PROTOCOL COVER PAGE

Brief Title:	A phase I clinical trial of the recombinant novel coronavirus vaccine (adenovirus type 5 vector) in healthy adults
Protocol Title:	A single-center, open-label, dose-escalating phase I clinical trial of the recombinant novel coronavirus vaccine (adenovirus type 5 vector) in healthy adults aged between 18 and 60 years in China.
Protocol Number:	JSVCT088
ClinicalTrials.gov	NCT04313127
Protocol Date:	April 19, 2020
Version:	Version 1.4 (final)
Phase:	Phase I
Sponsor:	Beijing Institute of Biotechnology Address: 20 East Street, Fengtai District, Beijing CanSino Biologics Inc. Address: 185 South Ave., TEDA West District, Tianjin
Principle Investigator	Feng-Cai Zhu, Jiangsu Provincial Center for Disease Control and Prevention Xu-Hua Guan, Hubei Provincial Center for Disease Control and Prevention Wei Wang, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology

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DOCUMENT HISTORY

Version No.	Version Date	Amendment
1.0	March 8	N/A
1.1	March 13	1st Amendment
1.2	March 14	2nd Amendment
1.3	March 17	3rd Amendment
1.4	April 19	4th 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 5.2 and 5.3	Lack of pre-clinical study results	5.3 and 5.2	Some of the pre-clinical study results have been added

Information of the 2nd Amendment			
Contents in Original Version (1.1)		**Contents in Altered Version (1.2)**	
Chapter	**Original Contents**	**Page/Row**	**Altered Contents**
Protocol summary and Chapter 8	This study has three groups, low dose group (2.5×10^{10}vp), middle dose group (5.0×10^{10}vp), and high dose group (1.0×10^{11}vp)	Protocol summary and Chapter 8	This study has three groups, low dose group (5×10^{10}vp), middle dose group (1.0×10^{11}vp), and high dose group (1.5×10^{11}vp)

Information of the 3rd Amendment			
Contents in Original Version (1.2)		**Contents in Altered Version (1.3)**	
Chapter	**Original Contents**	**Page/Row**	**Altered Contents**
Protocol summary and Chapter 8.2 Study endpoints	– Geometric mean titer of neutralizing antibody against SARS-CoV-2 on day 14, day 28, month 3, and month 6. – Seroconversion rate of neutralizing antibody against SARS-CoV-2 on day 14, day 28, month 3, and month 6. – Geometric mean fold	Protocol summary and Chapter 8.2 Study endpoints	– Geometric mean titer of neutralizing antibody against SARS-CoV-2 on day 14, day 28, and month 6. – Seroconversion rate of neutralizing antibody against SARS-CoV-2 on day 14, day 28, and month 6. – Geometric mean fold

	increase of neutralizing antibody against SARS-CoV-2 on day 14, day 28, month 3, and month 6.		increase of neutralizing antibody against SARS-CoV-2 on day 14, day 28, and month 6.
Chapter 10.1 Participants screening	Urine pregnancy test (female only)	Chapter 10.1 Participants screening	HCG pregnancy test (female only)
Information of the 4th Amendment			
Contents in Original Version (1.3)		**Contents in Altered Version (1.4)**	
Chapter	**Original Contents**	**Page/Row**	**Altered Contents**
Chapter 9.4 Withdraw from the study	If a participant is infected by SARS-CoV-2 between day 0 and day 28 post-vaccination, immunogenicity data from he or she will not be included in analysis, but all SARS-CoV-2 infections occurred within 1 year after the vaccination should be documented and reported following the same procedure of SAE reporting.	Chapter 9.4 Withdraw from the study	If a participant is infected by SARS-CoV-2 between day 0 and day 28 post-vaccination, immunogenicity data from he or she will not be included in analysis, but all SARS-CoV-2 infections occurred within 6 months after the vaccination should be documented and reported following the same procedure of SAE reporting.

PROTOCOL SUMMARY

Brief Title	A phase I clinical trial of the recombinant novel coronavirus vaccine (adenovirus type 5 vector) in healthy adults
Official Title	A single-center, open-label, dose-escalating phase I clinical trial of the recombinant novel coronavirus vaccine (adenovirus type 5 vector) in healthy adults aged between 18 and 60 years in China.
Objectives	**Primary objective:** To evaluate the safety and tolerability of the recombinant novel coronavirus vaccine (adenovirus type 5 vector) in healthy adults aged 18 to 60 years. **Secondary objective:** To evaluate the immune response of the recombinant novel coronavirus vaccine (adenovirus type 5 vector) in healthy adults aged 18 to 60 years.
Target disease	To prevent COVID-19 caused by SARS-CoV-2
Target population	Healthy adults aged between 18 and 60 years
Sample size	108 participants
Rational and background	The 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). The 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. Since the outbreak of COVID-19 in December 2019, it has caused a global public health emergency. Up to March 14, 2020, China has reported 81029 confirmed cases and a total of 3194 deaths. At present, there is no specific drug for COVID-19. The COVID-19 epidemic has brought heavy economic pressure and medical burden to China, which has seriously endangered the national security and public health. The recombinant novel coronavirus vaccine (adenovirus type 5 vector) was 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 vector and

	express 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. This is a phase I clinical trial to evaluate the safety, tolerability and immunogenicity of recombinant novel coronavirus vaccine (adenovirus type 5 vector) at 5×10^{10}vp, 1×10^{11}vp and 1.5×10^{11}vp in healthy adults aged between 18 and 60 years old.
Investigational vaccine	The recombinant novel coronavirus vaccine (adenovirus type 5 vector): Manufactures: Beijing Institute of Biotechnology and CanSino Biologics Inc. 0.5ml/ vial. Batch number: 202003001C. Valid until: 2022.02.28. Dosage: 5×10^{10}vp, 1×10^{11}vp and 1.5×10^{11}vp Immunization: intramuscular injection at the lateral deltoid muscle of the upper arm on day 0. Temperature for storage and transportation: at 2-8 ℃
Trial design	Study design: a single-center, open-label, dose-increasing study. Sample size: according to the "Technical guidelines for Vaccine Clinical Trials" issued by the China FDA, the sample size of each vaccine dose group is about 20-30 participants. In this study, 36 participants will be involved in the low-dose group, the middle-dose group and the high-dose group, respectively. A total of 108 participants will be recruited. Study process: This study is performed in three steps: first, the low dose group (5×10^{10}vp); then, the middle dose group (1×10^{11}vp); at last, the high dose group (1.5×10^{11}vp), with 36 participants in each group. The trial will be carried out step by step from the low dose group to the high dose group, and the participants will be recruited sequentially. During the study, if any safety problems of the vaccine is noted, recruiting process should be stopped. The participants will be screened before involved in the study, and all the contents of the study will be completed through 9 visits. Study groups and dose increasing process are shown in the following table.

	<table><tr><th>Dose-increasing steps</th><th>Study groups</th><th>No.</th></tr><tr><td>1</td><td>Low dose</td><td>36</td></tr><tr><td>2</td><td>Middle dose</td><td>36</td></tr><tr><td>3</td><td>High dose</td><td>36</td></tr><tr><td>Total</td><td>-</td><td>108</td></tr></table> Infection during the study period: During the study period, participants with fever, cough and other respiratory symptoms should immediately visit the designated hospital (Guanggu Hospital affiliated to Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology) and inform the investigators. The pharyngeal 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. If the disease of the COVID-19 case is classified as severe or fatal, severe or fatal case investigation should be carried out. In addition to SARS-CoV-2 nucleic acid detection, more than 20 kinds of pathogens will also be detected in the specimens for the differential diagnosis. Duration of the study: It takes about 6 months for each participant to participate in the study, from recruiting to the last visit. Some participates may withdraw the study during the course of the study.
Endpoints	**Primary endpoint:** Occurrence of adverse reactions within 7 days after vaccination. **Secondary endpoints:** Safety: − Occurrence of adverse events (AE) within 28 days after vaccination. − Occurrence of serious adverse events (SAE) within 28 days after vaccination. − Occurrence of serious adverse events during the whole follow-up period (6 months). − Changes of safety laboratory measures (hemoglobin, white blood cell count, total lymphocyte count, platelets, creatinine, alanine transaminase, neutrophil, glutamic oxaloacetic transaminase, total bilirubin, and fasting blood

