of urine pregnancy test);
(10) Body mass index (BMI) ≥35 kg/m^2;
(11) History of asthma, allergy to vaccines or vaccine ingredients, and serious adverse reactions to vaccines, such as urticaria, dyspnea, angioneuroedema;
(12) Congenital malformation or developmental disorder, genetic defect, severe malnutrition, etc;
(13) Autoimmune disease or immunodeficiency / immunosuppression;
(14) Serious chronic disease, serious cardiovascular disease, hypertension and diabetes that cannot

be controlled by drugs, hepatorenal disease, malignant tumor, etc;

(15) Serious nervous system disease (epilepsy, convulsion or convulsion) or psychosis;

(16) Thyroid disease or history of thyroidectomy, spleenlessness, functional spleenlessness, spleenlessness or splenectomy resulting from any condition;

(17) Diagnosed abnormal blood coagulation function (eg, lack of blood coagulation factors, blood coagulopathy, abnormal platelets) or obvious bruising or blood coagulation;

(18) Immunosuppressive therapy, cytotoxic therapy, inhaled corticosteroids (excluding allergic rhinitis corticosteroid spray therapy, acute non-complicated dermatitis superficial corticosteroid therapy) in the past 6 months ;

(19) Abnormal laboratory test results in the physical examination such as clinically significant abnormal hematology and biochemistry beyond the reference value range (only applicable to Phase I clinical trials) :

1) Blood routine index：Leukocyte count, hemoglobin, platelet count;

2) Blood biochemical index：Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), creatinine (CR), creatine phosphokinase (CPK)

3) Urine routine index：Urine protein (pro), urine sugar, urine red blood cell

(20) Long history of alcohol or drug abuse;

(21) Receipt of blood products within in the past 3 months ;

(22) Receipt of other investigational drugs in the past 30 days;

(23) Receipt of attenuated live vaccines in the past 14 days ;

(24) Receipt of inactivated or subunit vaccines in the past 7 days ;

(25) Acute diseases or acute exacerbation of chronic diseases in the past 7 days;

(26) Axillary temperature >37.0°C;

(27) According to the investigator's judgment, the subject has any other factors that are not suitable for the clinical trial.

8.3 Exclusion Criteria for the Second Dose

The subjects who experience any of events in the following (1) to (4) are forbidden to continue vaccination, but they can continue other study steps according to the investigator' judgement. For the subjects who experience any of the events in the following (5) to (6), the investigator will judge whether vaccination will be continued. For the subjects who experience any of the events in the following (7) to (10), the vaccination can be delayed within the protocol-permitted time window.

(1) Similar vaccines other than the investigational vaccines were used durng the study;

(2) Any serious adverse reactions which have a causal relationship with the vaccination;

(3) Severe anaphylaxis or hypersensitivity after vaccination (including urticaria/rash appears within 30 minutes after vaccination)；

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

(5) Acute or newly onset chronic disease after vaccination；

(6) Other reactions (including severe pain, severe swelling, severe limitation of movement, persistent high fever, severe headache or other systemic or local reactions) judged by the investigators;

(7) Acute diseases occur during vaccination (acute disease means moderate or severe disease with or without fever);

(8) Axillary temperature >37.0℃ during vaccination;

(9) Have vaccinated with subunit vaccine or inactivated vaccine within 7 days, immuned with live attenuated vaccine within 14 days;

(10) According to the investigator's judgment, the subject has any other factors that affect vaccination.

8.4 Subject Withdraw and Suspending Criteria

(1) Subjects request towithdraw;
(2) Intolerable adverse events, whether or not related to the investigational product;
(3) Subjects are not allowed to participate in this trial due to their health status;
(4) In case of any abnormal clinical manifestations of the subjects, the researcher should determine whether it is related to the vaccine, and judge whether the subjects suspend the clinical trial;
(5) Any other reasons considered by the investigator.

If the trial vaccine has been inoculated to the subject before suspending, the clinical trial data of the subject will be used for safety analysis. Subjects could not be replaced in the trail. After the subjects who have been vaccinated in the clinical trial withdraw or suspend the trial, the researcher should provide necessary guidance for any clinical situation related to the trial, and follow up until the a definitive diagnosis is obtained, or the health condition stabilizes or recovers.

9 Method and Procedure

9.1 Visit Plan

9.1.1 Visit Plan of Phase I Clinical Trial (Day 0,14 Schedule)

Table 9 Follow-up Visits of Phase I Clinical Trial (Day 0,14 Schedule)

Visits			0	1	2	3	4	5	6	7	8	9
Date of Visit		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 notification, subject enrolment		X										
Informed consent			X									
Demographic information			X									
Blood collection	Blood routine, blood biochemistry test		X		X		X	X				
	IgG and IgM screening		X									
	RT-PCR test of throat swab and anus swab		X									
	Serum antibody test (Neutralizing antibody, IgG, IgM, Antinuclear antibody)			X		X	X		X	X	X	X
	Inflammatory factor test			X		X	X		X			
	T cell response (IFN-γ detection)			X			X			X		
Urine routine test			X		X		X	X				
Urine pregnancy test (woman)				X			X					
Regular examination				X								
Inclusion/exclusion criteria screening				X			X					
Vaccination[b]				X			X					
Subject self-recording of the safety observation on diary cards[c]				X	X	X	X	X	X	X	X	
Adverse reaction/event monitoring (including level 3 or higher , SAE) [cd]				X	X	X	X	X	X	X	X	X
Records of concomitant use of drug/vaccine [cd]				X	X	X	X	X	X	X	X	X

a) Before each dose vaccination, inclusion/exclusion criteria screening is required.
b) Subjects will be observed for 30 minutes on site to determine the situation of adverse

events, especially acute allergic reactions,and then followed by regular follow-ups as required.

c) Safety observation includes assessment of adverse reactions/events and temperature measurement. Body temperature should be measured every day within 0~7 days after each dose vaccination and whenever fever is suspected. Safety observation data are required to be recorded in the diary cards within 14 days after the first dose and 28 days after the second dose. The investigator regularly interviews the subjects to verify and record adverse events and concomitant use of drugs / vaccines.

d) During D42-D194, only SAE and drug use associated with SAE are collected.

e) See "Visit Plan" for the time window.

Visit Plan：

Visit0 — Day-7~0-informed consent, collect blood, urine, throat and anus swabs, laboratory screening (including blood routine, blood biochemistry, urine routine, IgG&IgM, nucleic acid test).

Visit1—Day 0—eligible subjects enrolled, collect blood and urine (only for female), and the first dose administration.

Visit 2—the 3rd day (±1 day) after the first dose - verify the safety observations and concomitant use of drug and other vaccine, collect blood and urine.

Visit 3—the 7th day (+3 day) after the first dose- verify safety observations and concomitant use of drug and other vaccine, and collect blood.

Visit 4—the 14th day (+ 5 days) after the first dose- verify the safety observations and concomitant use of drug and other vaccine, collect blood, urine, and the second dose administration.

Visit 5—the 3rd day (±1 day) after the second dose - verify the safety observations and concomitant use of drug and other vaccine, collect blood and urine.

Visit 6—the 7th day (+3 day) after the second dose-verify the safety observations and concomitant use of drug and other vaccine, collect blood.

Visit 7 — The 14th day (+5 day) after the second dose- verify the safety observations and concomitant use of drug and other vaccine, collect blood.

