PROTOCOL COVER PAGE

Brief Title:	A phase II clinical trial of the recombinant novel coronavirus vaccine (adenovirus type 5 vector)
Full Title:	A randomized, double-blind, placebo-controlled phase II clinical trial of the recombinant novel coronavirus vaccine (adenovirus type 5 vector) in healthy adults aged 18 years and above in China.
Protocol Number:	JSVCT089
ClinicalTrials.gov	NCT04341389
Protocol Date:	May 9, 2020
Protocol Version:	Version 1.2 (final)
Phase:	Phase II
Sponsor:	Beijing Institute of Biotechnology CanSino Biologics Inc.
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DOCUMENT HISTORY

Version No.	Version Date	Amendment
1.0	March 25, 2020	N/A
1.1	April 02, 2020	1st Amendment
1.2	May 09, 2020	2nd Amendment

Information of the 1st Amendment

Contents in Original Version (1.0)		**Contents in Altered Version (1.1)**	
Chapter	**Original Contents**	**Page/Row**	**Altered Contents**
Chapter 9.1	Participants selection Healthy people aged 18 to 60 years are selected as the target population.	Chapter 9.1	Modified to: Participants selection Healthy people aged 18 years and above are selected as the target population.
Chapter 10.4.1	Methods of safety observation After vaccination, all participants will be required to stay in the designated temporary lodgment for safety observation for 14 days.	Chapter 10.4.1	Methods of safety observation Within 14 days after vaccination, the participants will be asked to complete the safety observation by themselves, and record the results on the "diary card".

Information of the 2nd Amendment

Contents in Original Version (1.1)		**Contents in Altered Version (1.2)**	
Chapter	**Original Contents**	**Page/Row**	**Altered Contents**
Chapter 3.5	Detection party National Institutes for Food and Drug Control, etc.	Chapter 3.5	Modified to: Detection party National Institutes for Food and Drug Control.

			Beijing Institute of Microbiology and Epidemiology
Chapter 8.2.2	Secondary endpoint: Immunogenicity	Chapter 8.2.2	Add: Secondary endpoint: Immunogenicity -The positive rate and level of IFN-γ stimulated by S protein overlapping peptide library at day 28 measured by ELISpot.
Chapter 8.3	Table 8-3-1-2 Clinical trial visit Blood Collection schedule	Chapter 8.3	Modified to: Table.8-3-1-2 Blood collection at scheduled visits Visit No.: V0; V1; V2; V3 Visit time: Day 0; Day 14; Day 28; Month 6 Visit interval: Day 0; V0+14 days; V0+28 days; V0+6 months Time window: —; (±2 days); (±3 days); (±15 days) SARS-CoV-2 antibody test: Fingertip blood; —; —; — HIV antibody test: Fingertip blood; —; —; Fingertip blood Virus preparation / cellular immunity (anticoagulant blood): 5ml; —; —; — Humoral immunity (procoagulant blood): 10ml; 10ml; 5ml; 10ml Cellular immunity (anticoagulant blood): —; —; 5ml; —
Chapter 9.4	Withdraw from the study: -The participants with SARS-CoV-2 infections during the period from the day of vaccination to 28 days after vaccination will not be included in the immunogenicity analysis, but all participants with SARS-CoV-2 infections occur within one year after vaccination should be analyzed in accordance with the requirements of SAE, especially the	Chapter 9.4	Modified to: Withdraw from the study: -The participants with SARS-CoV-2 infections during the period from the day of vaccination to 28 days after vaccination will not be included in the immunogenicity analysis, but all participants with SARS-CoV-2 infections occur within six months after vaccination should be analyzed in accordance with the requirements of SAE, especially the

	existence of ADE phenomenon.		existence of ADE phenomenon.
Chapter 10.4.5	Report of SAEs	Chapter 10.4.5	Add the contents of report procedures
Chapter 10.5	Collection and detection of biological samples	Chapter 10.5	Add: Collection and detection of biological samples 10.5.4 Detection of IFN-γ secreted by specific T cells 10.5.4.1 Detection time point IFN-γ secreted by specific T cells will be detected at day 0 and day 28 after vaccination. 10.5.4.2 Evaluation content The positive rate of T cell response on the 28th day of vaccination will be used as the main evaluation index of immunogenicity. The differences of antibody levels among different groups and the changes of T cell reaction positive rate at each time point pre-vaccination and the post-vaccination will be compared.

Chapter 11.1	Responsibilities of all parties Zhongnan Hospital of Wuhan University is involved in design, organization and arrangement, recruitment, SARS-CoV-2 antibody screening, urine pregnancy test, HIV test, registration, informed consent, physical examination, determination of excretion, sample collection and treatment, vaccination, observation, safety follow-up assistance, etc. National Institutes for Food and Drug Control is responsible for the detection of immunogenicity indicators and issues a test report.	Chapter 11.1	Modified to: Responsibilities of all parties Zhongnan Hospital of Wuhan University is involved in design, organization and arrangement, recruitment, SARS-CoV-2 antibody screening, urine pregnancy test, HIV test, registration, informed consent, physical examination, determination of excretion, sample collection and treatment, vaccination, observation, safety follow-up assistance, cellular immunity detection, etc., and assisted the medical waste disposal of the Wuhan Special Service Recuperation Center of the Chinese People's Armed Police Force. Be fully responsible for first aid during vaccination and establish a "green channel".

			National Institutes for Food and Drug Control and Beijing Institute of Microbiology and Epidemiology are responsible for the detection of humoral immunity indicators and issue test reports.
Chapter 1.3.2	Case report form (CRF).	Chapter 1.3.2	Modified CRF to eCRF

PROTOCOL SUMMARY

Brief Title	A phase II clinical trial of the recombinant novel coronavirus vaccine (adenovirus type 5 vector) in healthy adults
Official Title	A randomized, double-blind, placebo-controlled phase II clinical trial of the recombinant novel coronavirus vaccine (adenovirus type 5 vector) in healthy adults aged 18 years and above in China.
Objectives	To evaluate the immunogenicity and safety of the recombinant novel coronavirus vaccine (adenovirus type 5 vector) in healthy adults aged 18 years and above.
Target disease	To prevent COVID-19 caused by SARS-CoV-2
Target population	Healthy adults aged 18 years and above
Sample size	About 500 participants
Rational and background	SARS-CoV-2 is an unsegmented single-stranded positive-strand RNA virus, which belongs to the subfamily of the family Coronaviridae. Six coronaviruses are known to be able to infect humans, including 229E, OC43, HKU1, NL63, Middle East Respiratory Syndrome associated coronavirus (MERS-CoV) and severe acute respiratory syndrome associated coronavirus (SARS-CoV). SARS-CoV-2 is a novel coronavirus isolated from the secretions of lower respiratory tract of patients with unexplained pneumonia in Wuhan, which belongs to β genus. After the outbreak of SARS-CoV in 2002 and the outbreak of MERS-CoV in 2012, SARS-CoV-2 is the third highly pathogenic coronavirus found in humans in the past 20 years. The recombinant novel coronavirus vaccine (adenovirus type 5 vector) is jointly developed by the Beijing Institute of Biotechnology and CanSino Biologics Inc., to prevent COVID-19 caused by SARS-CoV-2 infection. The vaccine uses replication-defective human adenovirus type 5 as the vector and

	expresses the specific S protein of SARS-CoV-2, which is prepared by amplification and purification. Preclinical studies suggest that both humoral and cellular immune responses play important roles in protective immunity. Phase I clinical trial of this recombinant novel coronavirus vaccine (adenovirus vector) was launched in Wuhan on March 16, 2020. This trial included low, middle and high dose groups, 36 participants in each group, who were vaccinated with 5×10^{10}vp, 1×10^{11}vp and 1.5×10^{11}vp recombinant novel coronavirus vaccine (adenovirus vector), respectively. The results showed that the total incidence of adverse events within 7 days after vaccination in the low, middle and high dose groups was 77.8%, 86.1% and 72.2%, respectively, and the incidence of grade 3 adverse events was 5.6%, 5.6% and 16.7%, respectively, with no grade 4 adverse event. Low and middle dose recombinant novel coronavirus vaccine (adenovirus vector) showed good safety in human, and high dose recombinant novel coronavirus vaccine (adenovirus vector) showed clinically tolerable safety. The immunogenicity among low, middle and high dose groups showed a dose-response relationship. Based on the safety and immunogenicity results of phase I clinical trial, low dose (5×10^{10}vp) and middle dose (1×10^{11}vp) recombinant novel coronavirus vaccine (adenovirus vector) were selected for a larger phase II clinical trial to further evaluate the immunogenicity and safety of this recombinant novel coronavirus vaccine (adenovirus vector) in healthy adults aged 18 years and above.
Investigational vaccine	The recombinant novel coronavirus vaccine (adenovirus type 5 vector): Manufactures: Beijing Institute of Biotechnology and CanSino Biologics Inc. 0.5ml/vial (5×10^{10}vp).

	Batch numbers: 202003002C, 202003003C, 202003004C. Valid until: 2022.03.10. Package: vials Immunization: one shot intramuscular injection at the lateral deltoid muscle of the upper arm. Temperature for storage and transportation: at 2-8 ℃ Placebo control: Manufactures: Beijing Institute of Biotechnology and CanSino Biologics Inc. 0.5ml/vial (0vp). Batch number: P202003001C Valid until: 2022.03.09. Except for replication defective human type 5 adenovirus which can express SARS-CoV-2 S protein, other components of placebo control were consistent with those of the test vaccine and it was qualified by National Institutes for Food and Drug Control. Immunization: one shot intramuscular injection at the lateral deltoid muscle of the upper arm.

<table>
<tr>
<td>Trial design</td>
<td>
Study design: A randomized, double-blind, placebo-controlled phase II clinical trial.
Sample size: this phase 2 trial will be launched before we obtaining the immunogenicity data from the phase 1 trial. Therefore, the sample size of is not calculated, but determined based on expert experiences and the minimum sample size requirement in the technical guidelines for vaccine clinical trials issued by National Medical Products Administration, China. The final sample size is 250 in the middle dose group, 125 in the low dose group and 125 in the placebo group, with a total sample size of 500.
Randomization and blinding:
In this study, randomization and blindness will be achieved by blinding the investigational vaccines.
Study plan:
This trial includes three study groups: middle dose vaccine group (n=250), low dose vaccine group (n=125) and placebo control group (n=125). 4 visits are needed for each participant from screening before vaccination to completing the study. See the following table for grouping.
<table>
<tr><th>Group</th><th>Antigen content</th><th>No.</th></tr>
<tr><td>Middle</td><td>1×10^{11}vp</td><td>250</td></tr>
<tr><td>Low</td><td>5×10^{10}vp</td><td>125</td></tr>
<tr><td>Placebo</td><td>0vp</td><td>125</td></tr>
<tr><td>Total</td><td>-</td><td>500</td></tr>
</table>

Infection during the study period:
During the study period, participants with sustaining fever, cough and other respiratory symptoms should immediately visit the designated hospital (Zhongnan Hospital of Wuhan University) and inform the investigators. The nasopharyngeal
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	swabs or sputum and anal swabs will be collected and CT or other imaging examinations will be performed to identify SARS-CoV-2 associated infection. If a COVID-19 case is confirmed during the clinical trial, the case investigation should be carried out, and the virus preparation blood will be used for SARS-CoV-2 detection. If the severity of the COVID-19 case is classified as severe or fatal, severe or fatal case investigation should be carried out. Duration of the study: It will take about 6 months for each participant to complete the study, from recruiting to the last visit. Some participants may withdraw during the study.
Endpoints	**Primary endpoint:** 1.Safety endpoint. – The incidence of adverse reaction (AR) from 0 to 14 days after vaccination in each study group. 2.Immunogenicity endpoint. – Geometric mean titer (GMT) of specific antibody against SARS-CoV-2 S protein (ELISA method) at day 28 after vaccination in each study group. – The geometric mean titer (GMT) of SARS-CoV-2 specific neutralizing antibody (live SARS-CoV-2 and pseudovirus neutralization test) at day 28 after vaccination. **Secondary endpoints:** Safety: – The incidence of adverse events (AE) from 0 to 14 days after vaccination in each study group. – The incidence of adverse events (AE) from 0 to 28 days after

	vaccination in each study group. - The incidence of severe adverse events from 0 to 28 days after vaccination in each study group. - The incidence of serious adverse events within 6 months after vaccination in each study group. Immunogenicity: - Geometric mean titer (GMT) of specific antibodies against SARS-CoV-2 S protein (ELISA method) in each study group at day 14 and month 6 after vaccination. - Geometric mean titer (GMT) of SARS-CoV-2 specific neutralizing antibody (live SARS-CoV-2 and pseudovirus neutralization test) in each study group at month 6 after vaccination. - The seroconversion rate of SARS-CoV-2 S protein specific antibody (ELISA method) in each study group at day 14, day 28 and month 6 after vaccination. - The geometric mean fold increase of SARS-CoV-2 S protein specific antibody (ELISA method) in each study group at day14, day 28 and month 6 after vaccination. - The seroconversion rate of SARS-CoV-2 specific neutralizing antibody (live SARS-CoV-2 and pseudovirus neutralization test) in each study group at day 28 and month 6 after vaccination. - The geometric mean fold increase of SARS-CoV-2 specific neutralizing antibody (live SARS-CoV-2 and pseudovirus neutralization test) in each study group at day 28 and month 6 after vaccination. - Geometric mean titer (GMT) of specific neutralizing antibody against Ad5 vector at day 28 and month 6 after vaccination in each study group. - The geometric mean fold increase of specific neutralizing antibody against Ad5 vector in each study group at day 28

	and month 6 after vaccination. – At day 28 after vaccination, the positive rate, conversion rate and level of IFN-γ stimulated by S protein overlapping peptide library will be detected by ELISpot. For uncertain values: when calculating GMT, GMI and seroconversion of antibodies, if the antibody level is below the initial detection limit, half of the initial value will be calculated; if the antibody level is greater than the maximum detection limit, the maximum dilution will be calculated. **Exploratory Endpoints** – The consistency analysis of the specific antibody against SARS-CoV-2 S protein (ELISA method) and the specific neutralizing antibody. – The persistence of specific antibodies against SARS-CoV-2 S protein after vaccination in each study group.
Scheduled site visits	This study has 4 scheduled visits, including V0 (day 0), V1 (day 14), V2 (day 28), V3 (month 6) V0 (day 0): The participants will be screened, randomly divided into different groups, collected blood samples before vaccination, vaccinated and observed. V1 (day 14), V2 (day 28), V3 (month 6): Adverse events will be observed, peripheral venous blood will be collected each time to separate serum for immunogenicity detection.
Criteria for pausing or early termination	The investigators will collect daily reports of adverse events after vaccination and report to the Data Safety Monitoring Board (DSMB) every day. The DSMB independently analyzes the post-vaccination safety data in each dose group, and if an increased risk of participants is found in the course of the study, they will send notice to the principal investigator and the sponsor will immediately suspend or terminate the clinical trial. If there is a violation of the protocol, GCP or ethical requirements, the sponsor, the principal investigator, the ethics committee or the