	glucose) on day 7. Humoral immunogenicity: - Geometric mean titer of antigen-specific antibody on day 14, day 28, month 3, and month 6 measured by ELISA. - Seroconversion rate of antigen-specific antibody on day 14, day 28, month 3, and month 6 measured by ELISA. - Geometric mean fold increase of antigen-specific antibody on day 14, day 28, month 3, and month 6 measured by ELISA. - Geometric mean titer of neutralizing antibody against SARS-CoV-2 on day 14, day 28, and month 6. - Seroconversion rate of neutralizing antibody against SARS-CoV-2 on day 14, day 28, and month 6. - Geometric mean fold increase of neutralizing antibody against SARS-CoV-2 on day 14, day 28, and month 6. - Geometric mean titer of neutralizing antibody against Ad5 on day 14, day 28, month 3, and month 6. - Geometric mean fold increase of neutralizing antibody against Ad5 on day 14, day 28, month 3, and month 6. 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 taken; if the antibody level is greater than the maximum detection limit, the maximum dilution will be taken. Cellular immunogenicity: Cell-mediated responses on day 14, day 28, and month 6: - Positive rate and level of IFN-γ measured by ELISpot. - Intracellular cytokine staining (ICS) assay to measure positive rates and levels of IFN-γ, TNFα and IL-2 expressed by the active CD4+T and CD8+T lymphocyte. **Exploratory Endpoints** - The correlation between antigen-specific antibody measured by ELISA and neutralizing antibody against SARS-CoV-2. - The dose-response relationship of antigen-specific antibody measured by ELISA across the dose groups. - The persistence of the antigen-specific antibody measured by ELISA at month 6. - The correlation between the initial time of the antibody response and the dose groups. - The correlation between cell-mediated responses (ELISpot IFN-γ, and ICS positive rates of IFN-γ, TNFα and IL-2

	expressed by the active CD4+T and CD8+T lymphocyte) and the dose groups. - The persistence of the cell-mediated responses (ELISpot IFN-γ, and ICS positive rates of IFN-γ, TNFα and IL-2 expressed by the active CD4+T and CD8+T lymphocyte) at month 6. - The correlation between the initial time of the cell-mediated responses (ELISpot IFN-γ, and ICS positive rates of IFN-γ, TNFα and IL-2 expressed by the active CD4+T and CD8+T lymphocyte) and the dose groups.
Scheduled site visits	This study has 9 scheduled visits, including V0 (within 7 days before the vaccination), V1 (day 0), V2 (day 3), V3 (day 7), V4 (day 10), V5 (day 14), V6 (day 28), V7 (month 3), V8 (month 6). Chest CT scan and nucleic acid screening before the vaccination: - All the participants are examined by chest CT, and those with COVID-19 imaging features will be excluded. - Pharyngeal swabs or sputum and anal swabs are collected and detected by RT-PCR or/and NGS methods. Those with positive result will not be involved in the study. Humoral immune response: - V0 (within 7 days before the vaccination): blood will be collected and anti-S and anti-N protein specific IgM and IgG antibodies will be detected by chemiluminescent immunoassay. - V1 (before the first vaccination), V5 (day14), V6 (day 28), V7 (month 3) and V8 (month 6). 10ml of peripheral venous blood will be collected at each visit, and the serum antibodies will be detected by ELISA, neutralization test with SARS-CoV-2 and/or its pseudovirus. Cellular immune response: - V1 (before the vaccination), V5 (day 14), V6 (day 28), V8 (month 6), 20ml of peripheral venous blood will be collected at each visit, and the PBMC will be isolated to detect the level of specific T cell responses.
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. If an increased risk of participants is found in the course of the study, they send notice to the principal investigator and the sponsor immediately to suspend or terminate the recruiting of participants in clinical trial,

	during the dose-escalating procedure. 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 the right to suspend or terminate the study, and shall notify other parties and participants and explain the reasons. Administration of study injections and new enrollments will be paused, if: − One or more ≥grade 4 adverse reaction or serious adverse event may be associated with vaccination, or − Occurrence of grade 3 adverse events associated with vaccination in 15% of participants or more (including injection-site reaction, systemic reaction, and change of the safety laboratory measures), or − Required by sponsor, or − Required by regulatory authority, or − Required by institutional review board (IRB). The study may come to an early termination, if DSMB, sponsor and investigator agree that the risk increased and the risk-benefit for participants is no longer reasonable.
Initial analyses	Initial analyses: After the last participants completed V6 (day 28), data on the safety, humoral immunogenicity and cellular immunogenicity will be allowed for initial analyses. Final analyses: After the last participants completed V8 (month 6), data on the safety, humoral immunogenicity and cellular immunogenicity will be allowed for final analyses.
Inclusion criteria	− Aged between 18 and 60 years. − Able to understand the content of informed consent and willing to sign the informed consent − Able and willing to complete all the secluded 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 − Chest CT scan is normal (no COVID-19 imaging) − Pharyngeal swabs or sputum and anal swabs are negative for SARS-CoV-2 − A body mass index (BMI) are between 18.5 and 30.0 − Indexes of blood routine, biochemistry and other laboratory tests are within the normal ranges, or not clinical significant

	judged by doctors (including white blood cell count, lymphocyte count, neutrophils, platelets, hemoglobin, ALT, AST, total bilirubin, fasting blood glucose, creatinine) − 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 infection − 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
CLA	Chemiluminescence Assay
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 Titre
IEC	Independent Ethics Committee
ITT	Intent-to-treat
MCPENT	Micro-CPE Neutralization Test
NIFDC	National Institute for Food and Drug Control
NMPA	National Medical Products Administration
PBMC	Peripheral Blood Mononuclear Cells
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. We are going to evaluate the safety, tolerability, and immunogenicity the recombinant novel coronavirus vaccine (adenovirus type 5 vector) in healthy people aged 18-60 years old.

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

2. STUDY SITE

East Lake, Wuhan, Hubei Province

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
Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology

3.3 Contract Research Organization

Nanjing Sunrise Pharmaceutical Technology Co., Ltd.

3.4 Statistical Party

Shanghai Canming Medical Technology Co., Ltd

3.5 Clinical laboratory

3.5.1 National Institutes for Food and Drug Control

The main responsibilities in the study are:

(1) Detection of S protein antibody against SARS-CoV-2 by ELISA.

(2) Detection of neutralization antibody against SARS-CoV-2 (Pseudovirus neutralization test).

(3) Detection of neutralizing antibody against recombinant replication defective human type 5 adenovirus.

3.5.2 Hospital of the Central Theater of the Chinese people's Liberation Army

The main responsibilities in the study are:

(1) Pregnancy test.

(2) HIV antibody screening.

(3) Blood routine examination.

(4) Blood biochemical examination.

3.5.3 Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology

The main responsibilities in the research are:

(1) CT imaging screening.

(2) Detection of specific $CD4^+$ T cells and $CD8^+$ T cells.

(3) Detection of IFN-γ secretion by specific T cells.

3.5.4 Biosafety third-level laboratory for COVID-19 prevention and control in military medical expert group tent

The main responsibilities in the study are:

(1) SARS-CoV-2 antibody screening (chemiluminescence assay).

(2) SARS-CoV-2 nucleic acid screening.

3.5.5 Beijing Institute of Microbiology and Epidemiology

The main responsibilities in the study are:

Detection of neutralization antibody against SARS-CoV-2 (SARS-CoV-2 neutralization test).

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, mind dispirited or 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), developed by the Beijing Institute of Biotechnology and CanSino Biologics Inc. This vaccine is based

on a platform of mature 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 research and development of vaccines against COVID-19 are all in an early stage. Therefore, we have a summary of the research and development of MERS vaccines which might provide a reference to the current development of novel vaccine against COVID-19, shown in Table 4-3-2-1 and 4-3-2-2.