Visit 8 — The 28th day (+10 days) after the second dose - verify the safety observations and concomitant use of drug and other vaccine, collect blood.

Visit 8~Visit 9 — verify SAE observation, drug use associated with SAE, and other special circumstances.

Visit 9—day 180 (+30 day) after the second dose-verify SAE observation, drug use associated with SAE, and other special circumstances, and collect blood.

9.1.2 Visit Plan of Visit Plan of Phase I Clinical Trial (Day 0,28 Schedule)

Table10 Follow-up Visits of Phase I Clinical Trial (Day 0,28 Schedule)

Visits			0	1	2	3	4	5	6	7	8	9
Date of Visit		D-21～D0	D-7～D0	D0	D3[e]	D7[e]	D28[e]	D31[e]	D35[e]	D42[e]	D56[e]	D208[e]
Preliminary notification, subject enrolment		**X**										
Informed consent			**X**									
Demographic information			**X**									
Blood collection	Blood routine, blood biochemistry test		**X**		**X**		**X**	**X**				
	IgG and IgM screening		**X**									
	RT-PCR test of throat swab and anus swab		**X**									
	Serum antibody test (Neutralizing antibody, IgG, IgM, Antinuclear antibody)			**X**			**X**		**X**	**X**	**X**	**X**

Visits			0	1	2	3	4	5	6	7	8	9
Date of Visit		D-21～D0	D-7～D0	D0	D3[e]	D7[e]	D28[e]	D31[e]	D35[e]	D42[e]	D56[e]	D208[e]
	Inflammatory factor test			X		X	X		X			
	T cell response (IFN-γ detection)			X			X			X		
Urine routine test			X		X		X	X				
Urine pregnancy test (woman)				X			X					
Regular examination				X								
Inclusion/exclusion criteria screening				X			X					
Vaccination[b]				X			X					
Subject self-recording of the safety observation on diary cards[c]				X	X	X	X	X	X	X	X	
Adverse reaction/event monitoring (including level 3 or higher, SAE) [cd]				X	X	X	X	X	X	X	X	X
Records of concomitant use of drug/vaccine [cd]				X	X	X	X	X	X	X	X	X

a) Before each dose vaccination, inclusion/exclusion criteria screening is required.

b) Subjects will be observed for 30 minutes on site to determine the situation of adverse events, especially acute allergic reactions, and then followed by regular follow-ups as required.

c) Safety observation includes assessment of adverse reactions/events and temperature measurement. Body temperature should be measured every day within 0~7 days after each dose vaccination and whenever fever is suspected. Safety observation data are required to be recorded in the diary cards within 28 days after each dose. The investigator regularly interviews the subjects to verify and record adverse events and concomitant use of drugs/vaccines.

d) During D56-D208, only SAE and drug use associated with SAE are collected.

e) See “Visit Plan” for the time window.

Visit Plan：

Visit0 —Day-7~0- informed consent, collect blood, urine, throat and anus swabs, and laboratory screening (including blood routine, blood biochemistry, urine routine, IgG & IgM, and nucleic acid test).

Visit1—Day 0—eligible subjects enrolled, collect blood and urine (only for female), and the first dose administration.

Visit 2—the 3rd day (±1 day) after the first dose – verify safety observations and concomitant use of drug and other vaccine, collect blood and urine.

Visit 3—the 7th day (+3day) after the first dose - verify safety observations and concomitant use of drug and other vaccine, collect blood;

Visit 4—the 28th day (+10 day) after the first dose - verify safety observations and concomitant use of drug and other vaccine, the second dose administration.

Visit 5—the 3rd day (±1 day) of the second dose - verify safety observations and concomitant use of drug and other vaccine, collect blood and urine.

Visit 6—the 7th day (+3 day) of the second dose - verify safety observations and concomitant use of drug and other vaccine, collect blood.

Visit 7—the 14th day (+5 day) of the second dose - verify safety observations and concomitant use of drug and other vaccine, collect blood.

Visit 8—the 28th day (+10 day) of the second dose - verify safety observations and concomitant use of drug and other vaccine, collect blood.

Visit 8~Visit 9—verify SAE observation, drug use associated with SAE, and other special circumtances.

Visit 9—Day 180 (+30 day) after the second dose -verify safety observations and concomitant use of drug and other vaccine, collet blood.

9.1.3 Visit Plan of Phase II Clinical Trial (Day 0, 14 Schedule)

Table11 Follow-up Visits of Phase II Clinical Trial (Day 0,14 Schedule)

Visits		0	1	2	3	4	5	6	7
Date of Visit	D-21～D0	D-7～D0	D0	D7[e]	D14[e]	D21[e]	D28[e]	D42[e]	D194[e]
Preliminary notification, subject enrolment	X								
Informed consent		X							
Demographic information		X							
Neutralizing antibody & Antinuclear antibody test			X				X	X	X
RT-PCR test of throat swab and anus swab		X							
IgG and IgM screening		X							
General examination			X						
Urine pregnancy test (woman)			X		X				
Inclusion/exclusion criteria screening			X		X				
Vaccination[b]			X		X				
Subject self-recording of the safety observation on diary cards[c]			X	X	X	X	X	X	
Adverse reaction/event monitoring (including level 3 or higher , SAE)[cd]			X	X	X	X	X	X	X
Records of concomitant use of drug/vaccine [cd]			X	X	X	X	X	X	X

a) Before each dose vaccination, inclusion/exclusion criteria screening is required.

b) Subjects will be observed for 30 minutes on site to determine the situation of adverse events, especially acute allergic reactions, and then followed by regular follow-ups as required.

c) Safety observation includes assessment of adverse reactions/events and temperature measurement. Body temperature should be measured every day within 0~7 days after each dose vaccination and whenever fver is suspected. Safety observation data are required to be recorded in the diary cards within 7 days after the first dose and 28 days after the second dose. The investigator regularly interviews the sujects to verify and record adverse events and concomitant use of drugs/vaccines.

d) During D42-D194, only SAE and drug use associated with SAE are collected.

e) See “Visit Plan” for the time window.

Visit plan:

Visit0—Day-7~0-informed consent, IgG and IgM antibody, nucleic acid screening.

Visit1—Day 0- eligible subjects enrolled, collect blood, and the first dose administration.

Visit 2—the 7th day (+3 day) after the first dose - verify safety observations and concomitant use of drug and other vaccine.

Visit 3—the 14th day (+5 day) after the first dose -verify safety observations and concomitant use of drug and other vaccine, the second dose administration.

Visit 4—the 7th day (+3 day) after the second dose -verify safety observations and concomitant use of drug and other vaccine.

Visit 5—the 14th day (+5 day) after the second dose -verify safety observations, and concomitant use of drug and other vaccine, collect blood.

Visit 6—the 28th day (+10 day) after the second dose-verify safety observation, medication and

other vaccination records, collect blood.

Visit 6~ Visit 7—verify SAE observation, drug use associated with SAE, and other special circumstances.

Visit 7—Day 180 (+30 day) after the second dos -verify safety observation and concomitant use of drug and other vaccine, collect blood.