	administrative department shall have right to suspend or terminate the study, and shall notify other parties and participants and explain the reasons. Criteria for study suspension: - One or more ≥grade 4 adverse reaction or serious adverse event may be associated with vaccination Criteria for early termination of the study: - Grade 4 adverse reactions or serious adverse events that may be related to vaccination occur during the study, which will be discussed jointly by the investigators and the sponsor, and the DSMB will finally decide whether to terminate the trial. - Occurrence of grade 3 adverse events associated with vaccination in 15% of participants or more (including injection-site reaction, systemic reaction, and abnormal laboratory indexes), which will be discussed jointly by the investigators and the sponsor, and the DSMB will finally decide whether to terminate the trial, or - Required by sponsor, or - Required by ethics committee, or - Required by administrative department in charge.
Statistical analysis	First analysis: After the last participant complete V2 (day 28), data on the safety, humoral immunogenicity and cellular immunogenicity will be allowed for first analysis. Final analysis: After the last participant complete V3 (month 6), data on the safety, humoral immunogenicity and cellular immunogenicity will be allowed for final analysis.
Inclusion criteria	- Aged 18 years and above. - Able to understand the content of informed consent and willing to sign the informed consent - Able and willing to complete all the scheduled study process

	during the whole study follow-up period (about 6 months). – Negative in HIV diagnostic blood test – Axillary temperature ≤37.0°C – Negative serum IgM and IgG to the SARS-CoV-2 – A body mass index (BMI) is between 18.5 and 30.0 – General good health as established by medical history and physical examination.
Exclusion Criteria	– Family history of seizure, epilepsy, brain or mental disease – Participant that has an allergic history to any ingredient of vaccines – Woman who is pregnant, breast-feeding or positive in pregnancy test on day of enrollment, or is planning to be pregnant during the next 6 months – Any acute fever disease or infections – Have a medical history of SARS – Have serious cardiovascular diseases, such as arrhythmia, conduction block, myocardial infarction, severe hypertension and not well-controlled – Major chronic illness, such as asthma, diabetes, or thyroid disease, and not well-controlled – Hereditary angioneurotic edema or acquired angioneurotic edema – Urticaria in last one year – Asplenia or functional asplenia – Platelet disorder or other bleeding disorder may cause injection contraindication – Faint at the sight of blood or needles. – Prior administration of immunodepressant or corticosteroids, antianaphylaxis treatment, cytotoxic treatment in last 6 months – Prior administration of blood products in last 4 months – Prior administration of other research medicines in last 1

	month - Prior administration of attenuated vaccine in last 1 month - Prior administration of subunit vaccine or inactivated vaccine in last 14 days - Being treated for tuberculosis - Any condition that in the opinion of the investigators may interfere with the evaluation of study objectives
Role of the sponsor	Sponsors participate in the trial design and the protocol writing, but will not participate in other process of the trial, including data collection, statistical analysis, data interpretation and writing study report.

ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
Ad5	Replication Defective Human Adenovirus Serotype 5
COVID-19	Corona Virus Disease 2019
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ELISA	Enzyme-linked Immunosorbent Assay
ELISpot	Enzyme-linked Immunospot Assay
FAS	Full Analysis Set
GCP	Good Clinical Practice
GMI	Geometric Mean Fold Increase
GMP	Good Manufacturing Practice
GMT	Geometric Mean Titer
IEC	Independent Ethics Committee
ITT	Intent-to-treat
NIFDC	National Institutes for Food and Drug Control
NMPA	National Medical Products Administration
PPS	Per Protocol Set
SAE	Serious Adverse Event
SOP	Standard Operation Procedure
SS	Safety Set
vp	Virus Particle

TABLE OF CONTENTS

1. OBJECTIVE AND INTRODUCTION

The recombinant novel coronavirus vaccine (adenovirus type 5 vector) against the COVID-19 caused by SARS-CoV-2 is developed by the Beijing Institute of Biotechnology and CanSino Biologics Inc. The purpose of this study is to further evaluate the immunogenicity and safety of recombinant novel coronavirus vaccine (adenovirus vector) in healthy adults aged 18 and above.

The results of preclinical animal experiments showed that the recombinant novel coronavirus vaccine (adenovirus vector) could introduce significant immune responses in BALB/c mice, guinea pigs, ferrets and rhesus monkeys, and also demonstrated a good safety profile. The results of phase I clinical trial showed that low and middle dose recombinant novel coronavirus vaccine (adenovirus vector) showed good safety in human, and high dose recombinant novel coronavirus vaccine (adenovirus vector) showed clinically tolerable safety in human. The immunogenicity among low, middle and high dose groups showed a dose-response relationship.

The recombinant novel coronavirus vaccine (adenovirus type 5 vector) has been approved for clinical trial (2020JTL001). This protocol was made according to Good Clinical Practice (GCP), the Declaration of Helsinki, and local rules and regulations of China.

2. STUDY SITE

Study site: Wuhan Special Service Recuperation Center of the Chinese People's Armed

Police Force.

Recruitment institution: Hubei Provincial Center for Disease Control and Prevention, Zhongnan Hospital of Wuhan University.

3. RELATED PARTIES IN CLINICAL TRIAL

3.1 Sponsor

Beijing Institute of Biotechnology

CanSino Biologics Inc.

3.2 Investigator

Jiangsu Provincial Center for Disease Control and Prevention

Hubei Provincial Center for Disease Control and Prevention

Zhongnan Hospital of Wuhan University

3.3 Clinical Research Associate

Nanjing Sunrise Pharmaceutical Technology Co., Ltd.

3.4 Statistical Party

Shanghai Canming Medical Technology Co., Ltd

3.5 Detection Party

National Institutes for Food and Drug Control

Beijing Institute of Microbiology and Epidemiology

4. BACKGROUND AND RATIONALE

4.1 Introduction of pathogen

At the end of 2019, a novel coronavirus SARS-CoV-2 was first reported causing pneumonia outbreak in Wuhan, China. On February 11, 2020, the World Health Organization named the disease COVID-19.

SARS-CoV-2 belonging to the *Beta coronavirus* genus of coronavirus, is enveloped, 60~140nm in diameter, and its particles are round or oval, often pleomorphic. The gene of SARS-CoV-2 are obviously different from those of SARS-CoV and MERS-CoV. The SARS-CoV-2 has been found an 88% identity with the genome of (bat-SL-CoVZC45 and bat-SL-CoVZXC21) two species of coronavirus in bats in Zhoushan, China. The SARS-CoV-2 is the seventh coronavirus identified that could infect humans, which has not been reported before.

Coronavirus belongs to *Coronaviridae* family, *Orthocoronavirinae* subfamily. Coronavirus is a positive-strand single RNA virus. Globally, 10% to 30% of upper respiratory tract infections are caused by HCoV-229E, HCoV-OC43, HCoV-NL63 and HCoV-HKU1 coronaviruses, which are the second common causes of the common cold, rank only second to rhinoviruses. It is known that middle east respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) caused by coronavirus are serious infectious diseases.

The genome of coronavirus encodes spike protein (S), envelope protein (E), membrane protein (M) and nucleoprotein(N). S protein is the most important protein which is

related to the infectious capability of coronavirus. The S protein contains two subunits: S1 and S2, in which S1 mainly contains the receptor binding region, responsible for identifying cell receptors, and S2 contains the basic elements needed for membrane fusion. In the previous development of vaccines against SARS or MERS, S protein was regarded as the most important candidate antigen.

4.2 Disease and Epidemiological background.

The most common symptoms of the COVID-19 are fever, dry cough and fatigue. Some patients also have symptoms such as stuffy nose, runny nose, sore throat, myalgia and diarrhea. Most of the severe patients developed dyspnea and/or hypoxemia one week after the onset of the disease, and severe cases could rapidly develop into acute respiratory distress syndrome (ARDS), septic shock, metabolic acidosis, bleeding and coagulation dysfunction and multiple organ failure. It is worth noting that severe or critically ill patients often have moderate or low fever, even no obvious fever during the course of disease. The symptoms of some children or infants can be atypical, including diarrhea, vomiting and other gastrointestinal symptoms, or only mental weakness and shortness of breath. The symptoms of children are relatively mild. Mild patients could only have low fever, slight fatigue and no pneumonia. Most of the patients have a good prognosis and a small proportion of patient could be severe. For the elder people or/and those with chronic underlying diseases, the prognosis may not be good.

At present, the source of SARS-CoV-2 infection is the patients who infected.

Asymptomatic infection of SARS-CoV-2 may also be a source of infection. Respiratory droplets and close contact are the major routes of transmission. It is possible to spread through aerosol when exposed to high concentration of virus for a long time in a relatively closed environment. SARS-CoV-2 can also be separated from feces and urine, so attention should be paid to environmental pollution due to feces and urine. All people are generally susceptible.

4.3 Vaccine background.

4.3.1 Recombinant novel coronavirus Vaccine (adenovirus vector)

The recombinant novel coronavirus vaccine (adenovirus type 5 vector) is developed by the Beijing Institute of Biotechnology and CanSino Biologics Inc. This vaccine is based on a mature platform of recombinant replication defective human type 5 adenovirus vector, which could efficiently express the target antigen (S protein) in transfected/infected cells. It is expected that humoral and cellular immune responses against the S protein of SARS-CoV-2 can be induced after vaccination, and provide protection to the recipients.

4.3.2 Clinical Research Progress of MERS Vaccine

At present, the main kinds of novel coronavirus vaccines under research are as follows: Inactivated vaccine: composed of a complete virus, its pathogenicity loss still maintains all or part of the immunogenicity of the virus. After vaccination, the virus antigen can stimulate the body to produce immune response and achieve protective effect. The inactivated vaccine needs to go through the following steps: first, the virus strains are

cultured and screened on suitable cells to obtain the virus that represents the antigenic characteristics of the virus, high titer and stable virus, which can be used to establish a seed bank for large-scale production of vaccine in the future. The preparation of candidate vaccine through the process of culture, inactivation and purification is relatively simple, which is the traditional classical way of vaccine preparation. The main obstacles lie in two points: the study on the pathogenic mechanism and immunological mechanism of novel coronavirus is not in-depth, and it is possible to inactivate the whole virus with harmful components; second, live SARS-CoV-2 culture is required to be carried out under P3 biosafety conditions at present, and the production capacity will be limited.

Recombinant subunit vaccine: made from effective antigens that the virus can stimulate the body to produce protective immunity, which is safe and guaranteed, but it is generally small in size and poor in immunogenicity, so it needs some new technical means and adjuvants to increase its immunogenicity. Construction and design and effectiveness evaluation are key, and the development cycle is longer.

Adenovirus vector vaccine: The replication-defective human adenovirus type 5 vaccine containing the SARS-CoV-2 antigen gene can efficiently express the target antigen of SARS-CoV-2 in transfected/infected cells, thereby allowing the body to produce corresponding humoral and cellular immunity And can provide effective protection against diseases caused by SARS-CoV-2. The vaccine uses the same adenovirus vector platform as the approved recombinant Ebola virus disease vaccine, and has a certain research and development basis.

Attenuated influenza virus vector vaccine: the vaccine is vaccinated by intranasal drip, if successfully developed, it will have a certain effect on improving the vaccination rate. There are no reports of similar vaccines in other countries around the world.

mRNA vaccine: through in vitro synthesis of mRNA, of different antigen sequences against key targets of SARS-CoV-2 virus, and then delivered to the body, the cells in vivo are translated into antigenic proteins, thus activating the immune system and causing specific immune response. MRNA drug has the advantages of simple production, easy modification, rapid synthesis and low cost, but it has the defects of poor stability and strong immunogenicity. At present, most of the mRNA vaccine products are in the clinical stage and there are no products on the market. Among them, the most promising one is Moderna Therapeutics's mRNA-1273, a vaccine that has been tested in humans without even going through animal trials. If the current trial in Washington State goes well, the company hopes to have an early version of the vaccine available to high-risk people, such as health care workers, by the fall of 2020.

4.4 Advantages of this vaccine.

Based on the gene sequence of SARS-CoV-2, the target gene sequence of S protein was synthesized and packaged into the replication defective recombinant Ad5 vector to express S protein of SARS-CoV-2. In this project, we carried out large-scale preparation and quality control under GMP conditions, as well as a series of pharmacodynamic and toxicological evaluation. Animal experimental data has shown that this product can stimulate humoral immunity and cellular immunity. The main features of this product

are as follows: 1. Strong pertinence, this vaccine is designed according to SARS-CoV-2 sequence, and has good pertinence to this epidemic; 2. Mature technology, this vaccine and the approved recombinant Ebola disease vaccine are prepared by the same adenovirus vector technology, with standardized production process and perfect quality control system. 3. It is easy to be prepared on a large scale, and the large-scale preparation technology of this vaccine is mature which could meet the needs of large-scale population.

5. PRECLINICAL STUDIES WITH CANDIDATE Ad5-EBOV

5.1 Preclinical immunogenicity evaluation

5.1.1 Mouse model

5.1.1.1 Results of ELISA antibody

The geometric mean titers of anti-S protein IgG antibodies in high, middle and low groups were 137205 ±40120,57900 ±15950 and 220331 ±59612, 73608 ±14783 and 27025 ±15076 respectively on the 9th, 14th and 28th days after single vaccination (see figure below), and the geometric mean of antibody titers in high, middle and low groups were 137205 ±40120,57900 ±15950 and 220331 ±5961273608 ±14783 and 27025 ±15076respectively on the 9th, 14th and 28th day after single vaccination, respectively, and 220331 ±59612 and 73608 ±14783 and 27025 ±15076 respectively on the 14th day after vaccination. The results showed that Ad5-nCoV had good immunogenicity and the value of antibody increased with the time of vaccination in a dose-dependent manner.

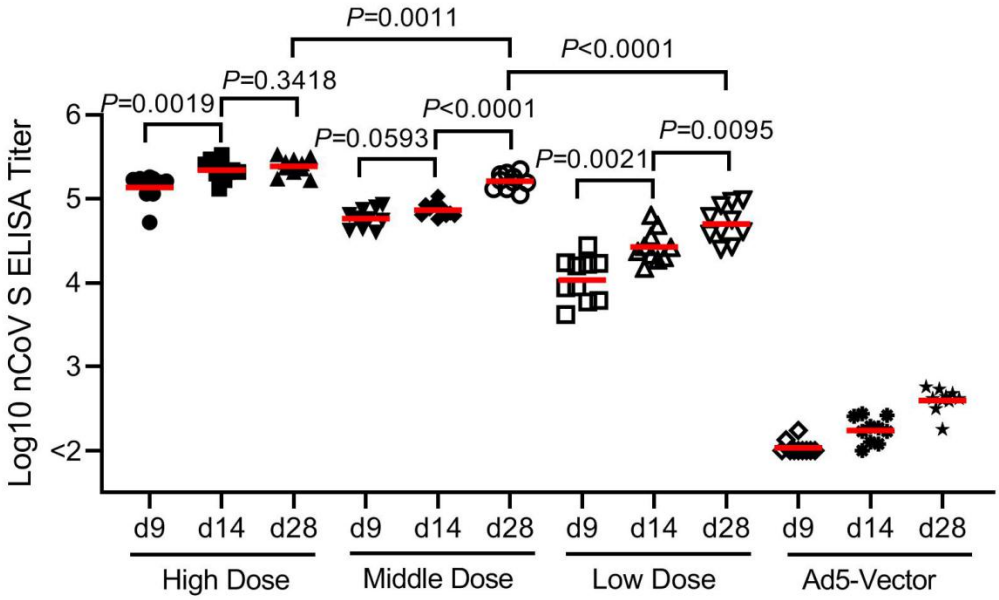


Fig.5-1-1-1. The level of anti-S protein IgG antibody in mice at day 9,14 and 28 after single vaccination.