Table 4-3-2-1 Potential candidate vaccines against MERS

Type	Vector and Antigen	Delivery system*	Research results
Virus vector	rAd5 encoding S1 protein	IM	Immunization with rAd5 constructor (rAd5-S1/F/CD40L) expressing CD40-targeted S1 fusion protein could provide hDPP4 transgenic mice with comprehensive protection against MERS-CoV challenge and prevent pulmonary perivascular hemorrhage.
	rAd5 or rAd41 encoding S protein	IM or IG	After intragastric administration of rAd5-S or rAd41-S, specific IgG antibody and neutralizing antibody could be produced in serum, but T cell response could not be detected. After intramuscular injection of Ad5-S or Ad41-S, not only functional antigen-specific T cell response but also systemic humoral response could be induced in spleen and lung lymphocytes of mice, which could last for several months.
	rAd5 encoding S protein or S1 protein	IM, then boosting immunity by IN	Immunized mice showed an antibody response to spike protein, which neutralized MERS-CoV in vitro. Compared with the mice inoculated with full-length S protein, a stronger neutralizing antibody response was observed in the mice expressing short S1 protein.
	ChAdOx1encodingS protein	IM or IN	A single dose of intranasal or intramuscular immunization can protect transgenic BALB/c mice from lethal virus attack. The immunogenicity and efficacy of immune pathways are similar.
	ChAdOx1encodingS protein	IM	Single-dose of immunization with ChAdOx1 MERS vaccine containing tissue plasminogen activator can produce 5 logarithmic logs of neutralizing antibodies in BALB/c mice
	MVA encoding S	IM	Immunized with MVA MERS vaccine containing F11 promoter to regulate

	protein		tissue plasminogen activator, 4.7 logs neutralizing antibodies were produced in BALB/c mice.
	MVA encodingS protein	IM or SC	Neutralizing antibody and CD8+ T cell response could be induced by both immune routes in mice. After transduction with hDPP4 receptor, the inoculated mice had a protective effect against MERS-CoV challenge infection.
	MVA encoding S protein	IM	Neutralizing antibody response was induced in immunized mice.
	MVAencoding N protein	IM or IP	In both routes of administration, CD8+ T cell response could be induced in immunized mice.
	NDV encodingS protein	IM	Neutralizing antibodies can be induced by recombinant NDV expressing MERS-CoV S protein in BALB/c mice and Bactrian camels.
Virus vector /Nanoparticles	rAd5 and MERS-CoV S Nanoparticles	IM	Heterogeneous priming-boosting with rAd5-S protein and aluminum adjuvant-recombined S protein in SPF BALB / c mice can induce Th1 and Th2 immune responses.
DNA	DNA encoding S protein	IM, then EP	DNA vaccine has immunogenicity in mice, camels and rhesus monkeys. When immunized rhesus monkeys are challenged with MERS-CoV, typical clinical symptoms, including pneumonia, are alleviated.
	DNA encoding S or S1 protein	IM	DNA encoding S1 protein produced stronger antibody and cellular immune response in mice than DNA encoding S protein. DNA encoding S1 and S proteins induced neutralizing antibodies, which cross-reacted with human and camel-derived MERS-CoV strains.
	DNA encoding S1 protein	IM	DNA encoding S1 protein produced stronger antibody and cellular immune response in mice than DNA encoding S protein. DNA encoding S1 and S proteins induced neutralizing antibodies, which cross-reacted with human and camel MERS-CoV strains.
Subunit	MERS-CoV S1 protein	SC	MERS-CoV S1 protein containing adjuvant (MF59) can protect hDPP4 transgenic mice from lethal MERS-CoV challenge, and its protective effect is closely related to the titer of neutralizing antibody.
	MERS-CoV S1 protein	IM	Immunization with S1 protein containing adjuvant (Advax HCXL adjuvant and Sigma adjuvant system can reduce and delay virus shedding in the upper respiratory tract of unimodal camel and provide comprehensive protection against MERS-CoV attack in alpaca.
	Based on Fd MERS-CoV S protein trimer	IM	The recombinant pre-fusion trimer MERS-CoV S protein induced high titer neutralizing antibody in BALB / cJ mice.
	Based on Fd RBD trimer	SC or IM	RBD-Fd containing adjuvant (aluminum) induces neutralizing antibodies in BALB/c mice and protects hDPP4 transgenic mice (83%) from lethal MERS-CoV attacks.
	Fusion of RBD and Fc	SC	Adjuvanted RBD-Fc could induce high titers of neutralizing antibodies in BALB/c mice and New Zealand white rabbits.
		SC	Vaccines containing Montanide ISA 51 as adjuvant could induce high titers of neutralizing antibodies in mice, antibody inhibits the binding of RBD to DPP4 receptor, thus neutralizing MERS-CoV infection.

		IN or SC	Vaccine with adjuvants (SC:Montanide ISA 51 adjuvant and IN:Poly adjuvant) elicited humoral immune responses in mice, through both SC and IN. Stronger systemic cellular immune response and local mucosal immune response were observed in mice immunized with IN pathway.
		IM	When hCD26 / DPP4 transgenic mice were immunized with adjuvant vaccine, AddaVax could induce neutralizing antibody and be protected from MERS-CoV infection.
		SC	Mice immunized with only the vaccine produced only detectable neutralizing antibodies and cellular immune responses. When the vaccine contains adjuvants, such as Freund's adjuvant, aluminum, monophosphoryl lipid A, Montanide ISA51 or MF59, the immunogenicity of the vaccine is improved. Facts have proved that MF59 has more advantages in enhancing the immunogenicity and resisting virus attack.
	Recombinant RBD	IM or SC	When subunit vaccine is used in combination with aluminum and CpG ODN, it can induce the best humoral and cellular immunity against RBD. Strong RBD specific antibodies and T cell responses were induced in mice immunized with IFA and CpG ODN vaccines, but the level of neutralizing antibodies induced was low.
	Recombinant RBD	IM	When challenged with MERS-CoV, rhesus monkeys immunized with a subunit vaccine containing aluminum adjuvant produced neutralizing antibodies and alleviated clinical symptoms.
	Recombinant N-terminal domain (rNTD) of S protein	IM	Neutralizing antibodies were produced by immunization with rNTD containing aluminum adjuvant MERS-CoV S protein, and the respiratory symptoms of BALB/c mice challenged with MERS-CoV were reduced.
Virus-like particles	MERS-CoV Virus-like particles	IM	Combined application of electrothermal vlps vaccine containing aluminum adjuvant can activate RBD specific humoral and cellular immune responses in rhesus monkeys.
	S protein Nanoparticles	IM	The S protein produced in the baculovirus insect cell expression system is assembled into about 25 nm nanoparticles. Mice immunized with these nanoparticles in the presence of aluminum adjuvants produced high titers of neutralizing antibodies.
	S protein Nanoparticles	IM	The vaccine and Matrix M1 adjuvant together activate S protein specific humoral immune response and protect hDPP4 transduced mice from virus infection.
	CPV virus particles express receptor binding region	IM	In the presence of adjuvant [aluminum or Poly (I: C)], mice immunized with chimeric VLPs showing RBD could induce neutralizing antibody response and cellular immune response.
	Influenza A virus particles expressing S protein	IM	In the case of combined adjuvants (aluminum and CpG ODN)), mice were immunized with chimeric VLPs showing RBD.
Nanoparticles	Ferritin expressing RBD	IM	Immunization with chaperna-mediated ferritin nanoparticles (with MF59 as adjuvant) showing MERS-CoV RBD could induce the binding of RBD specific antibody in BALB/c mice, which inhibited the binding of RBD to hDPP4 receptor protein.

Inactivated	MERS-CoV	IM	In the presence of adjuvants (aluminum and CpG ODN), mice vaccinated with inactivated vaccines produced neutralizing activity, but not cell-mediated immunity. The vaccine also protects hDPP4 transduced mice against MERS-CoV infection.
	MERS-CoV	IM	γ-ray inactivated MERS-CoV can induce hDPP4 transgenic mice to produce neutralizing antibodies and reduce virus load, but it may cause highly sensitive lung immunopathological response when challenged with MERS-CoV.
	Chimeric RABV expressing S1 protein	IM	Inactivated vaccine can induce high titer of neutralizing antibody in mice and protect hDPP4 transduced mice from MERS-CoV infection.
	MERS-CoV Mutation	—	The mutant was produced by deleting the E gene of MERS-CoV. The mutant is not infectious, but has the ability to replicate in a single cycle.
Attenuated	MERS-CoV Mutation	—	The mutant was produced by deleting the E gene of MERS-CoV. The mutant is not infectious, but has the ability to replicate in a single cycle.
	MERS-CoV Mutation	IN	The MERS-CoV was attenuated by mutant NSP16 (D130A), and the 288Mu330 C57BL/6 + C57BL/6 mice targeted by crispr-cas9 were protected from the attack of adaptive MERS-CoV.
	MV expressing full-length or truncated soluble S protein variants	IP	The recombinant MV has the ability of replication. Type I interferon receptor deficient (IFNAR-/-) CD46Ge mice immunized with recombinant MV could induce specific neutralizing antibodies against MV and S protein as well as cellular immune response. Recombinant MV can protect hDPP4 transduced mice from virus infection.
	MV expressing N protein	IP	Recombinant MV expressed MERS-CoV protein and induced N-specific T cell response in IFNAR-CD46Ge mice.
	Recombinant VSV expresses S protein	IN or IM	Recombinant VSV is obtained by replacing the glycoprotein of VSV with the S protein of MERS-CoV. Neutralizing antibodies and T cell responses were induced by recombinant virus after a single dose of intramuscular or intranasal immunization in rhesus monkeys.