9.1.4 Visit Plan of Phase II Clinical Trial (Day 0, 28 Schedule)

Table 12 Follow-up Visits of Phase II Clinical Trial Visit (Day 0, 28 Schedule)

Visits		0	1	2	3	4	5	6
Date of Visit	D-21～D0	D-7～D0	D0	D7[e]	D28[e]	D35[e]	D56[e]	D208[e]
Preliminary notification, subject enrolment	X							
Informed consent		X						
Demographic information		X						
Neutralizing antibody & Antinuclear antibody test			X				X	X
RT-PCR test of throat swab and anus swab		X						
IgG and IgM screening		X						
General examination			X					
Urine pregnancy test (woman)			X		X			
Inclusion/exclusion criteria screening			X		X			
Vaccination[b]			X		X			
Subject self-recording of the safety observation on diary cards[c]			X	X	X	X	X	
Adverse reaction/event monitoring (including level 3 or higher , SAE)[cd]			X	X	X	X	X	X
Records of concomitant use of drug/vaccine [cd]			X	X	X	X	X	X

a) Before each dose vaccination, inclusion/exclusion criteria screening is required.

b) Subjects will be observed for 30 minutes on site to determine the situation of adverse events, especially acute allergic reactios, and then followed by regular follow-ups as required.

c) Safety observation includes assessment of adverse reactions/events and temperature measurement. Body temperature should be measured every day within 0~7 days after each dose vaccination and whenever feveris suspected. Safety observation data are required to be recorded in the diary cards within 28 days after each dose. The investigator regularly interviews the subjects to verify and record adverse events and concomitant use of drugs/vaccines.

d) During D56-D208, only SAE and drug use associated with SAE are collected.

e) See “Visit Plan” for the time window.

Visit plan：

Visit0—Day7~0-informed consent, IgG and IgM antibody and nucleic acid screening.

Visit1—Day 0- eligible subjects enrolled, collect blood, and the first dose administration.

Visit 2—the 7th day (+3 day) after the first dose - verify safety observations and concomitant use of drug and other vaccine.

Visit 3—the 28th day (+10 day) after the first dose - verify safety observations and concomitant use of drug and other vaccine.

Visit 4—the 7th day (+3 day) after the second dose - verify safety observations and concomitant use of drug and other vaccine.

Visit 5—the 28th day (+10 day) after the second dose- verify safety observations and concomitant

use of drug and other vaccine, collect blood.
Visit 5~ Visit 6—verify SAE observation, drug use associated with SAE, and other special circumstances.
Visit 6—Day 180 (+30 day) after the second dose -verify safety observations and concomitant use of drug and other vaccine, collect blood.

9.2 Recruitment and Informed Consent

Recruitment notices will be issued to volunteers who meet the recruitment criteria. The informed consent should be explained to the volunteers in detail. In the premise of voluntary participation, the volunteers and the investigator jointly sign the informed consent in duplicate, and the volunteers keep the copies.

9.3 Screening and Random Enrollment

The subjects who is detected no abnormality during physical examination (women should receive urine pregnancy test to exclude pregnancy), meet the inclusion criteria and don't meet the exlusion criteria are eligible to be enrolled into the study. The screening number is S+ screening sequence number, such as "S0001". The enrolled subject will be assigned a study number in the order of enrollment. In the phase I clinical trial, study number of subjects for emergency and routine schedules are A001-A072 and B001-B072 respectively. In the phase II clinical trial, study number of subjects for emergency and routine shcdules are C001-C300 and D001-D300 respectively.

9.4 Vaccination

According to the study number of the subject, the vaccinator takes out the corresponding vaccine labelled with the same number and opens the package box, checks the information of label on the syringe, label in the package box, and label on the outer surface of package box, the vaccination should be carried outs with the condition that information on the three labels are confirmed consistency. After vaccination, the label in the backage box should be removed and pasted on the specific location of the original logbook, simultaneously, the vaccination information should be recorded in the original logbook.
See "7.3 Study plan" for immunization schedules.

9.5 Safety Follow-up Observation

Diary cards are distributed to subjects after each dose vaccination to record the solicited (local or systemic) within 0~7 days after vaccination, and the unsolicited adverse events within 0~28 days (0~14 days for the first dose of the emergency immunization) after vaccination. Subjects are required to fill in their diary cards in detail within 0-28 days after vaccination (0~14 days for the first dose of the emergency immunization), to record any clinical symptoms, concomitant use of drugs and other vaccines. The investigators verify the adverse events reported by subjects.
Systematic observation is carried out within 7 days after vaccination. Subjects are required to closely observe their own symptoms and vital signs and fill in the diary card every day. The investigator collected the safety data within 0~7 days after vaccination through visits (no less than 2 times of face-to-face visits for the phase I clinical trial)； the safety data within 8~28 days (8~14 days for the first dose of the emergency immunization) are collected by the combination of subjects' spontaneous report andinvestigators' regular follow-up. The follow-up safety observation will continue until the 28th day after vaccination.
The subjects are informed to record the adverse events at any time. Acute allergic reactions, serverity level 3 and above adverse events and SAE should be reported to the investigators timely. After the investigators are informed, they should conduct investigation, verification and follow-up until the

adverse event is solved, and finally complete the 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 level
- Relevance to vaccination
- Laboratory testing results
- Treatment measures

Timely treatment should be provided with regard to the acute allergic reactions and severity level 3 and above advere events, in order to relieve the sufferings of the subjects as soon as possible; in case of SAE after vaccination, green channel for medical rescue should be started and medical treatment shall be timely provided; drug treatment and medical treatment during each follow-up should be recorded in detail.

9.6 Sample Collection

- **Sample Collection Plan**

Samples from subjects are collected before and after immunization according to "9.1 Visit Plan", the collection plan is below:

Table 13 Sample Collection Plan of Phase I Clinical Trail (Day 0,14 Schedule)

Sample type	Times of visit	0	1	2	3	4	5	6	7	8	9
Venous blood(ml)	Date of visit	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/antinuclear antibody		**5**		**5**	**5**		**5**	**5**	**5**	**5**
	T cell response		**10**			**10**			**10**		
	Total	**8**	**20**	**8**	**10**	**28**	**8**	**10**	**15**	**5**	**5**
Fingertip blood(ml)	IgG, IgM Screening	**Appropriate amount**									
Urine(ml)	Urine routine	**5~10**		**5~10**		**5~10**	**5~10**				
	Urine pregnancy (Female)		**5~10**			**5~10**					
Throat & anus swab	RT-PCR test	**Appropriate amount**									

e: See"9.1 visit plan" for the time window.

Table14 Sample Collection Plan of Phase IClinical Trail (Day 0,28 Schedule)

Sample type	Times of visit	0	1	2	3	4	5	6	7	8	9
Venous	Date of visit	D-7～D0	D0	D3[e]	D7[e]	D28[e]	D31[e]	D35[e]	D42[e]	D56[e]	D208[e]

blood(ml)											
	Blood routine	**3**		**3**		**3**	**3**				
	Blood biochemistry	**5**		**5**		**5**	**5**				
	Inflammatory factor		**5**		**5**	**5**		**5**			
	Neutralizing antibody/antinuclear antibody		**5**			**5**		**5**	**5**	**5**	**5**
	T cell response		**10**			**10**			**10**		
	Total	**8**	**20**	**8**	**5**	**28**	**8**	**10**	**15**	**5**	**5**
Fingertip blood (ml)	IgG, IgM Screening	**Appropriate amount**									
Urine(ml)	Urine routine	**5~10**		**5~10**		**5~10**	**5~10**				
	Urine pregnancy (Female)		**5~10**			**5~10**					
Throat & anus swab	RT-PCR Test	**Appropriate amount**									

e: See “9.1 visit plan” for the time window.