5.1.1.2 Neutralizing antibody results

14 days after vaccination, the GMT of neutralizing antibody in high and middle dose groups was 58 ±43 and 13 ±27 respectively, while that in low dose group and placebo group was not determined, and the level of neutralizing antibody showed a dose-dependent relationship.

5.1.1.3 Cellular immune response

Fourteen days after the injection, the levels of IFN-γ, TNF-α and IL-2 expressed by CD8+ T cells and CD4+ T cells in the vaccine groups were significantly higher than those in Ad5 vector control group (P<0.001). It is suggested that intramuscular injection of the recombinant novel coronavirus vaccine (adenovirus type 5 vector) can induce strong specific cellular immune responses in mice. The results are showed in Figure 5-1-1-2 and Figure 5-1-1-3.

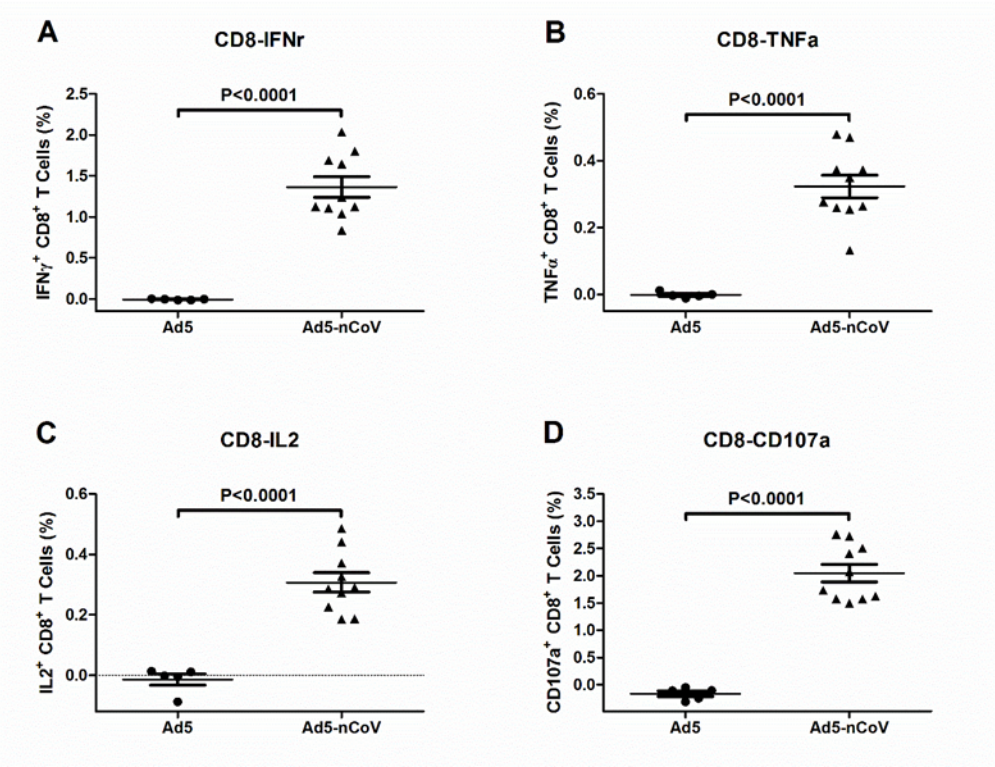


Figure 5-1-1-2. The CD8+ T cell immune responses post-vaccination.

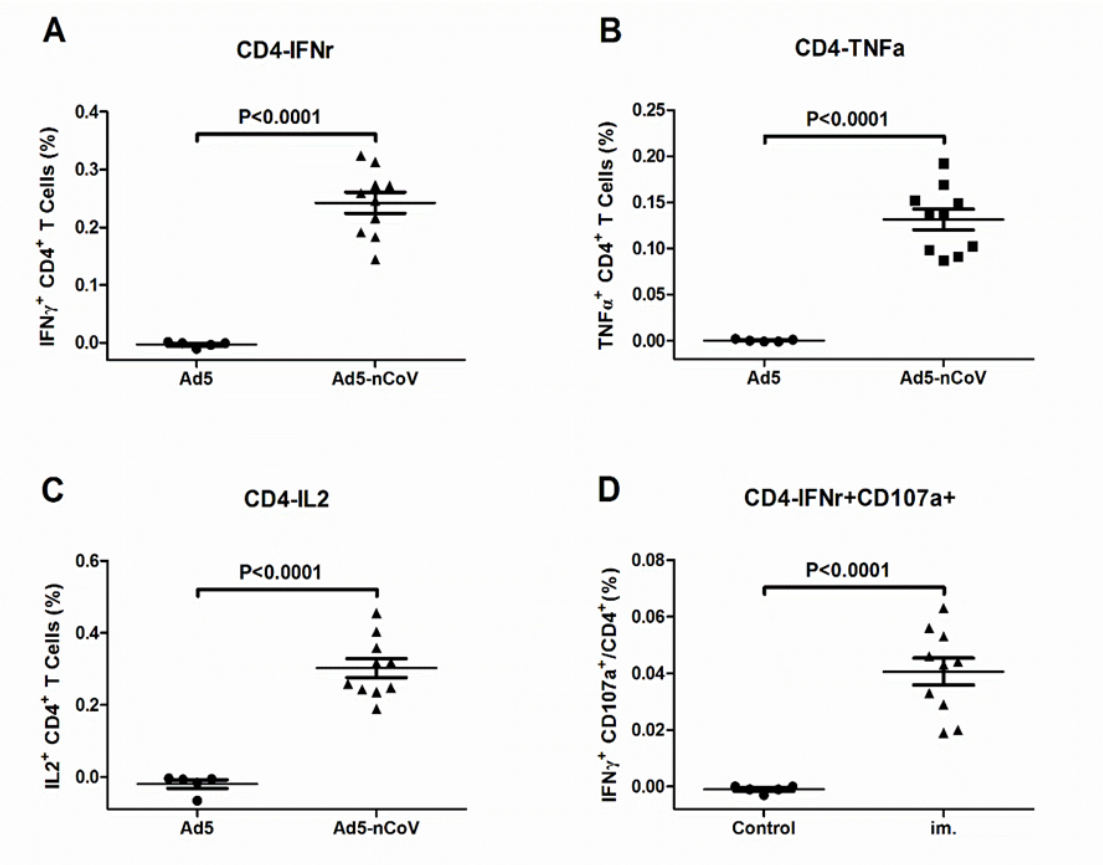


Figure 5-1-1-3 The CD4+ T cell immune responses post-vaccination.

5.1.2 Guinea pig model

5.1.2.1 Results of ELISA antibody

The anti-S protein IgG antibodies of guinea pigs were detected 14 and 28 days after single vaccination (see figure below). The geometric mean titers of antibodies in high, middle and low groups were 43386 ±27575, 36801 ±31736, 9997 ±8784 and 164408 ±84483, 87953 ±3794, 34551 ±21686, respectively, 14 days and 28 days after single vaccination, respectively. The results showed that Ad5-nCoV had good immunogenicity, and the antibody titers in high, middle and low groups were 164408 ±84483, 87953 ±3794, 34551 ±21686, respectively.

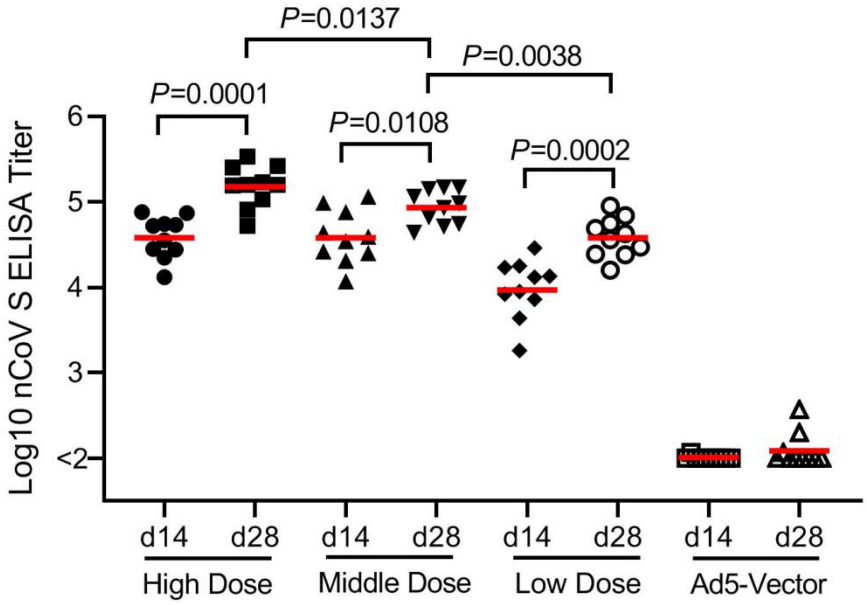


Figure 5-1-1-4 The level of anti-S protein IgG antibody in guinea pigs 14 and 28 days after the vaccination.

5.1.2.2 Results of neutralizing antibody

Only the neutralizing antibodies of guinea pigs in the high dose group were determined 14 days after vaccination, and the GMT value was 28 ±18. All individuals produced

neutralizing antibodies at this dose.

5.1.3 Rat model

In the toxicity test of single intramuscular injection to SD rats was performed at the dose of 5×10^{10}vp. Blood samples were collected on the day 15 after vaccinaiton, and the S protein specific IgG antibodies were detected by indirect ELISA. The results showed that the recombinant novel coronavirus vaccine (adenovirus type 5 vector) had good immunogenicity (Figure 5-1-1-5).

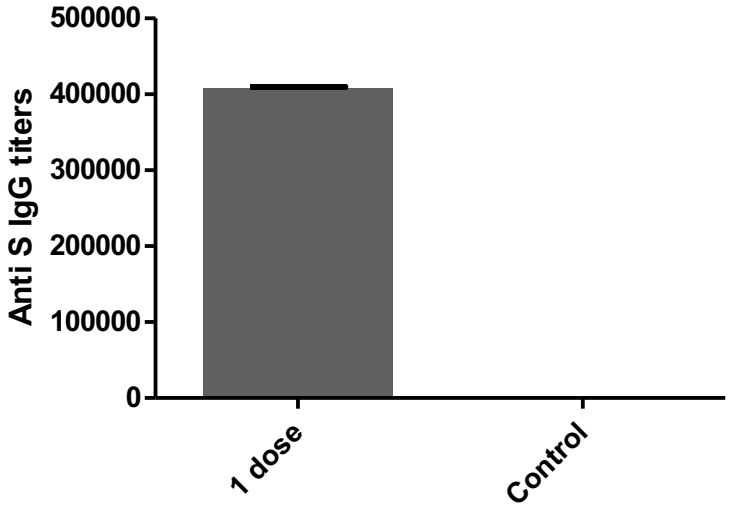


Figure 5-1-1-5 The level of anti-S protein antibody in rats 14 days after vaccination

5.1.4 Macaca fascicularis

In the toxicity test of repeated injection in macaca fascicularis for 2 weeks and recovery for 2 weeks was performed. Blood samples were collected on the 8th, 11th and 15th days after the first injection with dose of 5×10^{10}vp and 3 times of human doses (15×10^{10}vp), respectively. The S protein specific IgG antibody was determined by indirect ELISA method, and the neutralization antibody was also determined. The

results showed that the recombinant novel coronavirus vaccine (adenovirus type 5 vector) had good immunogenicity, and the value of anti-S protein antibody increased with the vaccination dose (Figure 5-1-1-6). At the same time, the vaccine can also stimulate specific CD8+ T cell immune response. On the 11th day after vaccination, the neutralization antibody values of high-dose group and low-dose group were 192 ±303 and 61 ±195 respectively (Figure 5-1-1-7).

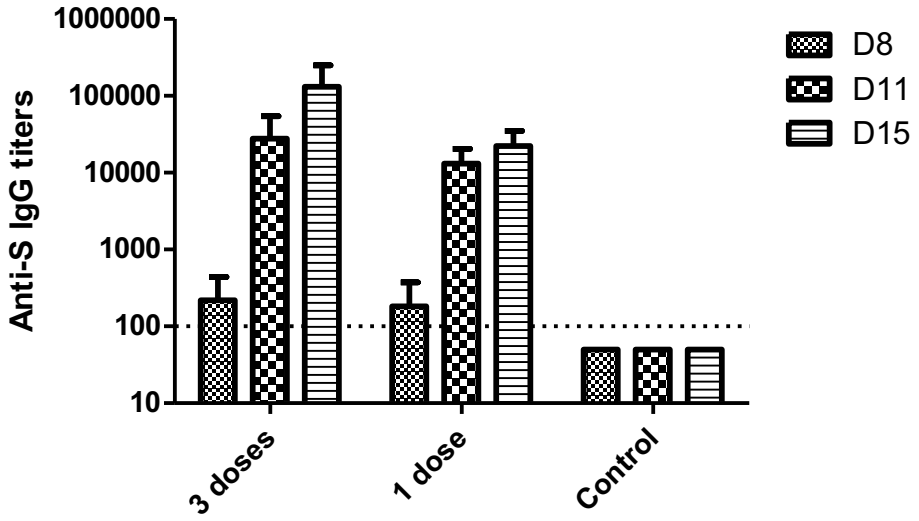


Figure 5-1-1-6 The anti-S protein antibody at day 8, 11 and 15 after the first vaccination

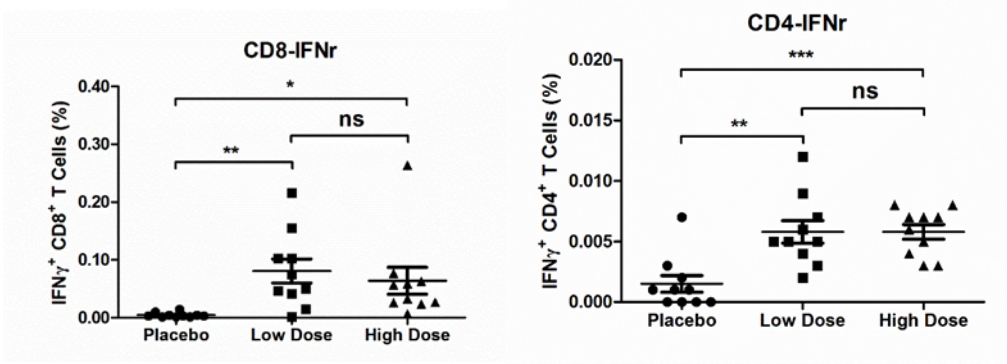


Figure 5-1-1-7 Specific cellular immune response of macaca fascicularis 13 days after first vaccination

5.2 Protective experiments in animals

5.2.1 Protective experiments in ACE2 transgenic mice

The viral load in lung tissue of model group was $10^{6.18}$ copies/ml at day 3 after infection. The viral load of lung tissue in the high dose group ($10^{3.11}$ copies/ml) was significantly lower than that in the control group at day 3 after infection ($p<0.001$). The viral load of lung tissue in the low dose group ($10^{3.90}$ copies/ml) was significantly lower than that in the control group at day 3 after infection ($p<0.001$). The results showed that the viral load in lung tissue decreased by 3.07 logarithmic value after high-dose vaccination and 2.28 logarithmic value after low-dose vaccination, as shown in figure 5-2-1-1.