Note:

rAd5: recombinant Replication Defective Human Adenovirus Serotype 5;

rAd41: recombinant Replication Defective Human Adenovirus Serotype 41;

MVA: Modified Vaccinia Virus Ankara; ChAdOx1: chimpanzee adenovirus:

MV: measles virus; CPV: canine parvovirus; RABV: rabies virus;

VLP: virus-like particles; NSP: nonstructural protein; RBD: receptor binding region.

RNTD: recombined N-terminal domain; Fc: human IgG Fc region;

IM: muscular; IN: intranasal; IP: intraperitoneal; SC: subcutaneous; IG: intragastric; EP: electroporation.

Table 4-3-2-2 MERS candidate vaccines grouped by vaccine type

Type	**Humoral response**	**Cellular response**	**protection**	**Clinical trial**
Subunit				
RBD	M,P	M,P	M,P	

S Nanoparticles	M		M	
Lock S before fusion	M			
NTD	M	M	MM	
DNA				
pVax1-S	M, P, C	M, P	P	Phase I
pVRC8400-S[1]	M, P		P	
pcDNA3.1(+)-S1 or S	M	M	M	
Virus sector				
VEEV-S	M			
VEEV-N		M	M	
MVA-S	M,C	M	M,C	Phase I
Ad5-S or S1	M	M		
Ad5-S[2]	M	M	M	
Ad41-S	M	M		
ChAdOx1-S	M	M	M	Phase I
MVvac2-S	M	M	M	
Newcastle-S	M,C			
VSV-S	M,P	P		
Rabies-S1	M		M	
Bac-S,E,M	P	P		
Bac-RBD+vp2	M	M		
Full virus				
Formalin inactivation	M		M	
MERS-ΔE				
MERS-dNSP16	M		M	
MERS-dORF3-5	M		M	

Humoral response includes all kind of antibody responses, in most cases neutralizing antibody is referred. Cell-mediated response refers to T cell activation markers including IFN-γ.

S: MERS-CoV spinous process protein; N: MERS-CoV capsid protein; RBD: receptor binding region;

NTD: N terminal domain; S1: spinous process protein receptor binding subunit; E: MERS-CoV envelope protein;

M (vaccine type): MERS-CoV membrane protein; vp2: canine parvovirus vp2 protein;

M (under protection): rats; P: non-human primates; C: camels.

[1] using S1 protein enhancer; [2] S nanoparticle enhancer

In the animal experiment, recombinant human adenovirus type 5 (Ad5) MERS vaccine expressing S protein, induced high level of humoral and cellular immune responses and a good immune persistence, which is expected to be a candidate vaccine to prevent MERS in clinical trials.

4.3.3 Experience of previous research on the Recombinant Human Type 5 Adenovirus Vector Based Ebola Vaccine (Ad5-EBOV).

The Recombinant Human Type 5 Adenovirus Vector Based Ebola Vaccine (Ad5-EBOV) are developed by the Beijing Institute of Biotechnology and CanSino Biologics Inc. based on the same platform of recombinant human type 5 adenovirus vector, which has

been approved by the China Food and Drug Administration in October 2017. The results of Ad5-EBOV in phase I clinical trial in China (mainland) and phase II clinical trial in Africa (Sierra Leone) are briefly summarized as follows:

Phase I clinical trial in Taizhou, China:

In December 2014, a phase I clinical trial to evaluate the safety, tolerability, and immunogenicity of Ad5-EBOV vaccine in 60-year-old Chinese population was conducted by Jiangsu Centers for Disease Control and Prevention. It was a single-center, dose-escalation, randomized, double-blind and placebo-controlled trial. In this study, a total of 120 participants were included. 60 participants were firstly recruited and randomly assigned to receive the low dose Ad5-EBOV or placebo in a ratio of 2:1. After the safety of the low dose vaccination is confirmed, another 60 participants were recruited and randomly assigned to receive the high dose Ad5-EBOV or placebo in a ratio of 2:1. Thus, 40 participants received the low dose vaccine, 40 received the high dose vaccine and 40 received the placebo.

The safety results showed that there was a dose-response relationship of overall adverse reactions and injection-site adverse reactions. A higher dose was associated with a higher incidence of adverse reactions. However, most of the reactions were mild (grade 1), such as pain at injection-site, and no grade 3 or more severe adverse reactions related to the vaccination were found, indicating that the Ad5-EBOV were well tolerant in participants. The immunogenicity data showed that the seropositive proportion of GP-specific antibodies in the low-dose and the high-dose groups were 95.00% and 100.00% respectively, on day 28 after immunization.

Phase I clinical trial in Hangzhou, China:

From April 3, 2015, the first affiliated Hospital, Zhejiang University started another phase I clinical trial to evaluate the safety, tolerability, and immunogenicity of recombinant Ebola virus disease vaccine (Ad5-EBOV) in Africans aged 18-60 years in China. This study is a single-center, open phase I clinical trial half male and female, with two dose groups, each group of 30 people, a total of 60 people, gradually enrolled

from low dose to high dose.

No serious adverse reactions were noted in all the participants. The specific antibody titers of Ebola GP in low and high dose groups were significantly increased at 14 days and 28 days after immunization, of 1370.9 and 1185.5 at day 14, and 1918.7 and 1684.7 at day 28 after immunization, respectively. The T cell immune responses also reached the peak on day 14 after immunization.

A single-center, randomized, double-blind, placebo-controlled phase II clinical study was conducted in Sierra Leone in October 2015 to evaluate the safety and immunogenicity of the Ad5-EBOV. A total of 500 healthy participants aged 18 to 50 were recruited and given a high-dose vaccine, a low-dose vaccine or a placebo at 2:1:1. Safety results showed that about 50-65% of participants reported at least one adverse reaction within 7 days after vaccination, most of which were mild and self-limited. There were no serious adverse events related to the vaccine. Ebola GP-specific antibody response was detected since day 14 (the GMT of the low dose group was 1251.0 and that of the high dose group was 1728.4), and reached the peak (1471.8 and 2043.1) on the day 28.

Clinical trial data show that the Ad5-EBOV based on recombinant human type 5 adenovirus vector platform has good safety and tolerability, and can induce high level of humoral and cellular immune response after vaccination.

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

The pre-clinical study results of this chapter will be updated in a form of appendix to this protocol, if more data from the pre-clinical studies become available.

5.1 Preclinical immunogenicity evaluation

The pre-clinical studies of immunogenicity in mice and guinea pigs was performed by the Institute of Biological Engineering, Academy of military Medicine, Academy of military Sciences. In addition, the Institute of Medical Experimental Animals of the Chinese Academy of Medical Sciences and the Harbin Veterinary Research Institute of the Chinese Academy of Agricultural Sciences performed the challenge study on mice, ferrets and rhesus monkeys, and sera were collected 14 days post-challenge for immunogenicity evaluation.

5.1.1 Mouse model

5.1.1.1 Experimental Design

Ten BALB/c mice in each dose group were immunized with low (5×10^7vp), middle (5×10^8vp) or high (5×10^9vp) dose of the recombinant novel coronavirus vaccine (adenovirus type 5 vector) or empty adenovirus (Ad5-NULL) as control. Blood samples were collected on the 9th, 14th, 28th, 42nd, 56th, 84th, 112th, 140th and 168th day after immunization to detect the specific ELISA antibody and neutralization antibody specific to S protein of SARS-CoV-2.

The cellular immune responses of BALB/c mice immunized with the recombinant novel coronavirus vaccine (adenovirus type 5 vector) at dose of 5×10^8vp was detected by flow cytometry and ELISpot.

5.1.1.2 Results of ELISA antibody.

The anti-S protein IgG antibodies of mice were detected at day 9 and 14 after a single dose immunization. On day 9 after immunization, the GMT of anti-S protein IgG antibodies in high, middle and low groups were 137205 ±40120, 57900 ±15950, 10961 ±7258, respectively; on day 14 after immunization, the GMT of anti-S protein IgG antibodies in high, middle and low groups were 220331 ±59612, 73608 ±14783, 27025 ±15076, respectively. The results showed that the recombinant novel coronavirus vaccine (adenovirus type 5 vector) had a good immunogenicity in BALB/c mice, and the antibody level increased in a dose-response relationship. The antibody responses had a similar characteristic consistent with that of the Ad5-EBOV, but the antibody titer was significantly higher than that of the Ad5-EBOV.