Table15 Sample Collection Plan of Phase II Clinical Trial (Day 0,14 Schedule)

Sample type	Times of visit	0	1	2	3	4	5	6	7
	Date of visit	D-7～D0	D0	D7[e]	D14[e]	D21[e]	D28[e]	D42[e]	D194[e]
Fingertip blood(ml)	IgG, IgM Screening	**Appropriate amount**							
Throat & anus swab	RT-PCR test	**Appropriate amount**							
Venous blood(ml)	Neutralizing antibody/antinuclear antibody	**-**	**3**	**-**		**-**	**3**	**3**	**3**
Urine(ml)	Urine pregnancy (Female)		**5~10**		**5~10**				

e: See “9.1 visit plan” for the time window.

Table16 Sample Collection Plan of Phase II Clinical Trial (Day 0,28 Schedule)

Sample type	Times of visit	0	1	2	3	4	5	6
	Date of visit	D-7～D0	D0	D7[e]	D28[e]	D35[e]	D56[e]	D208[e]
Fingertip blood (ml)	IgG, IgM Screening	**Appropriate amount**						
Throat & anus swab	RT-PCR test	**Appropriate amount**						
Venous blood(ml)	Neutralizing antibody/antinuclear antibody	**-**	**3**	**-**		**-**	**3**	**3**
Urine(ml)	Urine pregnancy (Female)		**5~10**		**5~10**			

- e: Time Frame see “9.1 visit plan”.

- **Sample Numbering Principle**

During the screening phase, the sample numbering rule is:” Screening number + collection serial

number", and the sample numbering rule after enrollment is "study number + collection serial number".

- **Sample Management**

All the samples collected on site should be sent to laboratory timely, completing the handover with the laboratory personnel.

Fo the blood samples used for serum antibody (including neutralizing antibody, Ig, IgM, and antinuclear antibody) detection, serum should be isolated timely and placed in two tubes (i.e. A tube for detection and B tube for backup, the amount of serum in A tube should be no less than 1ml and 0.5ml for the phase I and phase II clinical trial respectively). The serum isolation process should be recorded, and the serum should be stored under -20℃ or lower temperature.

The blood samples for T cell response assay (IFN-γ detection using Elispot method) also should be stored under 20℃or lower temperature timely. All the processes of sample handover, serum insolation, and sample preservation should be recorded.

9.7 Safety Assessment

9.7.1 Safety Obervation Index

Solicited local adverse events: pain, induration, swelling, redness, rash, pruritus

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

laboratory test:

Blood routine: white blood cell, hemoglobin, platelet;

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

Urine routine: urine protein , urine sugar, urine red blood cells.

9.7.2 Definition of Adverse Events/Reactions

The safety of vaccines will be evaluated according to the scope, intensity, and severity of the local adverse events, systemic adverse events, abnormality of vital signs as well as laboratory index, and the correlation of the above events with vaccination. All adverse medical events occurring during the trial (since signing of the informed consent form) should be collected and recorded, recorded and should be reported to the sponsor and CRA by the investigator.

- Adverse events (AE): Adverse medical events that occur after vaccination, but are not necessarily causally related to the trial vaccine.
- Adverse reactions: the adverse events related to the trial vaccination during the vaccination according to the prescribed dose and procedure.
- Serious adverse event (SAE): it refers to the events during the clinical trial that need hospitalization treatment, prolong hospitalization time, disability, affect working ability, endanger life or death, cause congenital malformation, etc.
- Solicitation/non-solicitation adverse events: In this trial, the solicitation period is 0-7 days after each dose of vaccination, and the non-solicitation period is 8-28 days. The solicited adverse events refer to the solicited symptoms occur within the solicitation period, and the unsolicited adverse events refer to the unsolicited symptoms occur within the solicitation period, and any symptoms occur within the non-solicitation period.

9.7.3 Outcome of adverse events

The outcomes of adverse events included: (1) recovered (2) not yet recovered (3) recoverd but has sequela (4) death (5) loss of follow-up/unknown.

9.7.4 Determination of Clinical Significance of Laboratory Indicators

The judgments of clinical significance include: (1) within the reference range (2) no clinical significance outside the reference range (3) clinical significance outside the reference range.

9.7.5 Correlation of Adverse Events with Vaccines

The investigators should try their best to explain the adverse events, and assess the possible casual relationship, i.e. the causal relationship between investigational vaccine and alternative causes (e.g. history of underlying disease, concomitant treatment). This applies to all AEs including serious and non-serious ones.

Causality assessment will be determined by the extent to which an event can be reasonably explained in one or more of the following areas:

Reactions with similar nature have been observed for the similar products;

The same event has been reported in the literatures of the drug products of the similar type;

The event appears with vaccination of the investigational vaccine and recurs after re-vaccination of the investigational vaccine.

According to the definition, all solicatied AEs occurring at the injection site will be considered to be associated with vaccination.

Causality of AE with vaccination should be assessed by the investigator on the basis of the following questions, whether there is a national possibility that the AE is caused by vaccination according to your judgement:

a. Definitely unrelated: adverse events are caused by other factors, such as the subject's clinical condition, other treatments or concomitant drugs.

b. Possibly unrelated: adverse events may be caused by other factors, such as the subject's clinical condition, other treatments or concomitant drug. The occurrence of the adverse events are inconsistent with the known information of the investigational vaccine.

c. Possibly related: adverse events are consistent with known information of the investigational vaccine and have a causal relationship with the investigational vaccine, but may also be related to other factors.

d. Probably related: the occurrence of adverse events are consistent with known information of the investigational vaccine and are causally related to the investigational vaccine and cannot be explained by other factors, such as the subject's clinical condition, other treatments or concomitant drugs.

e. Certainly related: the occurrence of adverse events are consistent with known information of the investigational vaccine and are causally related to the investigational vaccine and cannot be explained by other factors, such as the subject's clinical condition, other treatments or concomitant use. In addition, adverse events recur when subjects were re-administered the investigational vaccine.

9.7.6 Treatment of Adverse Event

The reactions such as redness, swelling, pain or (and) fever and general discomfort below grade 2 usually can spontaneously disappear and special treatment is not needed.

The investigators will carry out the investigation and medical follow-up such as disease history, physical examination, necessary laboratory test, and necessary treatment if the subjects experience any adverse events of grade 3 and higher, until the adverse events are solved. The corresponding investigation records including the symptoms, vital signs, diagnosis, and laboratory test results should be completed.

In case of the serious adverse event, investigator should promptly take the necessary measures and report within 24 hours. The pregnancy of any female sujects during the study will be treated as SAE.

During the study period, subjects with fever and respiratory symptoms such as cough should immediately go to the designated hospital for treatment. The throat swabs and anal swabs should be collected for nucleic acid testing, and CT examination should also be conducted to deterimine whether it is COVID-19. Once a COVID-19 occurs, it will be treated as SAE, especially it should be analysed that whether there is ADE phenomenon.