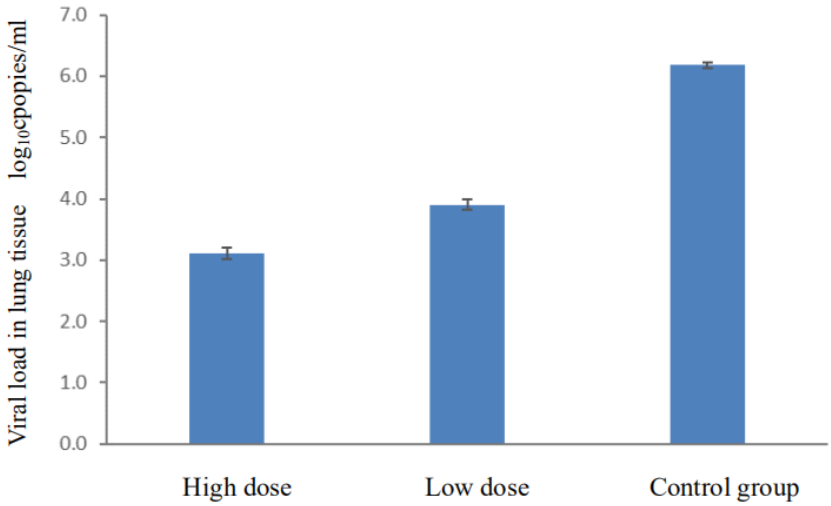


Fig. 5-2-1-1 Viral load in mouse lung tissue

The hACE2 transgenic mice were immunized with high-dose recombinant novel coronavirus vaccine (adenovirus vector) once and challenged at day 14, which could effectively alleviate the pathological changes of lung tissue in mice, while the lung tissue lesions in the low-dose group did not significantly alleviate.

In the model group, the body weight decreased by 3.36%, and the viral load in lung tissue was $10^{6.18}$ copies/ml. The lung tissue showed moderate interstitial pneumonia.

Compared with the control group, the body weight of mice in the high dose group (5×10^{9}vp) increased by 2.55% after infection and had no obvious symptoms. The viral load in lung tissue was $10^{3.11}$ copies/ml, and decreased by 3.07 logarithmic value. The lung tissue showed mild interstitial pneumonia and the pathological changes were alleviated.

Compared with the model group, the body weight of mice in the low dose group (5×10^{8}vp) decreased by 4.72% after infection, and the symptoms did not change significantly. The viral load in lung tissue decreased by $10^{3.90}$ copies/ml, and decreased by 2.28 logarithmic value. The lung tissue showed moderate interstitial pneumonia, and the pathological changes were not significantly alleviated.\

These results suggested that high-dose adenovirus vector vaccine showed significant protective effects on infected mice. Low-dose adenovirus vector vaccine showed significant antiviral effects.

5.2.2 Protective experiments in ferrets

24 ferrets (12 male and 12 female) were randomly assigned to three groups: high dose vaccine group (2×10^{10}vp, n=8), low dose vaccine group (2×10^{9}vp, n=8) and control group (n=8). Each ferret was injected intramuscularly once at day 0, and 500 μl was injected into the hind leg muscle. Blood samples were collected before vaccination, 14 days after vaccination and when the animals were killed, the serum was separated and then detected the antibody. The live SARS-CoV-2 virus was challenged at day 14 after

vaccination.

The results showed that the recombinant novel coronavirus vaccine (adenovirus vector) could induce the reaction of virus-specific ELISA antibody and neutralizing antibody within 2 weeks, and the replication level of upper respiratory tract virus in immunized animals was significantly lower than that in control animals, and the clearance time was significantly faster than that in control animals. The results showed that the recombinant novel coronavirus vaccine (adenovirus vector) had good immunogenicity and could provide immune protection against upper respiratory tract SARS-CoV-2 infection. No antibody-dependent enhancement was found in the lung and liver histopathology of the immunized animals.

5.2.3 Protective experiments in rhesus monkeys

12 female rhesus monkeys were randomly assigned to three groups: high dose vaccine group (2×10^{11}vp, n=4), low dose vaccine group (5×10^{10}vp, n=4) and control group (n=4). Each rhesus monkey was injected intramuscularly once at day 0. Blood samples were collected before vaccination, 14 days after vaccination and when the animals were killed, the serum was separated and then detected the antibody. The live SARS-CoV-2 virus was challenged at day 14 after vaccination. The body weight, body temperature, eating condition, X-ray manifestation of lungs and lung slices were observed after challenged. The copy number of SARS-CoV-2 was detected by quantitative PCR at day 5 after challenged. The number of SARS-CoV-2 were detected by cytopathic method. Blood biochemistry was detected at day 2 after challenge and on the day of execution. Serum IgG antibody and neutralization antibody titers were detected by ELISA.

After challenge, there was no significant increase in body temperature in the model group, and a high level of viral load was detected in pharynx swab, anal swab and lung tissue, and the lung tissue showed moderate interstitial pneumonia.

Compared with the model group, the body temperature of 3 mice in the low dose group exceeded 40 ℃, and the peak virus load of pharynx swab and anal swab decreased by 1.05 lg and 1.67 lg respectively. The highest decrease of viral load in lung tissue was 4.56lg. 2 showed mild interstitial pneumonia and 2 showed moderate interstitial pneumonia. The results suggest that low-dose vaccine has a certain protective effect.

Compared with the model group, the body temperature of one animal in the high dose group was higher than 40 ℃, and the peak value of virus load in pharynx swab and anal swab decreased by 1.82 lg and 3.61 lg, respectively. The highest decrease of viral load in lung tissue was 5.70lg. In the high dose group, 3 rats showed mild interstitial pneumonia, 1 showed moderate interstitial pneumonia, and more lymphocytes, macrophages and eosinophils could be seen around the alveolar septum and blood vessels. The results suggest that high-dose vaccine has a certain protective effect.

5.3 Safety evaluation in preclinical research

5.3.1 Toxicity experiment of single intramuscular injection in SD rats

No animal death or near death were observed in any groups. No abnormal changes were found in all animal indexes, including clinical observation, body weight and food intake. No obvious abnormal changes were found in the general anatomy of the animals in each group, so the histopathological examination was not carried out.

Under the experimental conditions, the recombinant novel coronavirus vaccine (adenovirus vector) was given to each SD rat by intramuscular injection at one dose, and no toxic reaction was observed. The maximum tolerated dose (MTD) of each rat was $\geq 0.5\times10^{11}$ vp/dose.

5.3.2 Toxicity experiment of repeated intramuscular injection in cynomolgus monkeys for 2 weeks and 2 weeks of recovery period

During the experiment, no death or near death was found in all groups, no abnormal reaction related to drug administration was found in clinical observation, and no allergic reaction symptoms were found in clinical observation after two times of administration. During the experiment, compared with the negative control group of the same sex during the same period, the other indexes of the animals in the low and high dose groups (1 dose and 3 dose) included body weight and weight gain, body temperature, ECG waveform and parameters, blood pressure, ophthalmic testing, clinicopathology (blood cell count, blood coagulation, blood biochemistry, urine analysis), T lymphocyte subsets (CD3+, CD4+, CD8+, CD4+/CD8+), serum cytokines (IL-2, IL-4, IL-5, IL-6, TNF- α, IFN-γ), C-reactive protein and serum complement (C3, C4) did not change significantly or showed no abnormal changes in toxic physiology.

5.4 Results of previous clinical studies

Phase I clinical trial of recombinant novel coronavirus vaccine (adenovirus vector) was launched in Wuhan on March 16, 2010. the trial included low, middle and high dose groups, 36 people in each group, and were inoculated with 5×10^{10}vp, 1×10^{11}vp and

1.5×10^{11}vp recombinant novel coronavirus vaccine (adenovirus vector), respectively. The results showed that the total incidence of adverse events within 7 days after immunity in the low, middle and high dose groups was 77.8%, 86.1% and 72.2%, respectively. The incidence of grade 3 adverse events was 5.6%, 5.6% and 16.7%, respectively. No level 4 adverse events were found. Low and middle dose recombinant novel coronavirus vaccine (adenovirus vector) showed good safety in human body, while high dose recombinant novel coronavirus vaccine (adenovirus vector) showed clinically tolerable safety in human body. the immunogenicity of low, middle and high dose groups showed a dose-response relationship.

Based on the safety and immunogenicity of phase I clinical trial, low dose (5×10^{10}vp) and middle dose (1×10^{11}vp) recombinant novel coronavirus vaccine (adenovirus vector) was selected to conduct a larger phase II clinical trial to further evaluate the immunogenicity and safety of recombinant novel coronavirus vaccine (adenovirus vector) in healthy adults aged 18 years and above.

6. BRIEF INTRODUCTION OF PRODUCT CHARACTERISTICS

6.1 Production technology

In addition to carrying different foreign genes, the biological characteristics of recombinant adenovirus, cell lines, culture medium and purification methods of recombinant novel coronavirus vaccine (adenovirus vector) and approved recombinant Ebola virus disease vaccine (adenovirus vector) were the same. Therefore, based on the company's existing adenovirus vector vaccine platform technology, this product was

developed by referring to the production process of Ebola vaccine. The basic contents of the construction of adenovirus vector platform were as follows.

In 2013, CanSino Biologics Inc and the National Research Institute of Canada (NRC) jointly developed the production process of 293 cell culture and recombinant type 5 adenovirus vector tuberculosis vaccine (Ad5-Ag85A). The vaccine has completed Phase Ia clinical studies (intramuscular injection) in Canada with good safety, and is currently undergoing Phase Ib studies (respiratory mucosal immunity).

After the Ebola outbreak in 2014, based on the Ad5-Ag85A process, the process validation of the 2L shake flask and 7L scale (5L cell culture volume) reactor was performed with the Ad5-EBOV recombinant adenovirus. In February 2015, the recombinant Ebola virus disease vaccine (adenovirus vector) was approved for clinical use. After that, the research institution further scaled up the 6 batches of the original liquid process and the finished product process, and finally determined the 50L scale production process, and completed the verification of 3 batches of the 50L scale production process. After approval, 10 batches of production were completed using the process. The results all met the quality standards and the consistency between batches was good.

Subsequently, multiple batches of 25L process research were carried out in the Marburg project using this platform process. The results showed that all the indicators met the quality standards drawn up by the enterprise, indicating that the adenovirus technology platform of the research and development institution was very mature and could be extended to similar adenovirus vector products for the prevention of other diseases.

The recombinant novel coronavirus vaccine (adenovirus vector) and the recombinant Ebola virus disease vaccine (adenovirus vector) use the same cell lines, culture medium and purification methods except that they carry different foreign genes. The research and development institution selected the approved Ebola vaccine production process to develop the recombinant novel coronavirus vaccine (adenovirus vector): completed a batch of 2L, a batch of 10L and 3 batches of 25L production. The results showed that the process could meet the production of novel coronavirus vaccine, and the detection indexes reached the proposed quality standard.

6.2 Formulation

This product is a recombinant virus vaccine made by inserting novel coronavirus's S antigen gene into human type 5 replication deficient adenovirus vector. Compared with the recombinant Ebola virus disease vaccine (adenovirus vector), only the antigen gene is different. Referring to the preparation formula and production process of recombinant Ebola virus vaccine (adenovirus vector), it was determined that the product was 0.5ml per vial and contained 5×10^{10}vp recombinant replication defective human type 5 adenovirus which expressing novel coronavirus S protein.

Except that the placebo did not contain replication-deficient human type 5 adenovirus which could express SARS-CoV-2 S protein, the other components of the placebo were consistent with the test vaccine. The specification is 0.5ml per bottle.

6.3 Stability research

According to the relevant provisions of the measures for Drug Registration Administration, the stability of novel coronavirus vaccine was studied. The accelerated

stability study was carried out for 8 weeks at 37±2℃, 6 months at 25±2℃, and long-term stability at 5±3℃ for 30 months.

6.4 Quality research and verification

This study is based on the viral biological products included in the 2015 Edition "China Pharmacopoeia" (third), the technical guiding principles for the prevention of live vaccine preparations using viruses as carriers, and the guiding principles for human gene therapy research and preparation quality control (hereinafter referred to as: guiding principles), combined with the quality standard of "Recombinant Ebola Vaccine (adenovirus Vector)" (Standard No. YBS05112019) and two batches of research data of this project, the quality standards of harvesting liquid, raw liquid, semi-finished product and finished product of recombinant novel coronavirus vaccine (adenovirus vector) were established.

6.5 Package

The vaccine will be packed in a box with a label. The label contains at least the following information: vaccine name, lot number, expiry date, preservation conditions and "only for clinical trial ".

Sample of label on the vial

Only for clinical trial
Vaccine number: XXX
0.5ml/vial
Exp:2022.03.10

Lot: 202003002C、202003003C、202003004C、P202003001C

Storage: at 2 ~ 8℃, avoid light

Beijing Institute of Biotechnology and CanSino Biologics Inc.

Sample of label on the packaging box

Only for clinical trial

Vaccine number: XXX

0.5ml/vial

Exp:2022.03.10

Lot: 202003002C、202003003C、202003004C、P202003001C

Storage: at 2 ~ 8℃, avoid light

Beijing Institute of Biotechnology and CanSino Biologics Inc.

6.6 Transportation and Storage

The vaccine must be stored in a safe, locked place to avoid unauthorized access. The vaccine storage conditions must be assessed in study center to ensure that the vaccine is stored under appropriate conditions in the study. The temperature of vaccine transportation from Beijing Institute of Biotechnology/CanSino Biologics Inc. to the research center, the remaining vaccine after inoculation back to the research center should be kept at 2-8℃. When the vaccines are received, the quantity, quality and maintenance of the cold chain must be checked, and the "vaccine delivery" form should be filled in.

The temperature of the monitoring instrument, transport and storage of the vaccine should be monitored (am and pm manually) daily. Once the temperature deviation happens, as the temperature over the provisions of the range of 2-8℃, the investigators and sponsors should be immediately informed, and the "cold chain deviation report form" should be filled in, too. The temperature-deviated vaccine should be identified, placed separately and suspended. Continual usage of vaccines must be under written approval by Beijing Institute of Biotechnology/CanSino Biologics Inc. Vaccines failed to meet the requirements for transportation or storage should be not be used.