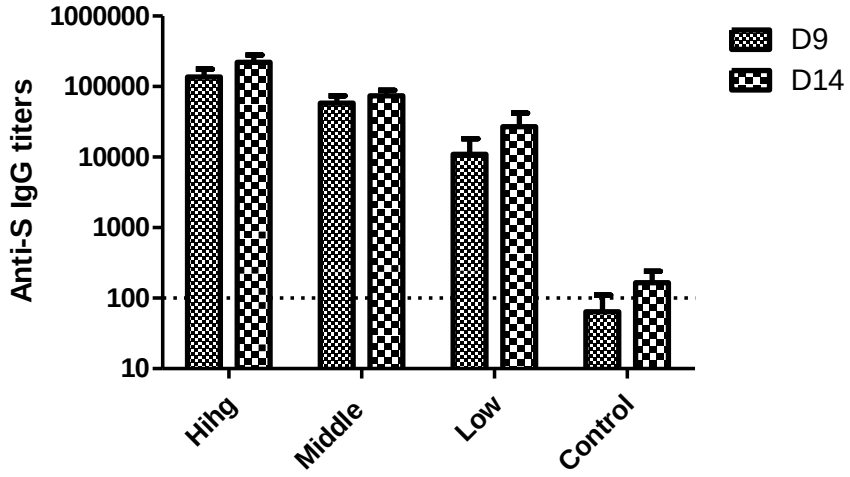

Fig.5-1-1-1. The level of anti-S protein IgG antibody in mice at day 9 and 14 after single immunization.

5.1.1.3 Neutralizing antibody results.

To be submitted.

5.1.1.4 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.

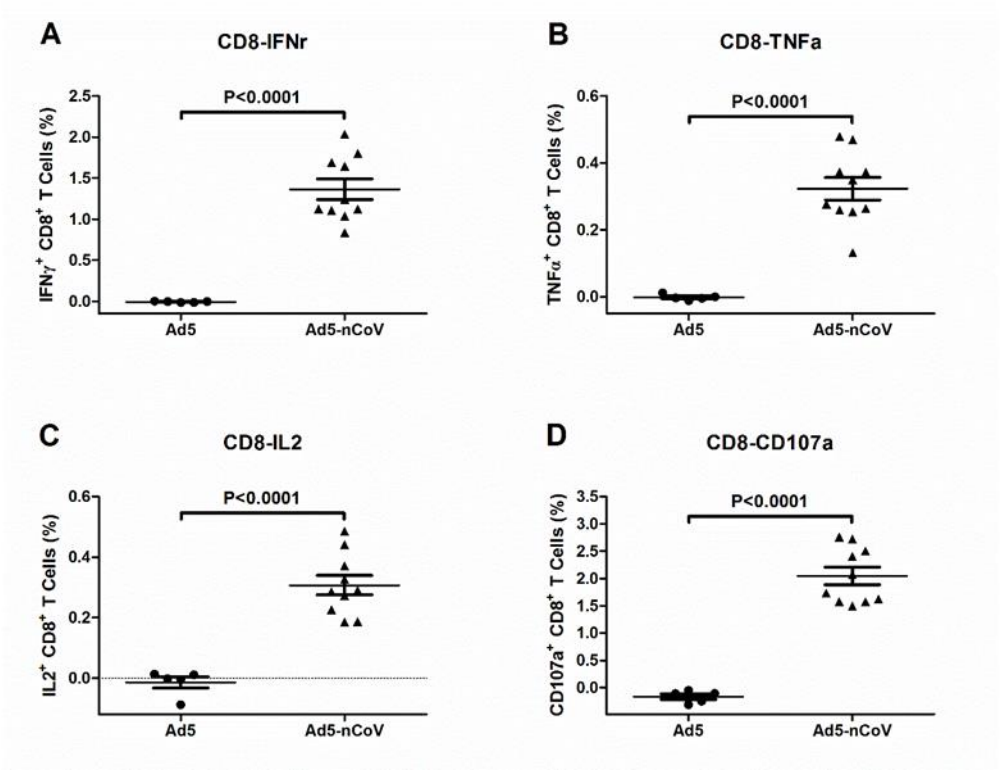

Figure 5-1-1-2. The CD8+ T cell immune responses post-vaccination.

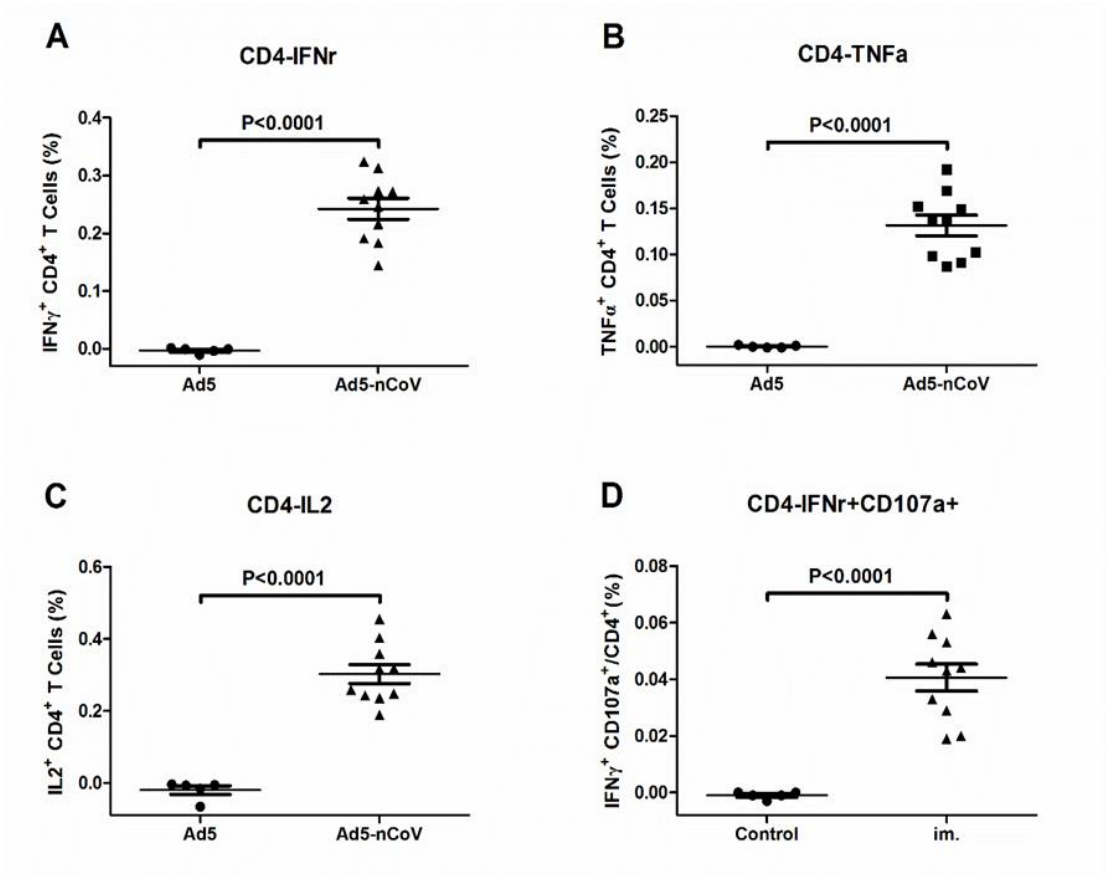

Figure 5-1-1-3 The CD4+ T cell immune responses post-vaccination.

5.1.2 Guinea pig model

5.1.2.1 Experimental Design

Ten guinea pigs in each dose group were immunized with low (5×10^7vp), medium (5×10^8vp) and high (5×10^9vp) dose recombinant novel coronavirus vaccine (adenovirus vector) by intramuscular injection with empty adenovirus (Ad5-NULL) as control. Blood samples were collected on the 14th, 28th, 42nd, 56th, 84th, 112th, 140th and 168th day after immunization to detect the S protein specific ELISA antibody and neutralization antibody of SARS-CoV.

5.1.2.2 Results of ELISA antibody

The anti-S protein IgG antibodies of guinea pigs were detected 14 days after single dose immunization (Figure 5-1-1-4). The geometric mean titers of antibodies in high, middle and low groups were 43386 ±27575, 36801 ±31736, 9997 ±8784, post-vaccination, respectively. The results showed that the recombinant novel coronavirus vaccine (adenovirus type 5 vector) had good immunogenicity and the antibody level showed an obvious dose-response relationship.