9.7.7 Reporting of Serious Adverse Events

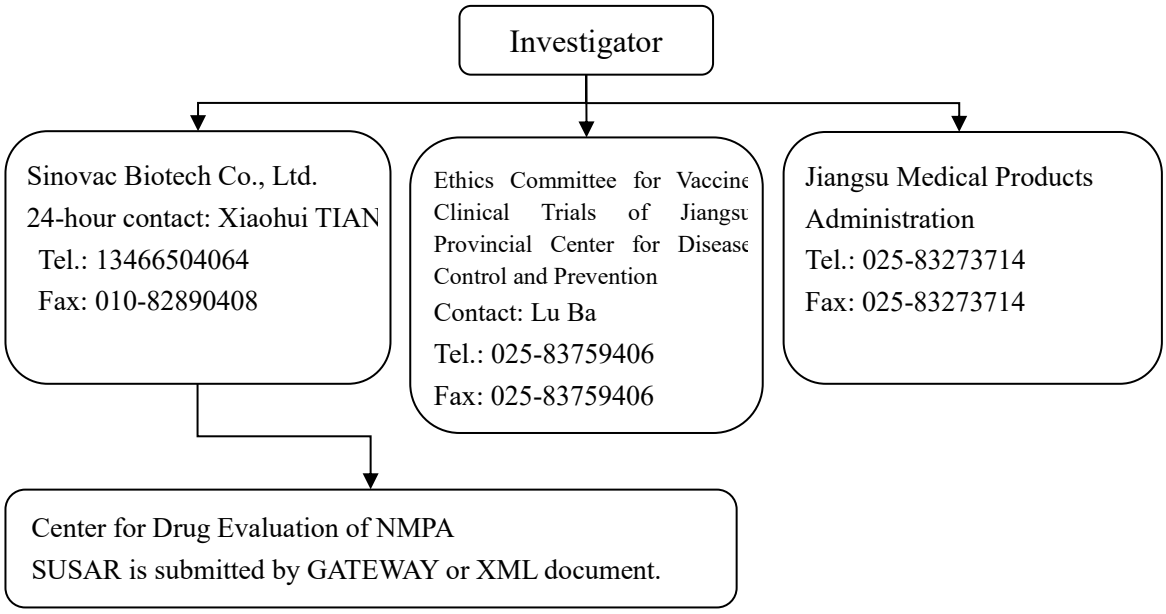
(1) The study institution should establish the emergency plan for handling of SAE. The investigator should immediately take measures and make records after he/she is informed of SAE. The investigator should report to the sponsor, the ethics committee and the local provincial drug regulatory authorities within 24 hours after the SAE is informed and submit the subsequent report. The study institution/ the investigator should timely transfer the latest safety information report related to the clinical trial of the sponsor to the ethics committee.
The ethics committee should receive the safety information reports such as SAE reports, timely grasp the occurrence and handling situations of SAE of the whole clinical trial, and carry out follow up review of the handling and reporting of SAE in the process of the clinical trial.

(2) When the sponsor receives information on vaccine safety from any source, an analysis and evaluation should be conducted, including the severity, relevance to the investigational vaccine, and whether it is an unexpected event.
During the drug clinical trial, the sponsor should quickly report the suspected unexpected serious adverse reactions (SUSARs) which are considered definitely or suspiciously related to the investigational drug in a maner of case safety report, according to the *Standards and Procedures for Rapid Reporting of Safety Data during Drug Clinical Trials*.

With regard to the fatal or life-threatening SUSARs, the sponsor should report them as soon as possible after beining informed within 7 natural days, and the relevant follow-up information should be reported within the subsequent 8 days (the day on which the sponsor is firstly informed is day 0); with regard to non-lethal or life-threatening SUSARs, the sponsor should report them as soon as possible within 15 naturak days; For other information indicating serious safety risk, the sponsor should also report them to the national drug evaluation institution, and make a medical and scientific judgment on each situation.

After the initial report, the sponsor should continue to follow up the SAE and submit new information or changes to the previous report in the form of follow-up report within 15 days since the date of obtaining new information. The sponsor should not arbitrarily change the investigator's judgment on the correlation between SAE and vaccine. If the opinions of the sponsor and the investigator are inconsistent, opinions of both parties should be recorded in detail in the repor, and the adverse event should be reported according to higher management requirements.

Under special circumstances, the invesgator and sponsor should promptly provide SAE-related information and safety reports as required by regulatory authorities and ethics committees.



9.7.8 Safety Evaluation Criteria

Solicited local adverse events, systemic adverse events and vital signs: The grading standard of solicited adverse events mainly refer to the *Guiding Principles for Grading Standards of Adverse Events in Clinical Trials of Vaccines for Prevention* (2019) [14] of NMPA. As shown in the table below, solicited adverse events and non-Solicited adverse events with the same symptoms are graded according to the following criteria:

Table17 Severity Grading Criteria for Local Adverse Events

	Grade 1	Grade 2	Grade 3	Grade 4
Pain	Not affecting or slightly affecting physical activity	Affecting physical activity	Affecting daily life	Loss of basic self-care ability, or hospitalization
Induration*#	Diameter 2.5 to <5 cm or area 6.25 to <25 cm^2 without affecting or slightly affecting daily life	5 to <10 cm in diameter or 25 to <100 cm^2 in area or affecting daily life	Diameter ⩾10 cm or area ⩾100 cm^2 or ulceration or secondary infection or phlebitis or aseptic abscess or wound drainage or seriously affecting daily life	Abscess, exfoliative dermatitis, dermal or deep tissue necrosis
Swelling #	Diameter 2.5 to <5 cm or area 6.25 to <25 cm^2 without affecting or slightly affecting daily life	5 to <10 cm in diameter or 25 to <100 cm^2 in area or affecting daily life	Diameter ⩾10 cm or area ⩾100 cm^2 or ulceration or secondary infection or phlebitis or aseptic abscess or wound drainage or seriously affecting daily life	Abscess, exfoliative dermatitis, dermal or deep tissue necrosis
Redness#	Diameter 2.5 to <5 cm or area 6.25 to <25 cm^2 without affecting or slightly affecting daily life	5 to <10 cm in diameter or 25 to <100 cm^2 in area or affecting daily life	Diameter ⩾10 cm or area ⩾100 cm^2 or ulceration or secondary infection or phlebitis or aseptic abscess or wound drainage or seriously affecting daily life	Abscess, exfoliative dermatitis, dermal or deep tissue necrosis
Rash* #	Diameter 2.5 to <5 cm or area 6.25 to <25 cm^2 without affecting or slightly affecting daily life	5 to <10 cm in diameter or 25 to <100 cm^2 in area or affecting daily life	Diameter ⩾10 cm or area ⩾100 cm^2 or ulceration or secondary infection or phlebitis or aseptic abscess or wound drainage or seriously affecting daily life	Abscess, exfoliative dermatitis, dermal or deep tissue necrosis
Pruritus	Itching at injection site, relieved within 48 hours	Itching at injection site, did not alleviate within 48 h after treatment	Affecting daily life	NA

* In addition to directly measuring the diameter for grading evaluation, sclerosis and rash should also record the progress of measurement results.

The maximum measured diameter or area should be used for induration and swelling, rash and red; evaluation and grading should be based on functional grade and actual measurement results, and higher grading indicators should be selected.