7. STUDY OBJECTIVES

To evaluate the immunogenicity and safety of the recombinant novel coronavirus vaccine (adenovirus type 5 vector) in healthy adults aged 18 years and above.

8. STUDY DESIGN

8.1 Design methods

This is a randomized, double-blind, placebo-controlled phase II clinical trial.

8.2 Study endpoints

8.2.1 Primary endpoints:

8.2.1.1 Safety

- The incidence of adverse reaction (AR) from 0 to 14 days after vaccination in each study group.

8.2.1.2 Immunogenicity

- Geometric mean titer (GMT) of specific antibody against SARS-CoV-2 S protein

(ELISA method) at day 28 after vaccination in each study group.

- The geometric mean titer (GMT) of SARS-CoV-2 specific neutralizing antibody (live SARS-CoV-2 and pseudovirus neutralization test) at day 28 after vaccination.

8.2.2 Secondary endpoint

8.2.2.1 Safety

- The incidence of adverse events (AE) from 0 to 14 days after vaccination in each study group.
- The incidence of adverse events (AE) from 0 to 28 days after vaccination in each study group.
- The incidence of severe adverse events from 0 to 28 days after vaccination in each study group.
- The incidence of serious adverse events within 6 months after vaccination in each study group.

8.2.2.1 Immunogenicity

- Geometric mean titer (GMT) of specific antibodies against SARS-CoV-2 S protein (ELISA method) in each study group at day 14 and month 6 after vaccination.
- Geometric mean titer (GMT) of SARS-CoV-2 specific neutralizing antibody (live SARS-CoV-2 and pseudovirus neutralization test) in each study group at month 6 after vaccination.
- The seroconversion rate of SARS-CoV-2 S protein specific antibody (ELISA method) in each study group at day 14, day 28 and month 6 after vaccination.
- The geometric mean fold increase of SARS-CoV-2 S protein specific antibody

(ELISA method) in each study group at day14, day 28 and month 6 after vaccination.

- The seroconversion rate of SARS-CoV-2 specific neutralizing antibody (live SARS-CoV-2 and pseudovirus neutralization test) in each study group at day 28 and month 6 after vaccination.
- The geometric mean fold increase of SARS-CoV-2 specific neutralizing antibody (live SARS-CoV-2 and pseudovirus neutralization test) in each study group at day 28 and month 6 after vaccination.
- Geometric mean titer (GMT) of specific neutralizing antibody against Ad5 vector at day 28 and month 6 after vaccination in each study group.
- The geometric mean fold increase of specific neutralizing antibody against Ad5 vector in each study group at day 28 and month 6 after vaccination.
- At day 28 after vaccination, the positive rate, conversion rate and level of IFN-γ stimulated by S protein overlapping peptide library will be detected by ELISpot.

For uncertain values: when calculating GMT, GMI and seroconversion of antibodies, if the antibody level is below the initial detection limit, half of the initial value will be calculated; if the antibody level is greater than the maximum detection limit, the maximum dilution will be calculated.

8.2.3 Exploratory endpoint

- The consistency analysis of the specific antibody against SARS-CoV-2 S protein (ELISA method) and the specific neutralizing antibody.
- The persistence of specific antibodies against SARS-CoV-2 S protein after

vaccination in each study group.

8.3 Study procedures

From beginning to the end of the study, each participant will complete 4 visits. The visit time, time window and the content of the visit are shown in the table 8-3-1-1 and 8-3-1-2.

Table.8-3-1-1 Visit schedule for the participants

Visit No.	V0	V1	V2	V3
Day/month	Day 0	Day 14	Day 28	Month 6
Visit interval	Day 0	V0+14 days	V0+28 days	V0+6 months
Time window	--	(±2 days)	(±3 days)	(±15 day)
Recruiting	●			
Demographic information collection	●			
SARS-CoV-2 antibody test	●			
HIV antibody test	●			●
Informed consent	●			
Physical examination: Height, weight, blood pressure	●			
Axillary temperature measurement	●			
HCG test (for women only)	●			
Medical history collection	●			
Inclusion and exclusion screening	●			
Allocation of vaccine ID	●			
Blood collection	●	●	●	●
Vaccination	●			
Observation for 30 minutes post-vaccination	●			
Safety visit (AR/AE)	●	●	●	●
Report serious adverse event (SAE)	●	●	●	●

Distribution of diary card (within 14 days)	●			
Return of diary card (within 14 days) and distribute a new diary card (after 14 days)		●		
Return of diary card (after 14 days)			●	
Record vaccination and visits	●	●	●	●
Recording of combined medications/combined vaccines	●	●	●	●

Table.8-3-1-2 Blood collection at scheduled visits

Visit No.	V0	V1	V2	V3
Visit time	Day 0	Day 14	Day 28	Month 6
Visit interval	Day 0	V0+14 days	V0+28 days	V0+6 months
Time window	--	(±2 days)	(±3 days)	(±15 days)
SARS-CoV-2 antibody test	Fingertip blood	--	--	--
HIV antibody test	Fingertip blood	--	--	Fingertip blood
Virus preparation/cellular immunity (anticoagulant blood)	5ml	--	--	--
Humoral immunity (procoagulant blood)	10ml	10ml	5ml	10ml
Cellular immunity (anticoagulant blood)	--	--	5ml	--

Total amount of blood collection: 45ml.

8.4 Sample size

This phase 2 trial will be launched before we obtaining the immunogenicity data from the phase 1 trial. Therefore, the sample size of is not calculated, but determined based

on expert experiences and the minimum sample size requirement in the technical guidelines for vaccine clinical trials issued by National Medical Products Administration, China. The final sample size is 250 in the middle dose group, 125 in the low dose group and 125 in the placebo group, with a total sample size of 500.

8.5 Criteria for suspending or early termination

The investigators will collect daily reports of adverse events after vaccination and report the newly added adverse events to the Data Safety Monitoring Board (DSMB) in time. The DSMB independently analyzes the post-vaccination safety data in each dose group, and if an increased risk of participants is found in the course of the study, it shall immediately notify the principal investigator and the sponsor to suspend or terminate the clinical trial. If there is a violation of the protocol, GCP or ethical requirements, the sponsor, principal investigator, ethics committee or administrative department shall have the right to suspend or terminate the study, and shall notify other parties and participants and explain the reasons.

Criteria for study suspension:

- One or more ≥grade 4 adverse reaction or serious adverse event may be associated with vaccination

Criteria for early termination of the study:

- Grade 4 adverse reactions or serious adverse events that may be related to vaccination occur during the study, which will be discussed jointly by the investigators and the sponsor, and the DSMB will finally decide whether to terminate the trial.

- Occurrence of grade 3 adverse events associated with vaccination in 15% of participants or more (including injection-site reaction, systemic reaction, and abnormal laboratory indexes), which will be discussed jointly by the investigators and the sponsor, and the DSMB will finally decide whether to terminate the trial, or
- Required by sponsor, or
- Required by ethics committee, or
- Required by administrative department in charge.

8.6 Duration of study

It will take about 6 months for each participant from recruiting to completing the last visit. Some participates may withdraw during the study.

9. PARTICIPANTS

9.1 Participants selection

Healthy people aged 18 years and above are selected as the target population, and informed in writing by informed consent approved by the ethics committee. On the premise that the volunteers themselves signed the informed consent, they could only participate in the study after passing the physical examination and the following inclusion and exclusion criteria. The investigator conducting the study, the relevant investigators, and any employee of the contract research organization (CRO) shall not be a participant.

9.2 Inclusion criteria

- Aged 18 years and above.
- Able to understand the content of informed consent and willing to sign the informed consent.
- Able and willing to complete all the scheduled study process during the whole study follow-up period (about 6 months).
- Negative in HIV diagnostic blood test.
- Axillary temperature ≤37.0°C.
- Negative serum IgM and IgG to the SARS-CoV-2.
- A body mass index (BMI) is between 18.5 and 30.0.
- General good health as established by medical history and physical examination.

9.3 Exclusion criteria

- Family history of seizure, epilepsy, brain or mental disease
- Participant that has an allergic history to any ingredient of vaccines
- Woman who is pregnant, breast-feeding or positive in pregnancy test on day of enrollment, or is planning to be pregnant during the next 6 months
- Any acute fever disease or infections
- Have a medical history of SARS
- Have serious cardiovascular diseases, such as arrhythmia, conduction block, myocardial infarction, severe hypertension and not well-controlled
- Major chronic illness, such as asthma, diabetes, or thyroid disease, and not well-controlled

- Hereditary angioneurotic edema or acquired angioneurotic edema
- Urticaria in last one year
- Asplenia or functional asplenia
- Platelet disorder or other bleeding disorder may cause injection contraindication
- Faint at the sight of blood or needles.
- Prior administration of immunodepressant or corticosteroids, antianaphylaxis treatment, cytotoxic treatment in last 6 months
- Prior administration of blood products in last 4 months
- Prior administration of other research medicines in last 1 month
- Prior administration of attenuated vaccine in last 1 month
- Prior administration of subunit vaccine or inactivated vaccine in last 14 days
- Being treated for tuberculosis
- Any condition that in the opinion of the investigators may interfere with the evaluation of study objectives.

9.4 Withdraw from the study

Participants have the right to withdraw from the study at any time during the study period, and the investigator should record the reason of withdraw:

- Participants become pregnant.
- Loss of contact.
- Request to withdraw without any reason.
- Withdraw for reasons unrelated to the study, such as long-term departure, relocation, etc., and the specific reason for withdrawal should be recorded.

- Withdrawal for reasons related to the study, such as intolerance of adverse reactions, intolerance of biological specimen collection, etc., and the specific reason for withdrawal should be recorded. If a participant withdraws because of AE or SAE, investigator should follow up the participant until the resolve of AE or SAE.
- Participants can require a complete withdraw from the study, all study behaviors could be stopped, including vaccination, biological specimen collection and safety observation. The data before withdrawal will not be used for analysis if he or she require so. If the participants allow the investigators use the data collected before the withdrawal, the data can be included in analysis.
- The participants with SARS-CoV-2 infections during the period from the day of vaccination to 28 days after vaccination will not be included in the immunogenicity analysis, but all participants with SARS-CoV-2 infections occur within six months after vaccination should be analyzed in accordance with the requirements of SAE, especially the existence of ADE phenomenon.
- Participants can require a partially withdraw from the study, such as refuse to vaccination or blood drawn only，but still participate in other procedures during the follow-up.

9.5 Complete of the study

9.5.1 Complete of the safety data collection

The safety of the participants who complete the vaccination is observed 28 days after the completion of the vaccination according to the program, as well as the SAE report

throughout the study period.

9.5.2 Complete of immunogenicity data collection

The participants meet the inclusion and exclusion criteria, are vaccinated according to the plan, and blood samples are collected before and after vaccination.

9.6 Protocol violation and protocol deviation

9.6.1 Protocol violation (including but not limited to)

- No informed consent singed by the participant.
- The enrolled participant does not meet the all the inclusion criteria or meet one or more exclusion criteria.
- The investigator improperly asks the participant to withdraw from the study.
- The participant received incorrect intervention (i.e. vaccinated with other groups of vaccines mistakenly).
- The participant received a vaccine fail to meet the requirements.
- Any other reasons identified by the investigators and confirmed by the principal investigator.

For any protocol violation, the investigators should report to the principal investigator and sponsor in time, and the principal investigator should handle the protocol violation properly, collect all relevant information about the involved participants, particularly the safety associated data and follow-up to ensure the safety of the participants. The principal investigator should also take proper measures to prevent the occurrence of similar protocol violation in the trial.

Investigators or monitors should report any protocol violation to principal investigator,

coordinators and ethics committees by fax or e-mail as soon as possible after knowing the protocol violation.

9.6.2 Protocol deviation (including but not limited to)

- Beyond the visiting time window.
- Low compliance of participants, and the participants do not complete the blood sample collection.
- Serious adverse events do not report in time (SAE).
- Participants are treated with unallowed drugs (intramuscular, oral or intravenous corticosteroids for ≥2mg/kg/days, continuous use for ≥14 days, or other immunosuppressants).
- The interval between vaccination with this vaccine and other vaccines is insufficient.
- Other reasons considered as protocol deviation by the principal investigator.

The protocol deviation should be recorded in detail. For the participants who exceeded the time window or had insufficient time interval of receiving other vaccines, the data of them can be included in the safety and immunogenicity analysis. For participants have other protocol deviation, the data of them can still be involved in the safety analysis, but can not be included in the immunogenicity analysis.

10. METHODS AND PROCEDURES

10.1 Participants screening

10.1.1 Screening before enrollment

Healthy people aged 18 years and above are selected as the target population, the

recruitment will be promoted by the recruitment advertisement approved by the ethics committee, and the volunteers will be selected before enrollment on the premise that they signed the informed consent approved by the ethics committee. Before they sign the informed consent, they will have enough time to think about it, and a withdrawn at any time during the trial is permitted.

Following operation will be performed during the selection:

- Demographic data.
- Physical examination, including general physical examination and laboratory examination.
- Medical history of disease.
- Meet all the inclusion criteria and do not meet any of the exclusion criteria.

10.1.2 Screening contents

10.1.2.1 Pregnancy test

Before vaccination, HCG detection will be performed on target women of childbearing age, those with negative test results can be enrolled.

10.1.2.2 HIV antibody screening

During the screening process, fingertip blood of all participants will be collected for HIV antibody screening by the rapid detection kit, those with negative results can be enrolled.

10.1.2.3 SARS-CoV-2 antibody screening

Fingertip blood of all participants will be collected for specific IgM and IgG antibodies against S and N test by the rapid detection kit, those who are positive for any of the

antibodies will not be enrolled.

10.2 Randomization and blinding

10.2.1 Randomization and grouping

In this study, randomization and blindness will be achieved by blinding the investigational vaccines. Qualified test vaccines and placebos will be provided by the sponsor, and then be blinded by a third party. SAS software will be used to generate random codes by block randomization, and the test vaccine and placebo will be randomly assigned to serial numbers (the vaccine for each participant has a unique serial number). Participants will be randomly divided into the middle dose group, low dose group, and placebo group at a ratio of 2:1:1.

The investigator will assign the random numbers in order of the eligible participants arrived at the place where study number assigned, and fill the screening number and initials into the corresponding column of the random number assignment table, the corresponding number is the study number. In order to control the selection bias of age and gender, the age and gender distribution among the groups should be balanced as much as possible.

10.2.2 Blind code preservation

The statistical blinding staff will write the blinding procedure of randomization to make blind code. The blind code includes the first-level blind code and the second-level blind code. The first-level blind code is the group code, and each vaccine number, or study number, corresponding to each group (low dose group, middle dose group, placebo group) is represented by a different letter. The second-level blind code will reveal the

final blind code, namely the name of the group (low dose group, middle dose group, placebo group). Two blind code copies will be put into envelopes, sealed and kept by the investigator and the sponsor respectively. Emergency letters are also made independently by the blinding staff, sealed and handed over to the investigator for storage. Blinding staff shall not participate in the clinical trial work, and at the same time, they shall not disclose the contents of blinding to any person participating in the clinical trial work.