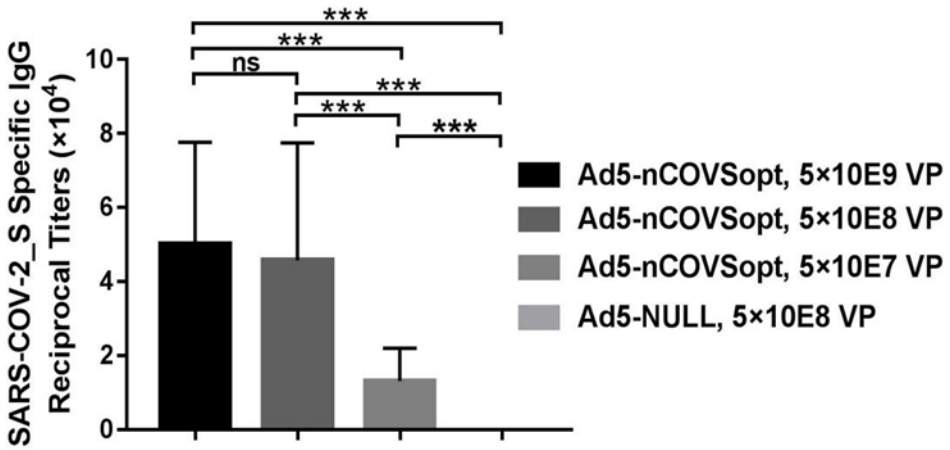

Figure 5-1-1-4 The level of anti-S protein IgG antibody in guinea pigs 14 days after the vaccination.

5.1.2.3 Results of neutralizing antibodies.

To be submitted.

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).

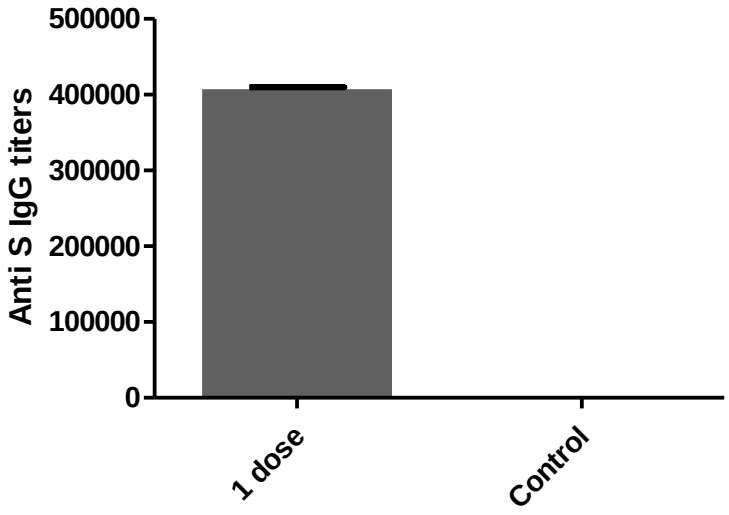

Figure 5-1-1-5 The level of anti-S protein antibody in rats 14 days after immunization

5.1.4 Crab-eating monkey (Macaca fascicularis)

In the toxicity test of repeated injection in crab-eating monkeys 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 immunization, the neutralization antibody values of high-dose group and low-dose group were 192 ±303 and 61 ±195 respectively (Figure 5-1-1-7).

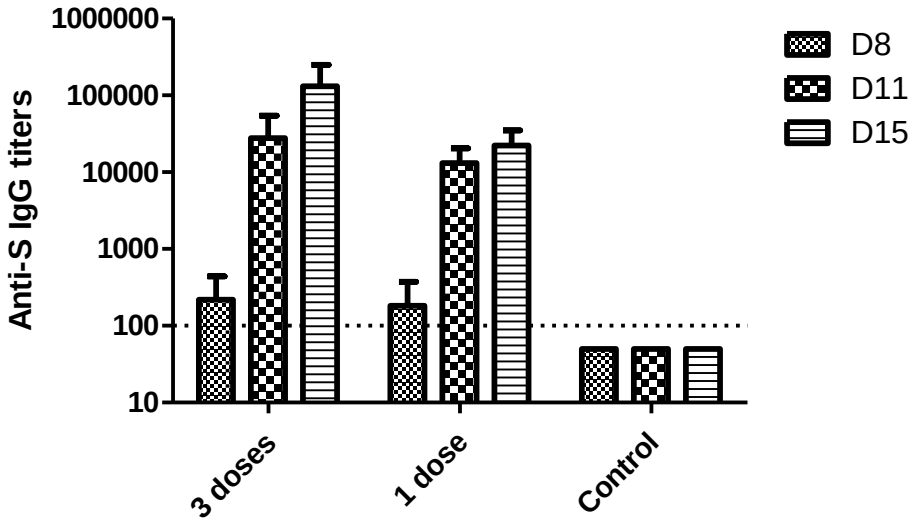

Figure 5-1-1-6 The anti-S protein antibody at day 8, 11 and 15 after the first vaccination

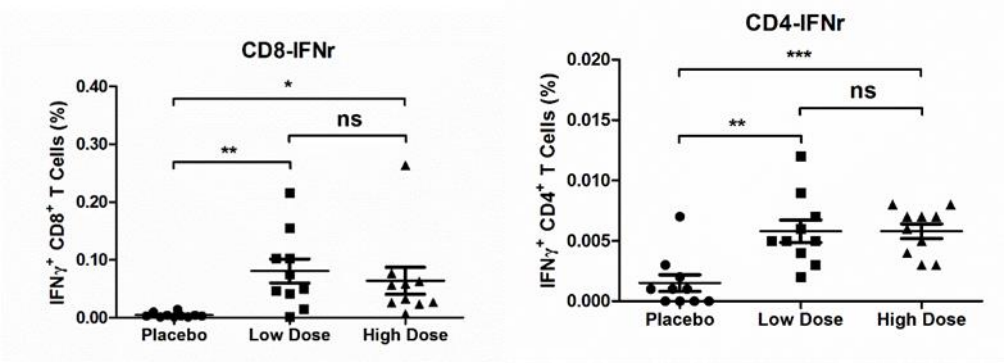

Figure 5-1-1-7 Specific cellular immune response of crab-eating monkey 13 days after first vaccination

5.2 Protective experiments in animals

The protective experiments in mice and cynomolgus monkeys were commissioned by the Institute of Medical Experimental Animals of the Chinese Academy of Medical Sciences, and the protective experiments in ferrets were commissioned by Harbin Veterinary Research Institute of Chinese Academy of Agricultural Sciences.

5.2.1 Protective experiments in ACE2 transgenic mice

Eighteen 4-6-week-old ACE2 transgenic female mice were randomly assigned to three groups: control group (model group, n=6), 5×10^{19}vp group (n=6) and 5×10^{8}vp group (n=6). Each mouse was injected at a dose of 100 μl intramuscularly once at day 0. Blood samples were collected before immunization, 14 days after immunization and when the

animals were killed. The serum was separated and then detected the antibody. The vaccinated mice was challenged by live SARS-CoV-2 virus at day 14 after vaccination. The body weight, SARS-CoV-2 copy number was measured by quantitative PCR at day 3, SARS-CoV-2 load detected by cytopathic method and immunopathological changes of lung tissue sections were observed.

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.

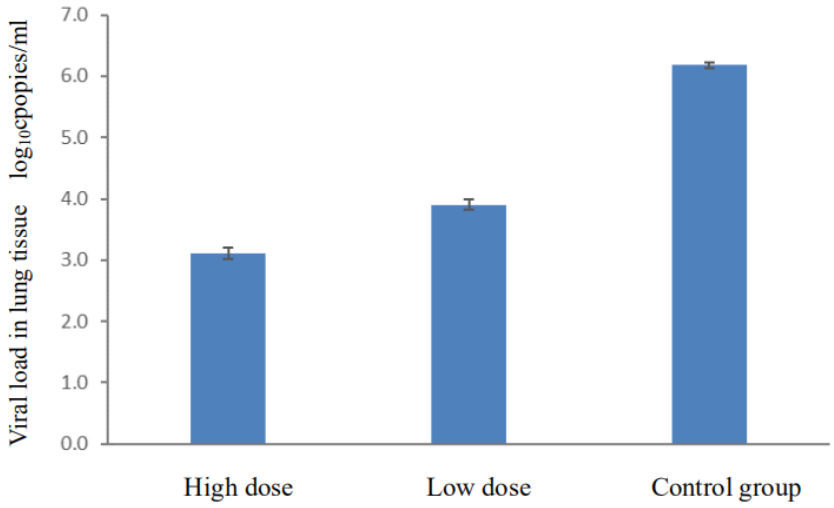

Fig. 5-2-1-1 Viral load in mouse lung tissue

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 (table 5-2-1-2).

Table. 5-2-1-2 Pathological changes of lung tissue of mice in each group at day 3 after infection

pathological changes Groups and animal number		Widening of alveolar septum	Inflammatory cell infiltration in alveolar septum	Exudation in pulmonary alveoli	Infiltration of perivascular inflammation cells	Perivascular edema	Bleeding	Other pathological changes
High-dose	1	++	+	+	—	—	—	—
	2	+	+	+	—	+	—	—
	3	+	+	+	—	—	—	—
Low-dose	1	++	+	+	—	+	—	—
	2	++	+	+	+	++	+	—
	3	+	+	+	—	++	—	—
Model	1	++	+	+	—	++	+	—
	2	+	+	+	+	++	—	—
	3	++	+	++	+	+	+	

+: mild pathological changes; ++: moderate pathological changes; +++: severe pathological changes; ++++: Extremely severe pathological changes.