Table18 Severity Grading Criteria for Systemic Adverse Events

	Grade 1	Grade 2	Grade 3	Grade 4
Acute allergic reaction*	Local urticaria (blisters), no treatment required	Local urticaria need treatment or mild angioedema, no treatment required	Extensive urticaria or angioedema treated or mild bronchospasm	Anaphylactic shock or life-threatening bronchospasm or laryngeal edema
Skin and mucosa abnormality	Erythema/pruritus/color change	Diffuse rash/maculopapular rash/dryness/desquamation	Blister/exudation/desquamation/ulcer	Exfoliative dermatitis involving mucosa, erythema multiforme, or suspected Stevens-Johnsons syndrome
Diarrhea	Mild or transient, 3-4 times/day, abnormal stool, or mild diarrhea lasting less than 1 week	Moderate or persistent, 5-7 times/day, abnormal stool, or diarrhea >1 week	>7 times/day, abnormal stool, or hemorrhagic diarrhea, orthostatic hypotension, electrolyte imbalance, requiring intravenous infusion >2L	Hypotensive shock, hospitalization
Anorexia	Decreased appetite, not affecting food intake	Decreased appetite, reduced food intake, not affecting body weight	Decreased appetite, and significantly reduced body weight	Need intervention (such as gastric tube feeding, parenteral nutrition)
Vomiting	1-2 times/24 hours without affecting activity	3-5 times/24 hours or affecting activity	>6 times within 24 hours or requiring intravenous fluid infusion	Hospitalization or other nutrition routes 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 requires intravenous fluids	life threatening (e.g., hypotensive shock)
Muscle pain (non-inoculated site)	Does not affect daily activities	Slightly affects daily activities	Severe muscle pain, seriously affects daily activities	Emergency or hospitalization
Headache	Not affecting daily activities, no treatment required	Transient, slightly affecting daily activities, may need treatment or intervention	Seriously affecting daily activities, need treatment or intervention	Intractability, need emergency or hospitalization
Cough	Transient, no treatment required	Persistent cough, effective treatment	Paroxysmal cough, uncontrolled treatment	Emergency or hospitalization
Fatigue	Normal activity is weakened <48 hours, without affecting the activity	Normal activity is weakened by 20%~50%>48 hours, slightly affecting the activity	Normal activity is weakened by >50%, seriously affecting daily activities, unable to work	unable to take care of oneself, emergency or hospitalization
Vital Signs				
Fever, axillary temperature	37.3～＜38.0	38.0～＜38.5	≥38.5	≥39.5, Lasting more than 3 days

* Refers to type I hypersensitivity

Laboratory indicators: first, the judgment of clinical significance is made. When the judgment is "abnormal and clinically significant", the grading will be made referring to the *Guiding Principles for Grading Standards of Adverse Events in Clinical Trials of Vaccines for Prevention* (2019) [14], *Guiding Principles for Grading Standards of Adverse Reactions in Clinical Trials of Vaccines for Prevention* (2005) (only creatinine indicators)[15] and the *Clinial Assessmet Grading Criteria* of the National Institutes of Health (NIH) and National Institute of Allergy and Infectious Diseases (NIAID) (Platelet Indicators Only) [16], as shown in the table below:

Table19 Severity Grading Criteria of Blood Routine Index Abnormality

Index/grade	Grade 1	Grade 2	Grade 3	Grade 4
Elevated white blood cell account (WBC, 10^9/L)	11~＜13	13～＜15	15～＜30	≥30
Decreased white blood cell account (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
Platelets account (10^9/L)	75-99.999	50-74.999	20-49.999	<20

Table 20 Severity Grading Criteria of Blood Biochemistry Index Abnormality

Index/grade	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
Total bilirubin increased (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

Note: ULN refers to the upper limit of the normal range.

Table21 Severity Grading Criteria of Routine Urinary Index Abnormality

Index/grade	Grade 1	Grade 2	Grade 3	Grade 4
Urinary protein (PRO) (Urine dipstick test)	1+	2+	3+or higher	NA
Urine Glucose (Urine dipstick test)	Trace～1+ or≤250mg	2+ or＞250～≤500mg	＞2+ or＞500mg	NA
Red blood cells (microscopy) [Red blood cell count per high magnification field of view (rbc/hpf) (Exclude female menstruation)]	6～＜10	≥10	Macroscopic hematuria with or without blood clots; or cylindrical urinary red blood cells; or need treatment	Emergency or hospitalization

For adverse events not covered in the above grading table, the intensity of adverse events was graded according to the following criteria:

Grade 1 (Mild): transient (<48 hours) or mild discomfort; no medical intervention/therapy required.

Grade 2 (Moderate): mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention/ therapy required.

Grade 3 (Severe): Marked limitation in activity; some assistance usually required; medical intervention/therapy required, hospitalizations possible.

Grade 4 (Life threatening): Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

Grade 5: Death.

9.8 Concomitant Drugs and Vaccines

9.8.1 Concomitant Drugs

－ In case of adverse events during the trial, necessary drug treatment and medical treatment are allowed.
－ In case of serious allergic reactions or life-threatening events, first aid measures should be taken immediately.
－ Investigators should record any information of concomitant drugs, including name, dosage form, dosage and administration route, administration time, etc.

9.8.2 Concomitant Vaccines

－ Other vaccines should be administered at least 7 days apart after the investigational vaccine administration.
－ Subjects can be administered with other vaccine such as rabies vaccinbe and tetanus vaccine against the emergency events during the clinical trial.
－ Relevant information of the concomitant vaccine should be recorded in detail, including the vaccine name, administration, vaccination time etc.

9.9 Immunogenicity Evaluation

Humoral immunity: blood samples collected at different time points were tested for neutralizing antibody, IgG and IgM (IgG and IgM tests are only applicable for Phase I clinical trials), and the seroconversion rate, positive rate, GMT and GMI of neutralizing antibody were calculated, as well as the positive rates of IgG and IgM antibodies were calculated.
Cellular immunity: (only applicable for Phase I clinical trial): blood sample collected at different time points were test for the specific T cell response by the IFN-γ detection using the Elispot method.

9.9.1 Evaluation Criteria

- Evaluation criteria for serum neutralizing antibody (Nab)

The criteria for determining serum antibody positivity are as follows:
- The seropositivity is defined as Nab titer is≥1:8

The criteria for determining serum antibody seroconversion are as follows
- The seroconversion is defined as a post-vaccination Nab titer ≥1:8 if seronegative (<1:8) at beseline, or a 4 fold increase of Nab titer if seropositive (≥1:8) at baseline.

- IgG and IgM Evaluation Criteria
  See the test kit instructions for details.

9.9.2 Laboratory Test Methods

➢ Serum antibody detection:
- Neutralizing antibody detection - microneutralization test method;
- (ELISA) IgG/IgM detection - Enzyme-linked immunosorbent assay (ELISA)

➢ Specific T cell response by the IFN-γdetection: Enzyme-linked immunospot assay (ELISPOT) (Peripheral blood mononuclear cells)

9.10 Data Management

9.10.1 Original Materials

The original materials include informed consent form, diary card, original logbook, etc., recording

the following basic data:
- Trial name, subject number
- Demographic data
- Inclusion/exclusion criteria
- Vaccination records
- Follow-up date and date of discontinuation of the trial discontinuation date of the subject
- Adverse events/reactions and the corresponding treatment and outcome
- Concomitant medical treatment and other vaccinations

All data should have original records, which should be properly kept by investigaors in a dedicated space. The original data should be archived in the study site, which is the true and complete evidence for the particpantion of the subjects in the clinical trial.

The investigators should carefully, accurately and timely make the original records. All the collected original data should be recoreded on the same day with that of the data collection. Additionally, the raw data should be recorded using the black sign pen, and the mistake record should be crossed out with the correct content being written beside it along with the signature of the modifier, instead of be altered directly.