10.2.3 Replacement vaccine

In order to prevent accidents such as damage to the blinded vaccine during the trial, additional replacement vaccines will be prepared for each group (8 boxes for the middle dose group, 4 boxes for the low dose group, and 4 boxes for the placebo group). The number of replacement vaccines is represented by four letters, each letter corresponding to 4 boxes of replacement vaccines. During the trial, when the replacement vaccine is needed, the vaccination staff will open the replacement vaccine letter corresponding to the participant's study number, and the participant will be vaccinated according to the replacement vaccine number recorded in the letter.

10.2.4 Unblinding

Unblinding time will be jointly decided by the sponsor and the investigator based on the progress of the study. The blinding documents will be jointly signed by the principal investigator, the sponsor and the statisticians.

After the last participant completed V2 (day 28), materials were sorted out, the blind review being completed, and an independent third party conducted unblinding for the

first analysis. Using the two-level unblinding method. The first unblinding is done after the blind review being completed and the data of the first analysis being locked, and then opened the first-level blind code, the group code corresponding to each participant is revealed, and the group is determined. The second unblinding will be carried out after the final statistical analysis report is finalized, and then open the second-level blind code to reveal the group corresponding to each group code. See 10.2.6 for blind state maintenance throughout the trial.

10.2.5 Emergency blind breaking regulations

If serious complications and adverse events occur during the trial, which affect the choice of treatment measures, the investigators can break the blindness urgently if they think it is necessary to know the group of the participant. When it is necessary to break the blindness, the person in charge of the study center will open the emergency letter corresponding to the participant's study number and reveal their grouping information. The randomization letter should be signed by the person in charge of the study center after use and kept properly. After unblinding, the principal study institutions, the sponsor, the ethics committee and the CRA shall be notified in time.

10.2.6 Blind state maintenance

During the implementation of this clinical trial, the double-blind state should be maintained, that is, neither the investigator nor the participants know whether the participant receive the vaccine or placebo.

The first analysis will be completed by an independent statistician, the statistician un-blinded independently for statistical analysis, and submitted the first analysis report to

the sponsor and the investigator. The grouping information of participants shall not be disclosed in the first analysis report. The study site will remain double-blind, and the blind code shall not be revealed during the entire clinical trial.

10.3 Vaccination

10.3.1 Investigational vaccine

The recombinant novel coronavirus vaccine (adenovirus type 5 vector) and placebo are developed by the Beijing Institute of Biotechnology and CanSino Biologics Inc.

The recombinant novel coronavirus vaccine (adenovirus type 5 vector) is a liquid formulation, using replication-defective human adenovirus type 5 as a vector, and express the specific S protein of the SARS-CoV-2. The quality of the test vaccine is in line with the "recombinant novel coronavirus vaccine (adenovirus type 5 vector) manufacturing and verification regulations (draft)" formulated by the sponsor. The recombinant novel coronavirus vaccine (adenovirus type 5 vector) has got the certification from National Institutes for Food and Drug Control.

The placebos contain no replication-defective human type 5 adenovirus that expressed the S protein of SARS-CoV-2, and the other ingredients were consistent with the test vaccine and were approved by National Institutes for Food and Drug Control.

In addition to providing adequate quantities of investigational vaccines, the sponsor shall provide replacement vaccines at 5 percent of the number of vaccines required for each group. If the investigational vaccine is damaged or otherwise unavailable, it should be discarded. Although in such cases (with the exception of cold-chain incidents) the sponsor need not be notified immediately, the investigator should keep a detailed record

of the damage to the investigational vaccine.

10.3.2 Immunization procedure and immunization pathway

All investigational vaccines will be immunized by single dose, and the immunization pathway is intramuscular injection of the lateral deltoid muscle of the upper arm.

Middle-dose group: 2 vials of test vaccine will be extracted with a syringe, the total volume is 1ml, and the total dosage is 1×10^{11}vp.

Low-dose group: 1 vial of test vaccine and 1 vial of placebo will be extracted with a syringe, the total volume is 1ml, and the total dosage is 5×10^{10}vp.

Placebo control group: 2 vials of placebos will be extracted with a syringe, the total volume is 1ml, and the total dosage is 0vp.

Before injection, 75% alcohol is used for disinfection at the injection site and then intramuscular vaccination will be administrated. Shaking the vaccine before use. No intravascular, intradermal or subcutaneous injection is allowed with the investigational vaccine. Participants should be carefully observed for at least 30 minutes after vaccination and appropriate emergency medical treatment should be in place to prevent possible allergic reactions after vaccination.

10-1-1-2 Distribution of investigational vaccine and placebo in each dose group

Dose group	Test vaccine	Placebo
Middle dose group	2 vials	0 vial
Low dose group	1vial	1 vial
Placebo group	0 vial	2 vials

10.3.3 Vaccine management

The sponsor should provide all the investigational vaccines, including the replacement vaccines.

The sponsor is responsible for transporting the investigational vaccine to the clinical trial site, along with a transportation temperature record (in accordance with the cold chain temperature of the vaccine) and the inspection report (qualified). The vaccine management personnel of the research institution and the vaccine management personnel at the test site shall jointly check and sign with the sponsor.

Special area should be used to store and lock the test vaccine to get rid of unauthorized persons. Vaccine is forbidden to inject other ones except participants.

The cold storage should be equipped with a temperature recorder to monitor the temperature of the cold storage in real time. The cold storage administrator inspects the cold storage every morning and afternoon and records the temperature of the cold storage to ensure the normal operation of the cold storage. If the cold storage temperature is found to exceed the cold chain preservation temperature of the vaccine, the cold chain temperature of the vaccine should be restored in time, and the test vaccine should be temporarily sealed and reported to the sponsor in writing in a timely manner. it must be approved in writing by the sponsor before it can continue to be used. Vaccines that do not meet the requirements should be sealed on the spot and continued use is strictly prohibited.

The investigational vaccine should be stored in a refrigerator or freezer and cold chain equipment is equipped with a thermometer with the vaccine administrator records

temperature every 15 minutes.

Vaccine administrators release the investigational vaccine to the vaccination staff according to number of participants and vaccine. The left test vaccine packing should be recycled after inoculation and detailed records of test vaccine and recycling packaging are needed

After the completion of the vaccination day, the vaccine administrator will check the remaining investigational vaccines and the packaging of the vaccinated vaccines, and all of them will be recycled into the warehouse.

At the end of the study, the investigators will check all the remaining vaccine and package and deliver them back to sponsors.

At any time, the total number of vaccines, unused or damaged vaccines must be consistent with the applicants provided, otherwise, description is needed to be provided by investigator.

10.3.4 Combined medication/vaccine

When the medical events happen during the study period, the participant are allowed to carry out the appropriate medical treatment, but the medical treatment should be recorded in time.

Other vaccination is not recommended except for emergency during the research period, such as rabies vaccine, tetanus vaccine, or other emergent vaccination need. Any vaccine used is required to be recorded during the study period.

10.4 Safety observation

10.4.1 Methods of safety observation

The contents of safety observation during the study period are as follows:

(1) After vaccination, all participants will be observed for 30 minutes at the study site.

(2) Within 14 days after vaccination, the participants will be asked to complete the safety observation by themselves, and record the results on the "diary card (within 14 days) ". Designated doctors will be responsible for following up the participants and instruct them to complete the diary card.

(3) From day 15 to day 28 after vaccination, the participants will be instructed to record any adverse events on the "diary card (after 14 days) " by themselves. On day 28, the investigators will visit the participants, retrospectively investigate and verify the contents of the safety observation.

(4) During the whole study period (about 6 months after vaccination), the serious adverse events will be observed by both active reporting by the participants and regular follow-up by the investigators.

10.4.2 Safety observation and grade of adverse reaction/event

10.4.2.1 Definition of adverse event and serious adverse event

Adverse events (AE): adverse medical events that occur after the patients or clinical trial participants receive a drug, but do not necessarily have a causal relationship with treatment.

Serious adverse events (SAE): events such as hospitalization, prolonging hospitalization time, disability, affecting working ability, endangering life or death, and

leading to congenital malformations that occur during the clinical trials.

10.4.2.2 Safety observation contents

Adverse events occurred 0-14 days after vaccination.

Serious adverse events occurred 0-28 days after vaccination.

Serious adverse events within 6 months after vaccination.

10.4.2.3 Adverse event classification standard

The adverse events will be graded and evaluated according to the "Guidelines of the Criteria for the Classification of Adverse Events in Clinical Trials for Vaccines" (No.102,2019) of the China Food and Drug Administration. For details, see tables 10-4-1-1, 10-4-1-2, 10-4-1-3.

Table 10-4-1-1 Grading for adverse events at the injection site

Symptoms	Grade 1	Grade 2	Grade 3	Grade 4
Pain	Do not affect or slightly affect physical activity	affect physical activity	Affect daily life	Loss of basic self-care ability or hospitalization
Induration*, swelling (optional)** #	Diameter 2.5~＜5 cm or area 6.25~25 cm^2 and does not affect or slightly affect daily life	Diameter 5~＜10 cm or area 25~＜100 cm^2 or affect 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 affect daily life	Abscess, exfoliative dermatitis, dermal or deep tissue necrosis
Rash*, redness (optional)** #	Diameter 2.5~＜5 cm or area 6.25~25 cm^2 and does not affect or slightly affect daily life	Diameter 5~＜10 cm or area 25~＜100 cm^2 or affect 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	Abscess, exfoliative dermatitis, dermal or deep tissue necrosis

			affect daily life	
Itch	Itching at the vaccination site, relieved by itself or within 48 hours after treatment	Itching at the vaccination site, which does not resolve within 48 hours after treatment	Affect daily life	NA
Cellulitis	NA	Non-injectable treatment is required (e.g. oral antibacterial, antifungal, antiviral therapy)	Intravenous treatment is required (e. G. intravenous antibacterial, antifungal, antiviral therapy)	Sepsis, or tissue necrosis, etc.

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

** the maximum measuring diameter or area should be used.

the evaluation and grading of induration and swelling, rash and redness should be based on the functional level and the actual measurement results, and the indicators with higher classification should be selected.

Table 10-4-1-2 Grading for systemic adverse events.

Systemic symptoms	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	Mild or transient, 3 to 4 times a day, abnormal stool, or mild diarrhea last less than 1 week	Moderate or persistent, 5-7 times a day, abnormal stool characteristics, or diarrhea ＞1 week	＞7 times/day, abnormal stool, or hemorrhagic diarrhea, orthostatic hypotension, electrolyte imbalance, need intravenous infusion ＞ 2L	Hypotension shock, hospitalization required

Constipation*	Need fecal softener and diet adjustment	Need a laxative.	Stubborn constipation requires manual dredging or use of enema	Toxic megacolon or intestinal obstruction
Dysphagia	Mild discomfort when swallowing	Diet is restricted	Diet and conversation are very limited; you can't eat solid food.	Can't eat liquid food; need parenteral nutrition.
Anorexia	Loss of appetite, but no reduction in food intake	Loss of appetite, reduced food intake, but no significant weight loss.	Loss of appetite and weight loss	Need for intervention (e.g. gastric tube feeding, parenteral nutrition)
Vomiting	1- 2 times/24 hours and does not affect the activity	3- 5 times/24 hours or activity is restricted	＞6 times/24 hours or need intravenous rehydration	Hypotension shock requires hospitalization or other means of nutrition
Nausea	Transient (<24 hours) or intermittent and food intake is normal	Continued nausea leads to reduced food intake (24-48 hours)	Persistent nausea results in almost no food intake (> 48 hours) or requires intravenous fluid replacement	Life-threatening (eg hypotension shock)
Non-injection-site muscle pain	Does not affect daily activities	Slightly affect daily activities	Severe muscle pain that seriously affects daily activities	Emergency or hospitalization
Arthritis	Mild pain with inflammation, erythema, or swelling of joints; but does not interfere with function	Moderate pain with inflammation, erythema, or swelling of joints; impairs function but does not affect daily activities	Severe pain with inflammation, erythema, or joint swelling; affecting daily activities	Permanent and/or disabling joint injury

Arthralgia	Mild pain without hindering function	Moderate pain; need analgesics and/or pain that impedes function but does not affect daily activities	Severe pain; need analgesics and/or pain affecting daily activities	Disability pain
Headache	Does not affect daily activities and requires no treatment	Transient, slightly affects daily activities and may require treatment or intervention	Seriously affects daily activities and requires treatment or intervention	Intractable and requires emergency or hospitalization
Syncope	Close to syncope without losing consciousness (pre-syncope)	Loss of consciousness without treatment	Loss of consciousness and needs treatment or hospitalization	NA
Emerging seizures	NA	NA	1-3 times seizures	Prolonged and multiple seizures (eg, continuity seizures) or difficult to control (eg, refractory epilepsy)
Cough	Transient, without treatment	Persistent cough, effective treatment	Paroxysmal cough, uncontrollable treatment	Emergency or hospitalization
Acute bronchospasm	Transient; no treatment needed; FEV1% is 70%-80%	Needs treatment; bronchodilator therapy returns to normal; FEV1% is 50%-70%	Bronchodilator treatment cannot return to normal; FEV1% is 25% -50% or continuous intercostal depression	Cyanosis; FEV1% <25%; or intubation required
Dyspnea	Dyspnea during exercise	Dyspnea during normal activity	Dyspnea at rest	Dyspnea, requiring oxygen therapy, hospitalization or assisted breathing

Non-injection-site itching (no skin lesions)	Slightly itchy without affecting or slightly affecting daily life	Itching affects daily life	Itching makes it impossible to carry on daily life.	NA
Abnormal skin and mucosa	Erythema/itching/color change	Diffuse rash/macular papule/dryness/desquamation	Blister/exudation/desquamation/ulcer	Exfoliative dermatitis involving mucous membrane, or erythema multiforme, or suspected Stevens-Johnsons syndrome
Insomnia*	Mild difficulty in falling asleep, not affecting or slightly affecting daily life	Moderate difficulty in falling asleep, affecting daily life	Serious difficulty in falling asleep, seriously affecting daily life, requiring treatment or hospitalization	NA
Irritate or suppress	Mild irritability or mild suppression	Irritability or lethargy	Inability to soothe or react poorly	NA
Mental disorders (including anxiety, depression, mania, and insanity) should report detailed symptoms	Minor symptoms, no need to visit or behavior does not affect or slightly affect daily life	Has clinical symptoms and needs medical attention or behavior that affects daily life	Need to be hospitalized or unable to support daily life	Have the tendency to harm themselves or others or acute insanity or loss of basic self-care ability
Acute allergic reaction **	Local urticaria (blister) without treatment	Local urticaria requiring treatment or mild angioedema without treatment	Extensive urticaria or angioedema requiring treatment or mild bronchospasm	Anaphylactic shock or life-threatening bronchospasm or throat edema

Fatigue	Does not affect daily activities	Affects normal daily activities	Seriously affects daily activities and cannot work	Emergency or hospitalization
Non-injection-site pain# (Specify the location when reporting)	Minor pain that does not affect or slightly affect daily life	Pain affects daily life	Pain can't carry on daily life	Disability pain, loss of basic self-care ability
Sore throat ***	Transient, without treatment, without affecting daily activities	Sore throat, slightly affecting daily activities	Severe sore throat that seriously affects daily activities and requires medication	

Note: FEV1% refers to forced expiratory volume per second (FEV1)/forced vital capacity (FVC).