Criteria for grading of pathological changes:

Widening of alveolar septum: +, mild pathological changes, slight widening of alveolar septum. ++, moderate pathological changes, the alveolar septum was significantly widened, and the lesion range was larger than 1/4. +++, severe pathological changes, the alveolar septum was significantly broadened, and the alveolar septum was widened, fused and the alveolar cavity was significantly narrowed. The lesion area was larger than 2/4. ++++, extremely severe pathological changes, the alveolar septum was widened, fused, and the alveolar cavity was narrowed significantly so that it disappeared. The local lung tissues were consolidated, and the lesion range was larger than 3/4.

Other pathological changes (exudation in pulmonary alveoli, infiltration of perivascular inflammation cells, edema perivascular, bleeding, etc.): +, mild pathological changes, lesion range was less than 1/4 of lung tissue section. ++, moderate pathological changes, the lesion range was about 1/4 ~ 2/4 of the lung tissue section. +++, severe pathological changes, the lesion range was about 2/4 ~ 3/4 of the lung tissue section. ++++, extremely severe pathological changes, the lesion range was larger than 3/4 of the lung tissue section

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 immunization, 14 days after immunization 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 are to be submitted.

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 immunization, 14 days after immunization 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.

The results are to be submitted.

5.3 Safety evaluation in preclinical research

Beijing Zhaoyan New Drug Research Center Co., Ltd. was entrusted to carry out pharmacological and toxicological research.

5.3.1 Systemic active allergic reaction in guinea pigs

5.3.1.1 Experimental design

The sensitization effects of recombinant novel coronavirus vaccine (adenovirus vector) had been examined in guinea pigs. 36 experimental animals were assigned to 4 groups: negative control group, positive control group, low group (0.1 dose) and high group (1 dose). The negative control group was sensitized and activated with sodium chloride injection, the positive control group was sensitized and activated with human serum albumin, and the test groups were sensitized and activated with provided reagent. The drug was given three times at an interval of one day, and the systemic allergic reaction of the animals was observed after stimulation.

5.3.1.1 Experimental results

The results are to be submitted.

5.3.2 Toxicity experiment of single intramuscular injection in SD rats

5.3.2.1 Experimental design

The acute toxic effects of recombinant novel coronavirus vaccine (adenovirus vector) had been examined in SD rats. 20 experimental animals were assigned to 2 groups: negative control group and test group (1 dose). Clinical observation and monitoring of body weight and food intake after a single intramuscular injection.

5.3.2.1 Experimental results

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.

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

5.3.3.1 Experimental design

The toxic effects of repeated intramuscular injection in cynomolgus monkeys for 2 weeks and 2 weeks of recovery period with recombinant novel coronavirus vaccine (adenovirus vector). 30 experimental animals were assigned to 3 groups: negative control group (sodium chloride injection), low dose group (1 dose) and high dose group (3 dose) were given twice at intervals of 2 weeks. Clinical observation and monitoring of body weight, body temperature, electrocardiogram, blood pressure, visual inspection, clinical cases, T lymphocyte subsets, cytokines and C-reactive proteins, complement and serum-specific IgG antibodies after administration.

5.3.3.1 Experimental results

Up to the third day after the last administration (D18), 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. Three days after the last dose (D18), there was no abnormality in the anatomy of euthanasia.

Under the experimental conditions, the recombinant novel coronavirus vaccine (adenovirus vector) was repeated intramuscularly injected with 1 dose (5×10^{10} vp/0.5 mL of each) and 3 doses (1.5×10^{11} vp/1.5 mL of each), respectively. The drug was given once every 2 weeks for a total of 2 times, and no obvious toxic reaction was found in each group at day 3 after the last dose (D18). One week after administration (D8), some

animals could produce weak specific IgG antibody against adenovirus vector and strong specific IgG antibody against S antigen.

5.4 Summary for preclinical studies

The results are to be submitted.

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 and a batch of 10L production. The results showed that the process could meet the production of novel coronavirus vaccine, and the detection indexes reached the proposed quality standard. Subsequently, three batches of 25L and one batch of 50L production were carried out respectively, which are being tested as of the time of declaration.

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 recombinant replication defective human adenovirus type 5×10^{10}vp expressing novel coronavirus S protein.

6.3 Stability research

The recombinant novel coronavirus vaccine (adenovirus vector) was in liquid form and stored at 2 ~ 8 ℃.

In the production process of the product, the cells were treated by culture, virus infection and purification to make the original liquid, which was diluted with stabilizer to form a semi-finished product, and then sub-packaged into a finished product.

According to the characteristics of the vaccine production process and the relevant provisions of the Drug Registration Administration measures, the stability of the finished product was studied.

The accelerated stability of the finished product was studied at 37±2 ℃ for 8 weeks and 25±2 ℃ for 6 months, and the long-term stability at 5±3 ℃ for 30 months. At present, the experiment is under way.

6.4 Quality research and verification

This study is based on the viral biological products, 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) included in the 2015 Edition "China Pharmacopoeia" (third), 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 and duration of vaccine, vaccine preservation conditions and "only for clinical research ".

Sample of label on the vial

Only for clinical trial
Recombinant Novel Coronavirus Vaccine
(Adenovirus Type 5 Vector)
5×10^{10}vp/vial Lot:202003001C
Date:2020.03.01 Exp:2022.02.28
Storage: at 2 ~ 8℃, avoid light
Beijing Institute of Biotechnology and CanSino Biologics Inc

Sample of label on the packaging box

Only for clinical studies Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector) 5×10^{10}vp/vial Lot:202003001C Date:2020.03.01 Exp:2022.02.28 Storage: at 2 ~ 8℃, avoid light Beijing Institute of Biotechnology and CanSino Biologics Inc Address: No. 20, east street, Fengtai district, Beijing No.185, South Street, Economic and technological Development Zone, Tianjin

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

Primary objective: to evaluate the safety and tolerability of the recombinant novel coronavirus vaccine (adenovirus type 5 vector) in healthy adults aged between 18 and 60 years old.

Secondary objective: to evaluate the immune response induced by the recombinant novel coronavirus vaccine (adenovirus type 5 vector) in healthy adults aged between 18 and 60 years old.

8. STUDY DESIGN

8.1 Design methods

This study is performed in three steps: first, the low dose group (5×10^{10}vp); then, the middle dose group (1×10^{11}vp); at last, the high dose group (1.5×10^{11}vp), with 36 participants in each group. The trial will be carried out step by step from the low dose group to the high dose group, and the participants will be recruited sequentially. The safety data will be evaluated every day, during the study, if any safety problems of the vaccine is noted, recruiting process should be stopped.

8.2 Study endpoints

8.2.1 Primary endpoints

– Occurrence of adverse reactions within 7 days after vaccination.

8.2.2 Secondary endpoint

8.2.2.1 Safety:

- Occurrence of adverse events (AE) within 28 days after vaccination.
- Occurrence of serious adverse events (SAE) within 28 days after vaccination.
- Occurrence of serious adverse events during the whole follow-up period (6 months).
- Changes of safety laboratory measures (hemoglobin, white blood cell count, total lymphocyte count, platelets, creatinine, alanine transaminase, neutrophil, glutamic oxaloacetic transaminase, total bilirubin, and fasting blood glucose) on day 7.

8.2.2.2 Humoral immunogenicity:

- Geometric mean titer of antigen-specific antibody on day 14, day 28, month 3, and month 6 measured by ELISA.
- Seroconversion rate of antigen-specific antibody on day 14, day 28, month 3, and month 6 measured by ELISA.
- Geometric mean fold increase of antigen-specific antibody on day 14, day 28, month 3, and month 6 measured by ELISA.
- Geometric mean titer of neutralizing antibody against SARS-CoV-2 on day 14, day 28, and month 6.
- Seroconversion rate of neutralizing antibody against SARS-CoV-2 on day 14, day 28, and month 6.
- Geometric mean fold increase of neutralizing antibody against SARS-CoV-2 on day 14, day 28, and month 6.
- Geometric mean titer of neutralizing antibody against Ad5 on day 14, day 28, month 3, and month 6.
- Geometric mean fold increase of neutralizing antibody against Ad5 on day 14, day 28, month 3, and month 6.

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 used; if the antibody level is greater than the detection limit, the maximum dilution will be used.