9.10.2 Case Report Forms (CRF)

"Electronic Data Capture (EDC) System" is adopted to establish the electronic CRF in this trial.

Electronic CRF is used to record the data of clinical trials, which is an important component of clinical trials and study reports. The electronic CRF is required to be inputted according to the system using instructions and CRF filling-in instructions, using the normative language.

All data on the electronic CRF are derived from the original material and are consistent with original data. Any entry, verification, modification, cleaning and quality control processes of electronic CRF data will be recorded in the EDC system. After data cleaning, the principle investigator should confirm the data in each CRF and sign with electronic signature.

Only investigator and approved staff are allowed to access to the EDC system during the trial period.

9.10.3 Data Lock

Final data verification should be carried out after the completion of all the data entry, verification and data cleaning work. The analyzed population, the situation of protocol violation as well as its impact on the analyzed population should be determined according to the assessment indicators, and then the database is locked.

9.10.4 Subject Privacy Protection and Data Utilization Scope

All information concerning the identity of the subject will be kept confidential and the name of the subject will not appear in any publication or report of the study. The study records will be provided to the sponsor representative in the presence of the investigator for the purpose of collecting medical data. In addition, the CRA, auditors, representatives of the Ethics Committee of Vaccine Clinical Trials of the Jiangsu CDC, and representatives of the National Drug Administration (NMPA) can review the original material of subjects related to this study as required, to confirm the accuracy of the data collected in this study. The original data obtained in this study are only for publication of papers or results related to this project.

9.11 Statistical Analysis

9.11.1 Analysis Set

9.11.1.1 Safety Analysis Set (Safety Set, SS)

All randomized subjects who completed at least one vaccination were included in the safety evaluation set. Subjects who are vaccinated with the wrong vaccine will be tansfered to the group of actually administered vaccine according to the ASaT principle (All Subjects as Treated), for the safety evaluation.
Safety sets in this study include generl safety set (SS), safety set of dose 1 (SS1), and safety set of dose 2 (SS2).Among them, the general SS includes subjects who have completed at least one dose of vaccination; the SS1 includes subjects who have completed the first dose of vaccination; the SS2 includes subjects who have completed the second dose of vaccination.

9.11.1.2 Immunogenicity Analysis Set

Full Analysis Set (FAS): A population defined according to the principle of intent analysis (ITT), including all the subjects who have been randomized, have received at least one dose of vaccination, have finished blood collection before/after vaccination for at leat one time with the corresponding antibody assay results provided. The subjects who are vaccinated with the wrong vaccine will be kept in the originally assigned group according to the ITT principle, for the immunogenicity evaluation.
Per-Protocol Set (PPS): A subset of FAS, including all the subjects who meet the inclusion criteria and don't meet the exclusion criteria, have been randomized, have finished the full-course vaccination within the protocol required time window, and have finished the blood collection before/after vaccination with the corresponding antibody assay results provided. Subjects who meet the following conditions are not allowed to enter PPS:
1) Those who violate the test scheme;
2) Those who are vaccinated with the wrong vaccine;
3) Use of protocol prohibited vaccines or drugs:
①Other investigational or unlicensed products (drugs or vaccines)
②long-term use (lasting more than 14 days) of immunosuppressive or other immunomodulatory drugs (inhaled or topical steroids are allowed)
③Immunoglobulin and/or blood preparations
4) Newly diagnosed autoimmune diseases, including human immunodeficiency virus (HIV) infection;
5) Other situations affecting the evaluation of vaccine immunogenicity.

9.11.2 Statistical Analysis Methods

9.11.2.1 General Principles

Measuring data are described by means, standard deviations, medians, maximum, and minimum value; counting data or grade data are described by frequencies. All statistical analyses are performed using statistical software SAS 9.4.

9.11.2.2 Characteristics of Subject Population

The number of subjects who were screened, enrolled and completed the trial, and the number of subjects in each statistical analysis data set should be summarized, and the reasons for the dropout should be analyzed. The list of subjects who failed in screening, who dropped out and who did not enter each analysis set were listed separately.

9.11.2.3 Evaluation of Immunogenicity

The seroconversion rate and positive rate of antibodies in the medium dosage group, high dosage group, and placebo group should be calculated respectively, and Clopper-Pearson method will be adopted to calculate the corresponding 95% confidence interval. Chi-square test/Fisher exact

probability method will be used to conduct statistical test on difference between groups.
Geometric mean titer (GMT) and geometric mean increase (GMI) of the serum antibody, as well as the corresponding 95%CI in the experimental group and the control group should be calculated, and and the difference between groups was statistically tested using the ANOVA after log-transfermation of the anytibody titer.
The positive rates of IgG, IgM antibody and specific T cell response after immunization should be analyzed by the same statistical method as the analysis of positive rate of neutralizing antibody.

9.11.2.4 Evaluation of Safety

Adverse events were medically coded using MedDRA. This study mainly analyzes the adverse events after vaccination, and the adverse events before vaccination will be listed.
The number of episodes, number of involved subjects, as well as the incidence rate of overall AEs, the vaccine-related AEs, and the vaccine-unrelated AEs in all the groups should be calculated separately, and the differences between groups will be statistically tested using the Fisher exact probability method. The severity, dose distribution and time distribution of general AEs as well as the vaccine-related AEs should be statistically analyzed. The list of the vaccine-related AEs, vaccine-unrelated AEs should be made separately. The AEs after each dose should be statistically analyzed based on the safety set of each dose respectively.
The number of epidoses, number of involved subjects, as well as the incidence rate of overall SAEs, the vaccine-related SAEs, and the vaccine-unrelated SAEs in all groups should be calculated separately, and the differences between groups will be statistically tested using the Fisher exact probability method. The list of the SAEs should be made.
The changes of blood routine, blood biochemistry and urine routine test results before and after the vaccination are statistically described, and the changes of clinical significance before and after vaccination will be described in the form of cross table.

9.11.2.5 Processing of Missing Data

With regard to the statistical analysis of FAS, the missing data of the post-vaccination antibody test result will be filled by the method of Last Observation Carried Forward (LOCF). The missing data of the pre-vaccination antibody result will be filled with the maximum of pre-vaccination antibody results among all the subjects. In terms of the evaluation of the exploratory and safety endpoints, missing data will not be filled.

10 Monitoring of Clinical Trials

10.1 Responsibilities of the Sponsor

The sponsor executes and maintains the quality assurance and quality control system, compiles quality management documents to ensure that the clinical trial is carried out in accordance with regulations, and that data, records and reports meet the requirements of GCP, other regulations and the protocol.

10.2 Responsibilities of the Investigator

The principal investigator should manage and clearly divide all personnel involved in the clinical trial. The personal data of the subjects should be kept confidential by the investigators. Documents provided to the sponsor should be identified only by the subject number. The identification list of subjects is kept in the investigator documents. In accordance with GCP principles, the original materials of each subject are allowed to be monitored, audited and verified.

10.3 Personnel Training

Before the start of the trial, the sponsor and the principal investigator should train the staff involved in the clinical trial in a meeting manner. The training contents include clinical trial protocol, trial implementation procedure, time arrangement, operation precautions, trial data filling-in, etc. Newly added CRA or investigator during the trial should be trained individually during the trial. If the sponsor or principal investigator deems it necessary, retraining may be conducted. Each training should have training records.