* For constipation and insomnia, pay attention to the changes before and after vaccination.

** Refers to type I hypersensitivity.

Refers to pain in non-injection-site other than muscle pain, arthralgia, and headache.

*** Refer to the "Guidelines of the Criteria for the Classification of Adverse Reactions in Preventive Vaccine Clinical Trials" by the China Food and Drug Administration

Among the above systemic adverse events, diarrhea, fatigue, nausea, anorexia, vomiting, sore throat, headache, cough, arthralgia, non-injection-site muscle pain, non-injection-site itching, abnormal skin and mucosa, acute allergic reactions, syncope, acute bronchospasm, and dyspnea are solicited adverse events, and the rest are unsolicited adverse events.

Table 10-4-1-3 Grading for the vital signs

Sign	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Fever* (Axillary temperature (℃)	37.3～＜38.0	38.0～＜38.5	38.5～＜39.5	≥39.5, last more than 3 days

Note: * The axillary temperature is usually used in China, and if necessary, it is converted into oral temperature and anal temperature. Generally, oral temperature=axillary temperature + 0.2°C; anal temperature=axillary temperature + (0.3 ~ 0.5°C). When persistent high fever occurs, the cause of the high fever should be identified as soon as possible.

10.4.2.4 General principles for the grading for other adverse events

The intensity of adverse events not mentioned in the rating table shall be evaluated according to the following criteria.

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild: short-term (< 48h) or mild discomfort, does not affect activity, no need for treatment	Moderate: mild or moderate limitation of activity, which may require medical treatment, no or only mild treatment	Severe: obviously limited activity, need to see a doctor and receive treatment, may need to be hospitalized	Critical: may be life-threatening, activities are severely restricted, and need monitoring and treatment	Death

10.4.3 Outcome of AE

The outcomes of adverse reaction/event include: (1) Recovery; (2) Not yet recovered; (3) Recovered but sequelae; (4) Death; (5) Loss of visit

10.4.4 Relationship between AE and vaccination

Investigators should make the best interpretation of AE, and assess the possible causal relationship between vaccination and reactions (such as history of underlying diseases, combined treatment of causation). This applies to all AEs, including severe ones and non-severe ones.

The assessment of causality will be reasonably explained in the following or more aspects of the event:

- The similar reaction to the solution was observed in the past;
- identical events of similar types solution have been reported in the literature;
- the incident occurred along with the time of the vaccination, and again after the secondary vaccination

According to definitions, all the solicited AE (that is, the local adverse event of the collection of the report) will be considered to be related to vaccination.

The causal relationship of AE should be evaluated according to the following questions, and according to your judgment, the reasonable possibility of relationship between AE and vaccination is caused by the vaccination:

- Related: there is a suspicion that a link between vaccine and the AE (do not need to be determined); the vaccine has a reasonable potential for promoting the AE.
- Unrelated: there is no suspicion that a link exists between vaccine and the AE; there are other more likely causes, and vaccination has not been suspected to promote the AE.

10.4.5 Reporting of SAEs

Any serious adverse event must be reported immediately (within 24 hours of the investigator's knowledge of the event) by telephone or fax to the sponsors, JSCDC IRB, and Hubei Medical Products Administration, at the following number:

Representative of sponsor: Wei Chen, Tel: +86-13910789661

JSCDC IRB: Hui-Yuan Cai, Tel: +86-025-83759406; Fax: +86-025-83759406

Hubei Medical Products Administration: Tel: +86-027-87111695

Upon receipt of information about vaccine safety from any source, the sponsor shall

conduct an analysis and assessment, including severity, relevance to the study, and whether it is an expected adverse event.

For suspicious and unexpectedly serious adverse reactions that are fatal or life-threatening, the sponsor shall report to National Medical Products Administration as soon as possible, no more than 7 natural days, and update the relevant information within the following 8 days. For information about suspicious and unanticipated serious adverse reactions that are not fatal or life-threatening, or other potential serious safety risks, the sponsor shall report to National Medical Products Administration as soon as possible after it is first known, but not more than 15 natural days.

10.4.6 Record of safety observation

Any clinically meaningful adverse event occurred after vaccination should be recorded in the diary card.

Verification and medical visits by investigator respond to adverse events are required, such as investigation of medical history, physical examination and necessary laboratory examination (if required). Participants should receive appropriate medical treatment until the adverse event decline completed with complete records.

The record of adverse events should include the following:

- Description of adverse events
- Start and end time of adverse events
- Severity (grade)
- Relationship with vaccination
- Laboratory findings

- Treatment measures

- Outcome

If there are allergies, SAE, or a grade 3 adverse events or above happening in safety observation period, medical treatment should be provided until symptoms disappeared or stabilization of symptoms.

10.4.7 Medical treatment of AE

If the participants report injection-site or systemic adverse reactions or events or serious adverse events, investigators should provide appropriate treatment or medical consultation to reduce or remove suffering. The medical treatment of green channel could be started if it is necessary. The medical procedures and outcome should be exactly recorded.

10.5 Collection and detection of biological samples

10.5.1 Detection of ELISA Antibody against SARS-CoV-2 S protein

10.5.1.1 Detection time point

Specific S protein antibody titers in serum against SARS-CoV-2 will be detected on day 0, day 14, day 28 and month 6 after vaccination.

10.5.1.2 Evaluation content

The level of specific S protein antibody in serum against SARS-CoV-2 on day 28 post-vaccination will be used as the primary evaluation time point for immunogenicity. The differences of antibody levels among different groups and the changes of antibodies at various time points pre-vaccination and the post-vaccination will be compared.

10.5.2 Detection of neutralizing antibody against SARS-CoV-2

10.5.2.1 Detection time point

Serum neutralizing antibody titers against SARS-CoV-2 will be determined at day 0, day 28 and month 6 after vaccination.

10.5.2.2Evaluation content

The level of serum neutralizing antibody against SARS-CoV-2 on day 28 of vaccination will be used as the primary evaluation index of immunogenicity. The differences of antibody levels among different groups and the changes of antibodies at various time points pre-vaccination and the post-vaccination will be compared.

10.5.3 Detection of neutralizing antibody to recombinant replication defective human type 5 adenovirus

10.5.3.1 Detection time point

Serum neutralizing antibody titers against recombinant replication defective human type 5 adenovirus will be detected at day 0, day 28, and month 6 after vaccination.

10.5.3.2 Evaluation content

The levels of neutralizing antibodies against human type 5 adenovirus, the growth times of antibodies and the differences among groups will be compared pre-vaccination and the post-vaccination. To explore the correlation between the level of baseline neutralizing antibody against human type 5 adenovirus and S protein ELISA antibody and T cell response.

10.5.4 Detection of IFN-γ secreted by specific T cells

10.5.4.1 Detection time point

IFN-γ secreted by specific T cells will be detected at day 0 and day 28 after vaccination.

10.5.4.2 Evaluation content

The positive rate of T cell response on the 28th day of vaccination will be used as the

main evaluation index of immunogenicity. The differences of antibody levels among different groups and the changes of T cell reaction positive rate at each time point pre-vaccination and the post-vaccination will be compared.

10.5.5 Surveillance and laboratory diagnosis of SARS-CoV-2 infection during clinical trials

During the observation period of the clinical trial, the participants with persistent fever and respiratory symptoms such as cough should immediately go to the designated hospital (Zhongnan Hospital of Wuhan University) and inform the researchers. Nasopharyngeal swabs (or sputum) and anal swabs were collected and CT and other imaging examinations were performed to determine whether the disease was caused by novel coronavirus infection. Once novel coronavirus's infection occurs during the clinical trial, it is necessary to conduct a case investigation and conduct novel coronavirus testing on the blood for virus preparation. Severe cases or death cases need to continue to carry out special investigation of critical cases or death cases, mainly to analyze whether there is an ADE phenomenon.

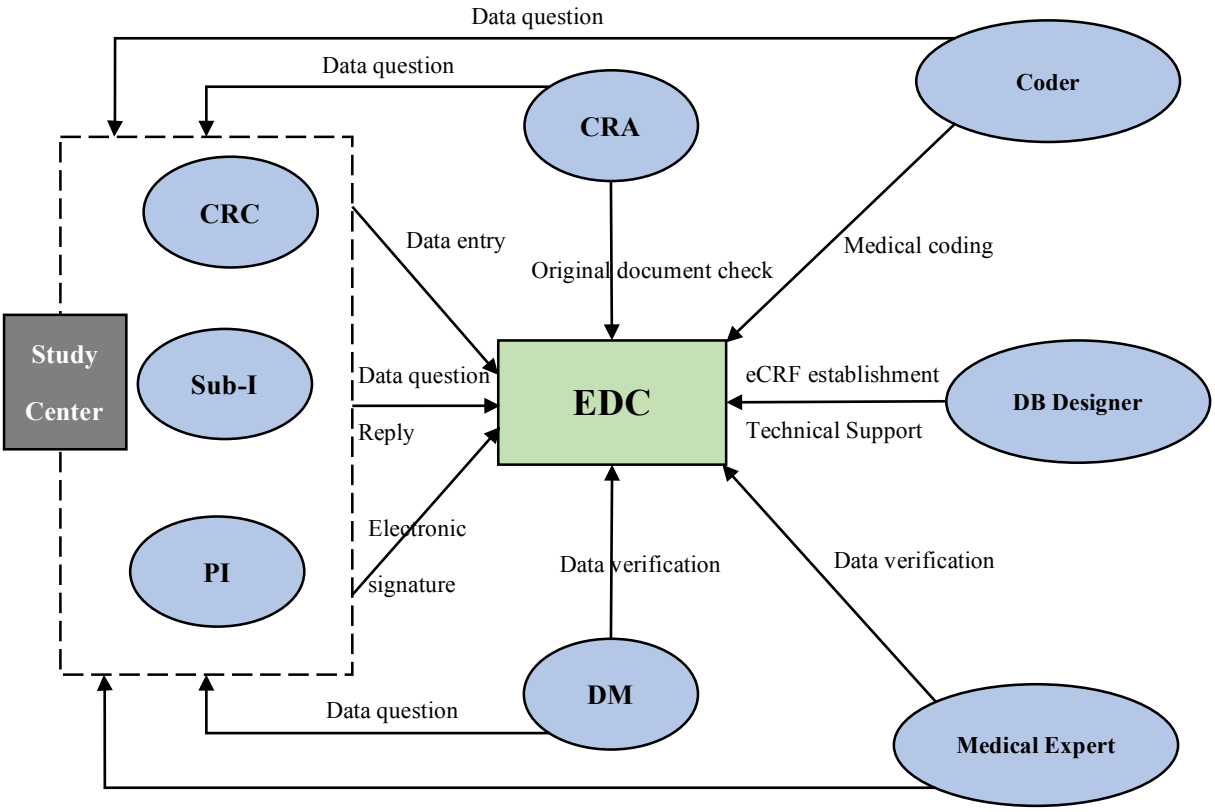
In addition to SARS-CoV-2 nucleic acid detection, multiple pathogens will be detected for differential diagnosis of nasopharyngeal swabs/sputum and anal swabs.

10.6 Data management

In this study, the electronic data collection (EDC) system is used to collect and manage the study data. The system keeps a complete modification track to ensure the authenticity, completeness and accuracy of the clinical trial data. The data management process should comply with the GCP specification to ensure the traceability of the

clinical trial data.

10.6.1 Data collection, entry and reporting



10.6.2 Data collection roles and responsibilities

Data collection roles	Abbreviation	Responsibilities
Clinical research coordinator	CRC	1. Input data; 2. Answer questions;
Sub-investigator	Sub-I	1. Input data; 2. Answer questions;
Principal investigator	PI	1. Input data; 2. Answer questions; 3. Approve and confirm (approve);
Clinical research associate	CRA	1. Source file consistency verification (verify); 2. To question;

		3. Close the query;
Project manager	PM	1. Read-only;
Data manager	DM	1. To question; 2. Close the query; 3. Freezing/thawing data; 4. Lock the data;
Medical coder	coder	1. Encoding; 2. To question.

10.6.3 Design and establishment of database

The study database (eCRF) is established by the database designer, and the database is established by CDISC standard as much as possible.

After the database is established and tested, the authorized personnel of various roles, such as PI, Sub-I, CRC, PM, CRA, DM, etc., can be officially put online after training. The data administrator writing the data management plan (DMP), DMP should be finalized before the first participant screening.

10.6.4 Data entry

The investigator or the person authorized by the investigator completes the online data entry in time after completing the visit.

The investigator need to approve and confirm the data on the eCRF in order to confirm that the data recorded in the eCRF are true. After data entry is completed, any data changes need to be explained and will be automatically recorded in the system.

10.6.5 Monitoring of data records

Auditors should conduct regular and irregular audits of data records entered into the EDC to ensure that all the input data are consistent with the original documents. If there

is any inconsistency, the auditors needs to send queries to the investigators in the corresponding place in the EDC system, and the investigators need to verify the original data and update the input until the EDC system is complete. Before locking the library, the auditors should carefully verify the original data of the participants and the necessary signatures of the investigators.

10.6.6 Data verification

Data managers query and manage the test data according to the data verification plan (DVP).

When data is entered into the EDC system, if there is illogical data, the system will automatically check and query. These queries need investigators or authorized personnel to review and answer, when the updated data makes the logical verification not valid, queries will automatically shut down. Automatically closed queries, DM can be audited, when the problems are not solved, DM can manually add questions and continue to communicate with the study center until the problems are solved.

In addition to the automatic verification of the system, the queries checked by SAS programming or data administrator can be manually added to the EDC system when the investigators are required to clarify, verify or confirm.

Before locking the database, the data administrator needs to make sure that all the queries are cleaned up, and the investigators complete the electronic signature on the EDC system to ensure the integrity and accuracy of patient data.

10.6.7 Medical coding

Medical coders carry out medical coding for unsolicited adverse events. Adverse events

will be encoded according to the MedDRA (version 21.1 or above).

During the coding process, DM can query the investigators in real time if any medical terms cannot be coded due to improper, inaccurate or vague provision of medical terms. The medical code needs to be reviewed before the database is locked.

10.6.8 The database lock

After completing the data lock list, according to the procedures for database lock, data managers, statistical analysts, clinical auditor representatives, and investigator representatives will sign and approve database lock. It is exported by the data administrator to the database in the specified format, and then handed over to the statisticians for statistical analysis. After the database is locked, if there is definite evidence to prove that it is necessary to unlock, the investigators and relevant personnels must sign the unlocking document.

10.6.9 External data management

Immunogenicity data is managed as external data. For data transmission requirements, please refer to "External Data Transmission Protocol". The data administrator audits and verifies the external data.

10.6.10 Archive eCRF

At the end of the trial, the eCRF of each patient is exported to PDF for electronic archiving, and the CD-ROM was stored in the Wuhan Special Service Recuperation Center of the Chinese People's Armed Police Force for a period of 5 years after the completion of the trial.

10.7 Statistics plan and statistical analysis

10.7.1 Statistics plan

In this study, the statistical analysis includes first analysis and the final analysis.

10.7.1.1 First analysis

After the last participant complete the Visit 2 (28 days after vaccination), the research database has been entered, audited and locked, first analysis will be done by the statistical party. The statistical analysis report shall first be reviewed by the DSMB and determined that the report shall be carried out in strict accordance with the first statistical analysis plan before it can be submitted to the researcher and sponsor.

10.7.1.2 The final analysis

After the last participant complete the Visit 3 (month 6 after vaccination), the safety and immunogenicity data from Visit 2 (day 28) to Visit 3 (month 6) will be sorted for final analysis and summary.

10.7.2 Statistical analysis plan

The sponsor shall entrust the statistical party to undertake the task of statistical analysis and participate in the whole process from the design, implementation of the experiment to analysis and summarization, after the formulation of the test scheme has been completed and approved by the Ethics Committee, the sponsor shall be responsible for coordinating the establishment of the database and the formulation of the statistical analysis plan to determine the analytical data set and statistical methods (see "First Statistical Analysis Plan" and "Final Statistical Analysis Plan" for details).

10.7.3 Analyzed data sets selection

Data set for safety evaluation

All participants who received vaccination should be included in the safety evaluation. Data that violate the scheme should not be excluded.

Data set for immunogenicity evaluation

Full analysis set (FAS): FAS is based on ITT (intention to treat analysis) principle to determine the participants. All of the participants that meet the inclusion/exclusion criteria, receiving vaccination, and have at least one blood testing result after vaccination, will be included in the FAS set for immunogenicity.

Per-protocol set (PPS): It is a subset of FAS. The participants in the data set will be more compliant to the scheme, with no significant deviation or violation of protocol, all meet the selection/exclusion criteria and complete vaccination within the vaccination time window according to the requirements of the scheme, and the participants who being collected blood at day 0, day 14, day 28 and month 6 month will be included in the PPS set. This method of analysis does not include participants who violate the protocol, and confirmed COVID-19 cases after vaccination.

In this study, the FAS is the primary analysis set for immunogenicity evaluation, but the PPS will also be analyzed at the same time. Any difference of analysis results existed between PPS and FAS, will be discussed in the report.

10.7.4 Data statistical methods

In statistical analysis, the number of completed cases will be checked first; then the demographic and baseline characteristics of each group are going to be analyzed to examine the comparability between groups; the evaluation of vaccine effect included the determination of evaluation indicators and the comparison of effects between

groups; safety evaluation included statistics of clinical adverse reactions/events.

Exclusion cases: did not meet the selected case criteria; without follow up data and information after vaccination; serious lack of information and data; Participants met the withdrawal criteria but did not withdraw; Participants received the wrong vaccination or incorrect dose.

Safety analysis is mainly descriptive analysis of incidence rate of adverse reaction or adverse events. A chi-square test can be used to compare the proportion of participants with adverse reactions in different groups, Fisher's exact test will be used when it is necessary. Analysis of immunogenicity indicators on antibody levels need to do logarithmic transformation, the results of analysis should be shown in GMT, standard deviation, median, minimum and maximum values and 95% confidence intervals. Chi-square test can be used to compare categorical indicators between groups such as positive conversion rate of immune response, if it is necessary, Fisher's exact test will be used. All statistical calculations will be processed by SAS 9.4 statistical analysis system. $P \leq 0.05$ will be considered as statistically significant different (see the first statistical analysis plan and the final statistical analysis plan for details).

11. CLINICAL MONITORING AND CONTROLLING OF EXPERIMENTS

11.1 Responsibilities of all parties

Quality assurance system is maintained by sponsor to ensure that the research is conducted. The data collection, records and reports should be complied with the

requirements of the GCP and protocol. The protocol of clinical trial and all relevant procedures should be fully comprehended by investigator and monitor including investigational vaccine information, obtain informed consent procedures, reporting procedures of adverse events (including serious adverse events) and the EDC data entry program completion.

The main investigators should have a clear mandate for the division and management of all the investigators involved in clinical trials and should develop SOP for all research positions.

The personal data of the participants should be kept confidentially by investigators. eCRF or other documents shall be identified only through participant ID. The participants' identification list and the selection of the registration form (including the full name, age and address) are saved by the investigators. According to the GCP principle, the original data of each participant is allowed to be monitored, inspected by administration department.

The monitoring should be carried out according to the laws of a certain time. The consistence of original data and information in eCRF will be checked to assure accuracy and the completion. If eCRF and original data are inconsistent, urging to investigators is required as soon as possible. The monitor will evaluate the informed consent process, vaccine transportation storage and the progress of the documents. Compliance to protocol will be examined to observe procedure and discuss some issues with investigators. There must be monitoring records. After the study, the monitor shall provide a copy of the audit record to the sponsor.

The DSMB will independently analyzes the post-vaccination safety data of participants in each dose group based on the reported data, and if the DSMB finds an increased risk of participants in the course of the study, the principal investigator and sponsor need to be notified immediately to suspend or terminate the clinical trial.

Jiangsu Provincial Center for Disease Control and Prevention is responsible for the overall design, organization and formulation of related technical programs, and writes a summary of the research.

Hubei Provincial Center for Disease Control and Prevention is involved in design, organization, recruitment, vaccination, vaccine management, safety follow-up and quality control, adverse event reporting and handling.

Zhongnan Hospital of Wuhan University is involved in design, organization and arrangement, recruitment, SARS-CoV-2 antibody screening, urine pregnancy test, HIV test, registration, informed consent, physical examination, determination of excretion, sample collection and treatment, vaccination, observation, safety follow-up assistance, cellular immunity detection, etc., and assisted the medical waste disposal of the Wuhan Special Service Recuperation Center of the Chinese People's Armed Police Force. Be fully responsible for first aid during vaccination and establish a "green channel".

Wuhan Special Service Recuperation Center of the Chinese People's Armed Police Force is responsible for providing test sites and convalescent observation sites, participating in screening, registration, informed consent, physical examination, determination of entry, sample collection, observation, and safety follow-up assistance, and is responsible for site sterilization and medical waste disposal.

National Institutes for Food and Drug Control and Beijing Institute of Microbiology and Epidemiology are responsible for the detection of humoral immunity indicators and issue the detection reports.

11.2 Quality control of investigational vaccine

Investigational vaccines should be managed specifically. The vaccine management and recording system should be available from sponsor to investigator and accept the supervision of the monitor. The number of vaccines, people vaccinated, remaining quantities and the received amount of damage need to be recorded in the work log.

The sponsor will responsible for the delivery of the investigational vaccine. When the investigators found that damaged package of the vaccine, vaccine modification or the bulk material cannot be shaken to dissolve, the investigational vaccine will be returned to the sponsor without use. If the transportation and preservation process in cold chain system was damaged, the vaccine should not be used. They should be separately stored and clearly marked and returned to the sponsor by the responsible person for management. Investigators must sign the vaccine transfer receipt to confirm all vaccines received, the receipt shall be stated briefly the information of received vaccine including the amount, the package, cold chain system.

At the end of the study, the investigators will check all the remaining vaccine, and the inner packaging of the empty vaccine and the vaccine containing residual liquid should be fully recovered for the counting management of the vaccine by the researcher and the sponsor. The total number of remaining investigational vaccines and used vaccines should be the

same as the number of vaccines received by the investigators and returned to the sponsor, and the investigators should sign the vaccine handover form to confirm that all remaining investigational vaccines and used vaccines have been returned to the sponsor.

When returning the vaccine, the researcher returns the vaccine handover order to the sponsor, and the researcher has the responsibility to explain any differences in the quantity of the vaccine.

11.3 Controlling of files

11.3.1 Original files

Original data includes the participants' demographic data, inquiry results of medical history, examination results, laboratory test results, immunization records, records of bleed, combined medication and adverse events/reaction and treatment and outcome etc. All information shall be recorded in the original medical records, and kept in a special room. The original data will be archived in the research center, and it is the basis of data authenticity and integrity.

Visit recording and other original records should be carefully, accurately and immediately filled by investigators. All the raw data should be collected in the record of inoculation and visit. The raw records include the following basic data:

-Items of experiments, participants’ ID

-Demographic data

-Inclusion/exclusion criteria

-Physical examination results

-Laboratory test results (including Immunology)

-Vaccination record

-The date of the visit and the date of termination of clinical trial

-Adverse events /reactions and their treatment and outcome

-Blood collection record

-Concomitant drug treatment, medical treatment and other vaccination

11.3.2 Electronic case report form

Two copies of carbonless eCRF are provided for every participant. The first page of eCRF will be saved by the sponsors, and the second will be preserved by the investigators. Only investigators and approved staff are allowed to visit eCRF during the trial.

For the participants who terminated the trial early, the cause of the early termination should be mentioned in eCRF.

The situation of each stage of the participants should be reflected in eCRF during the trial. Names of the participants cannot be shown in eCRF, the appropriate code or the names in initials could be used.

All the data on the eCRF comes from the raw data and will be consistent with the original data. All the data recorded in the eCRF should be recorded in the original data.

The clinical trial inspector entrusted by the sponsor shall have access to the eCRF, the informed consent and all the original materials at any time.

Written documents should be issued after modified by the sponsors, investigators and other relevant parts about clinical trials communication, meetings, protocol and SOP, and all their agreement documents will be copied in two files and saved respectively.

11.3.3 Storage of files

Preservation of clinical trial data must be accorded to GCP. Investigators should save data at least 5 years more than the end of clinical trials while the clinical trial data should be permanently preserved by sponsors.

11.4 Quality control of biological sample

Serum samples for antibody detection should be collected within 5 hours after centrifugation with a hemolysis rate of serum ≤2% and the error rate ≤1%.

11.5 Ownership and publication

All data/information generated in the research center (except the medical records of the participants) belong to sponsors. If the written contract confidentiality terms of this study should be offset with this statement, processed by prevail of this statement.

Before the research results in submission, speaking, teaching or other form of public (collectively referred to as "publication"), a content copy must be submitted to sponsors to obtain written approval, and the results can be published. The confidential information and personal information of the participants (such as the name or initials) cannot be included in research results.

11.6 Confidential

The sponsor, investigators, ethics committee (IEC) or representatives of full authorized management have the right to access the clinical trial data, but the relevant

content cannot be used for any other clinical trials or disclosed to any other person or entity.

A confidentiality agreement must be signed by the investigators to verify their awareness and agreement with the information in this research is kept confidential.

The investigators and other investigators should keep all the information provided by the sponsors and all the data/information generated in the research center (except the medical records of the participants) confidential. This information and data cannot be used for any other purpose out of this study. This restriction does not apply to: (1) research information is publicly but not due to the violation of investigators and investigators; (2) public the research information to the IRB/IEC for the purpose of evaluation; (3) to provide proper medical assistance lead to information disclosure; or (4) research results published after sponsor authorized. If the written contract confidentiality terms of this study should be offset with this statement, processed by prevail of this contract terms.

12. TIMELINE

This study is supposed to last 9 months from the preparation before the study to the completion of the final summary report, and the clinical trial schedule is shown in the following table (for reference only):

Clinical trial schedule	Estimated time
1.Preparation before the study	30 days
2.Reviewed and Approved by Ethics Committee	5 days

3.The first participant recruited into the group	3month
4.The last participant complete Visit 2	
5. First analysis	10 days
6. First analysis report	
7. The last participant complete Visit 3	6 months
8.Final Analysis	14 days
9.Summary Report	

13. THE ETHICS COMMITTEE APPROVAL

13.1 Ethical review and approval

The Principal investigator should submit the clinical trial protocol and all necessary appendix documents to The Ethics Committee for the initial review as required

- Clinical Trial Protocol (indicate the version number/date)
- Informed Consent (indicate the version number/date)
- Participant recruitment materials (indicate the version number/date)
- eCRF (indicate the version number/date)
- Diary Card (indicate the version number/date)
- Vaccination visit records (indicate the version number/date)
- Investigator’s Brochure
- Principal Investigator’s CV
- Drug clinical trial approval from the National Medical Products Administration

- Research vaccine inspection reports or batch issuance documents
- Research agreement signed with the sponsor

The certificate of approval should be issued to the investigator after getting the approval of the ethics committee. The investigator should submit a copy of the certificate of approval to the sponsor.

13.2 Follow-up Auditing

To audit the method of participant recruitment, if the information offered to the Participants or impartial witness was completed, understandable; if the informed consent was offered appropriately, if the SAE was reported in time. If there was SAE occurred on the Participants, they could get immediate medical treatment.

During the research period, the Ethics Committee should monitor that if the ratio of risk and benefit increased and if the participants' rights and interests are effectively protected.

13.3 Potential danger and danger minimization

13.3.1 Benefit and Risk

The Participants/participants in this study will not pay for the investigational vaccines and will obtain the reasonable transportation expenses, lost income, blood donation, and nutrition fee compensation. The participants will get one shot of the recombinant novel coronavirus vaccine (adenovirus type 5 vector). The participants might be protected against COVID-19 caused by SARS-CoV-2 infection in a period of

time after vaccination. At the same time, there may be some adverse reactions following injection. Common vaccination adverse reactions include: fever, tenderness and swelling on the injection site, redness. The adverse reactions are usually relieved in the 3-5 days after they occur. In the clinical study of adenovirus vaccine abroad, it has been reported in other country's clinical study results that adenovirus vector may cause a prolonged clotting time in a period, but will not influence the safety of life generally. Foreign adenovirus vector vaccines have been approved to be put on the market. The recombinant Ebola virus disease vaccine based on the same adenovirus vector platform has been approved in China and has shown good safety in practical use. In addition, the recent VSV vector vaccine clinical studies have found that vaccination may cause joint pain, which need to be observed in the study.

At present, there is no vaccine against COVID-19 available in the world. If the participants are not willing to receive the research vaccine, there is no other vaccine against COVID-19 is available.

13.3.2 Vaccination

Regular qualified vaccination consumables will be made available together with sterile inoculation following the standard method, strictly to avoid the adverse events caused by improper inoculation or mirrors.

If≥grade 3 adverse reactions or SAE that (maybe) related to the investigational vaccine occur during the safety observation period, the Participants should get immediate medical treatment. When necessary, Green channel for medical treatment should be started immediately for emergency treatment.

13.3.3 Blood Sample collection

Venous blood samples should be collected by experienced nurses who have gotten trained in accordance with the procedures after the qualification audit of the primary investigator to minimize the pain or danger of participants (including pain and venous puncture site infection which is not common)