10.4 Subject Compliance Guarantee

According to the clinical trial protocol, a concise, clear and well organized volunteer recruitment form and informed consent form were formulated.
Train the doctor responsible for the informed explaination to communicate with volunteers in plain and understandable language so as to be fully informed.
Screen the subjects strictly according to the inclusion and exclusion criteria.
The Follow-up personnel should have a high sense of responsibility and dedication to improve their communication skills and affinity through training. In the process of safety follow-up, measures should be taken to ensure effective contact between subjects and investigators, and adverse reactions should be disposed timely with the related health consultation provided.

10.5 Report of Deviations/Violations of Protocol

Field investigators authorized by the principal investigator should report to the principle investigator immediately after they discover clinical trial protocol deviations/violations or receive reports of deviations/violations of that. The ongoing deviations/violations (except for over-window vaccination/sample collection) should be timely stopped. In terms of the deviation/violation of the protocol that has occurred, written/e-mail responses from sponsor and principal investigators should be awaited.

10.6 Vaccine Management in Clinical Trials

10.6.1 Definition and Treatment of Cold Chain Failure

Once the refrigerator storing the vaccine has a temperature of <2℃ and >8℃, it is recorded as cold chain failure. Once there is a cold chain failure, the vaccine should be transported to a light-protected environment for storage as soon as possible, with reprting to the sponsor in time. The decision of whether stop or continue using the vaccine should be made according to the written/e-mail responses from sponsor.

10.6.2 Receiving of Vaccine for Trial

When the sponsor delivers the trial vaccine to the study site, the investigator must sign the vaccine receipt form, on which the information (e.g. complete package, and normal cold chain system indication etc.) should be described briefly. When the investigator finds that the vaccine is damaged, spoiled, or has lumps that cannot be shaken in it, such vaccine should be prohibited to be used, and should be returned to the sponsor. In the case of cold chain failure or freeze during the transport or storage process, the vaccine can not be used. The vaccine with the above problems should be marked with '×' on the surface of the outer package and stored separately, managed by a dedicated staff and finally returned to the sponsor.

10.6.3 Management of Trial Vaccines

Trial vaccines should be managed by a dedicated staff and supervised by CRA. The vaccine receipt and transfer record should include the number of received vaccine, the number of vaccinated subjects, the number of remaining vaccine and the number of losses. The investigators will calculate

the number of all the trial vaccine.When the field work is completed, the remaining trial vaccines are counted and returned to the sponsor when the study site.

10.7 Management of Clinical Trial Sample

Specimens used for blood routine, blood biochemistry, urine routine, inflammatory factors, anti-nuclear antibodies and T-cell response testing should be disposed by the testing institution as medical waste after completion of the testing. The backup serum is temporarily stored by the study site institution, until a verified immunogenicity test report is issued by the testing institution. The backup serum can be stored or processed by the sponsor after the project is completed, and its use needs the approval of the ethics committee and the informed consent of the subjects.

10.8 Preservation of Clinical Trial Data

The clinical trial data must be kept according to the requirements of the Appendix 2 of GCP, and study institution should keep the clinical trial data for at least 5 years after the trial termination. The sponsor should keep the clinical trial data for at least 5 years after the drug is marketed.

10.9 Ending Criteria for Clinical Trials

-Samples collected in the clinical trial are sent to the testing institution, and the corresponding testing reports are issued.
-All subjects completed the required visit, and the original data and documents of the clinical trial are transferred to the archivist for archiving and preservation;
-The remaining amount of the trial vaccine is accurate and handed over to the sponsor;
-The statistical analysis report and summary report meet the requirements of the sponsor.

11 Ethical Approval

11.1 Review and Approval

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

11.2 Implementation of On-site Supervision

In the whole process of the trial, the ethics committee should supervise whether there are ethical problems of harming the subjects, whether the subjects get treatment, compensation and corresponding measures when they are harmed by the trial, and evaluate the degree of risk they bear.

11.2.1 Informed Consent Form and Informed Consent

It should be ensured that the method of selection of subjects and relevant information provided to subjects are complete and easy to understand, and the method of obtaining informed consent is appropriate. During the whole process of the trial, the ethics committee should regularly review the progress of the trial and assess the risks and benefits of the subjects.

11.2.2 The Potential Hazards and Hazard Minimization

If the adverse reactions are determined to be related to vaccination (the injection site abscess and rash after vaccination), the subjects will be treated in time according to relevant regulations.
If a life-threatening event occurs, the subject will be escorted to the hospital for treatment

immediately and the corresponding report should be made.

Under strict supervision, the trained and experienced medical personnel conduct vaccination and venous blood collection in accordance with the prescribed procedures, so as to minimize the injury and suffering caused by vaccination and blood collection (including pain and local infection at the venipuncture site with little probability).

11.2.3 Protection Measures for Subjects

Clinical trials were conducted in county/city centers for Disease Control and prevention with vaccination qualifications. The sponsor examine the study site strictly according to the requirement of the GCP, before the start of the clinical trial. The environment and facilities of the study site should meet the requirements of *The Guiding Principles for Quality Management of Vaccine Clinical Trials (Trial)*. The emergency plan for the damage and emergency of the subjects should be prepared by the study site. Doctors and nurses with corresponding qualifications and experience should be arranged in the physical examination room and blood collection room in order to strictly grasp the inclusion/exclusion criteria and collect blood smoothly. The first-aid room should be equipped with appropriate first-aid facilities, equipment and drugs, and the first-aid doctors shall have corresponding qualifications and capabilities. When the subjects have adverse events at the study site, they should be treated in the on-site emergency room in time. If they need emergency hospitalization treatment, the ambulance equipped on the study site will send the subjects to the agreement hospital for treatment after the condition is stable though the on-site treatment. The ambulance should also be equipped with necessary first-aid facilities and drugs.

The study site signs a green channel agreement with a local county-level and above general hospital. During the enrollment of the subjects, the agreement hospital should be notified to prepare for timely treatment. Measures shall be taken to ensure that the emergency adverse events can be dealt with in a timely manner, such as personnel responsibilities, telephone number and rescue route. The effective contact between the subjects and the investigator should be maintained, so that any adverse events can be reported and disposed quickly. When the subjects need to be hospitalized for emergency treatment after serious adverse events, the agreement hospital can provide green channel services such as medical treatment, hospitalization and medical security, to ensure that the subjects can be treated in time. The investigator followed up the progress of the event and completed the investigation record until the end of the serious adverse event.

11.3 Confidentiality

It should be ensured that the personal secrets of the subjects are not disclosed under the conditions of the trial enrollment, biological sample collection, report and publication. The recorded information of the test samples only includes the subject number, sample number, sampling time, and testing indicators. Only the main personnel of the study have the anthority to obtain electronica or written copies.

12 Revision of Clinical Trial Protocol

After the sponsor and investigator sign the clinical trial protocol, if there is any modification to the protocol, all the modified protocols shall be re signed and dated by the main investigator and sponsor, and the protocol before modification shall be attached.

All modification plans shall be reported to the ethics committee and approved by the ethics committee before implementation. When modifying the scheme, it is necessary to point out whether it is necessary to modify the informed consent form and electronic CRF form.

13 The Publicity and Publication of Data

After the completion of this clinical trial, if the test results need to be open and/or published, the positive results and the negative results will be open and/or published together.

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