8.2.2.3 Cellular immunogenicity:

Cell-mediated responses on day 14, day 28, and month 6:

- Positive rate and level of IFN-γ measured by ELISpot.
- Intracellular cytokine staining (ICS) assay to measure positive rates and levels of IFN-γ, TNFα and IL-2 expressed by the active CD4+T and CD8+T lymphocyte.

8.2.3 Exploratory research endpoint

- The correlation between antigen-specific antibody measured by ELISA and neutralizing antibody against SARS-CoV-2.

- The dose-response relationship of antigen-specific antibody measured by ELISA across the dose groups.
- The persistence of the antigen-specific antibody measured by ELISA at month 6.
- The correlation between the initial time of the antibody response and the dose groups.
- The correlation between cell-mediated responses (ELISpot IFN-γ, ICS positive rates of IFN-γ, TNFα and IL-2 expressed by the active CD4+T and CD8+T lymphocyte) and the dose groups.
- The persistence of the cell-mediated responses (ELISpot IFN-γ, ICS positive rates of IFN-γ, TNFα and IL-2 expressed by the active CD4+T and CD8+T lymphocyte) at month 6.
- The correlation between the initial time of the cell-mediated responses (ELISpot IFN-γ, ICS positive rates of IFN-γ, TNFα and IL-2 expressed by the active CD4+T and CD8+T lymphocyte) and the dose groups.

8.3 Study Procedures

From beginning to the end of the study, each participant will complete 9 visits. The visit time, window period and the procedures at 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	V4	V5	V6	V7	V8
Day/month	Day-7 to -1	Day 0	Day 3	Day 7	Day 10	Day 14	Day 28	Month 3	Month 6
Visit interval	Day-7 to -1	Day 0	V1+3 days	V1+7days	V1+10 days	V1+14 days	V1+28 days	V6+2 months	V6+5 months
Time window	--	--	(±1 day)	(±1 day)	(±1 day)	(±2 day)	(±3 day)	(±5 day)	(±15 day)
Recruiting, informed consent	●	●							
Demographic information collection	●	●							
Medical history collection and preliminary screening	●								
Physical examination: Height, weight, blood pressure)	●								
HCG test (for women only)		●							
Blood routine	●			●					
Blood biochemical test		●		●					
HIV antibody test	●								●
Nucleic acid test (pharyngeal swab/sputum)	●								
Nucleic acid test (anal swab)	●								
Axillary temperature measurement	●	●							
Inclusion and exclusion screening	●	●							
Allocation of vaccine ID		●							
Record on the Visit Record Form	●	●							

Blood collection (humoral immunity)	●	●				●	●	●	●
Blood collection (cell immunity)		●				●	●		●
Vaccination		●							
Observation for 6 hours 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	V4	V5	V6	V7	V8
Visit time	Day-7 to -1	Day 0	Day 3	Day 7	Day 10	Day 14	Day 28	Month 3	Month 6
Visit interval	Day-7 to -1	Day 0	V1+3 days	V1+7days	V1+10 days	V1+14 days	V1+28 days	V6+2 months	V6+5 months

Time window	--	--	(±1 day)	(±1 day)	(±1 day)	(±2 day)	(±3 day)	(±5 day)	(±15 day)
Blood routine (anticoagulant blood)	2ml	--	--	2ml	--	--	--	--	--
Blood biochemistry and HCG (procoagulant blood)	--	3ml	--	3ml	--	--	--	--	--
HIV test (procoagulant blood)	3ml	--	--	--	--	--	--	--	3ml
Humoral immunity (procoagulant blood)	5ml	10ml	--	--	--	10ml	10ml	10ml	10ml
Cellular immunity (EDTA anticoagulant blood)	--	20ml	--	--	--	20ml	20ml	--	20ml
Total blood collection	10ml	33ml	--	5ml	--	30ml	30ml	10ml	33ml

Total amount of blood collection: 151ml.

8.4 Sample size

According to the "Technical guidelines for Vaccine Clinical Trials" issued by the China FDA, the sample size of each vaccine dose group is about 20-30 participants. In this study, 36 participants will be involved in the low-dose group, the middle-dose group and the high-dose group, respectively. A total of 108 participants will be recruited.

8.5 Criteria for pausing 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. If an increased risk of participants is found in the course of the study, they send notice to the principal investigator and the sponsor immediately to suspend or terminate the recruiting of participants in clinical trial, during the dose-escalating procedure. 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.

Administration of study injections and new enrollments will be paused, if:

- One or more ≥grade 4 adverse reaction or serious adverse event may be associated with vaccination, or
- Occurrence of grade 3 adverse events associated with vaccination in 15% of participants or more (including injection-site reaction, systemic reaction, and change of the safety laboratory measures), or

- Required by sponsor, or
- Required by regulatory authority, or
- Required by institutional review board (IRB).

The study may come to an early termination, if DSMB, sponsor and investigator agree that the risk increased and the risk-benefit for participants is no longer reasonable.

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 course of the study.

9 PARTICIPANTS

9.1 Participants selection

Healthy people aged from 18 to 60 years were 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 researchers, and any employee of the contract research organization (CRO) shall not be a participant.

9.2 Inclusion criteria

- Aged between 18 and 60 years.
- Able to understand the content of informed consent and willing to sign the informed consent.
- Able and willing to complete all the secluded 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.
- Chest CT scan is normal (no COVID-19 imaging).
- Pharyngeal swabs or sputum and anal swabs are negative for SARS-CoV-2.
- A body mass index (BMI) are between 18.5 and 30.0.
- Indexes of blood routine, biochemistry and other laboratory tests are within the normal ranges, or not clinical significant judged by doctors (including white blood cell count, lymphocyte count, neutrophils, platelets, hemoglobin, ALT, AST, total bilirubin, fasting blood glucose, creatinine).
- 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 infection
- 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 withdraw 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.
- If a participant is infected by SARS-CoV-2 between day 0 and day 28 post-vaccination, immunogenicity data from he or she will not be included in analysis, but all SARS-CoV-2 infections occurred within 6 months after the vaccination should be documented and reported following the same procedure of SAE reporting, especial attention should be paid in case of the occurrence of antibody-dependent enhancement (ADE).
- 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 participants who take the vaccination, and complete safety observation from day 0 to 28, and reported SAEs till the end of the study will be considered as complete of the safety data collection.

9.5.2 Complete of immunogenicity data collection

The participants who meet the inclusion and do not meet any exclusion criteria, take the vaccination, and complete the blood collection within day 28 post-vaccination will be considered as complete of the immunogenicity data collection.

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 as soon as possible after knowing the protocol violation by fax or e-mail.

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 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 from 18 to 60 years were selected as the target population, the recruitment was promoted by the recruitment advertisement approved by the ethics committee, and the volunteers were 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, 3ml of coagulative venous blood of all participants will be collected for antibody screening, those with negative results can be enrolled.

10.1.2.3 Blood routine test

During the screening process, 2ml of anticoagulant venous blood will be collected from all participants for blood routine test, those with the tested indexes in the normal range, or determined by the doctor as not clinically significant could be enrolled.

10.1.2.4 Blood biochemical test

During the screening process, 3ml of procoagulant venous blood will be collected from all participants for blood biochemical test, those with the tested indexes in the normal range, or determined by the doctor as not clinically significant could be enrolled.

10.1.2.5 Antibody screening

Specific IgM and IgG antibodies against S and N in the serum of the participates will be tested by chemiluminescence assay, those who are positive for any of the antibodies will not be enrolled.

10.1.2.6 Nucleic acid of SARS-CoV-2 screening

Pharyngeal swabs or sputum and anal swabs are collected and detected by RT-PCR or /and NGS methods. Those who are positive for the nucleic acid of SARS-CoV-2 will not be enrolled.

10.1.2.7 Chest CT screening

All the participants will have a chest CT, and those who have COVID-19 imaging features will not be enrolled.

10.2 Enrollment

Eligible participants will be screened and assigned a study ID in order. A total of 108 participants will be allocated to the low, middle or high dose groups sequentially, with 36 participants per group.

10.3 Vaccine inoculation

10.3.1 Investigational vaccine

The investigational vaccine used in this study is a novel recombinant coronavirus vaccine (adenovirus type 5 vector) jointly developed by Beijing Institute of Biotechnology and CanSino Biologics Inc.

The investigational vaccine 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 low, middle and high doses were 5×10^{10}vp (0.5ml), 1×10^{11}vp (1.0ml), and 1.5×10^{11}vp (1.5ml), and the quality is in line with the “recombinant new coronavirus vaccine manufacturing and verification regulations (draft)". The investigational vaccine has got the certification from National Institutes for Food and Drug Control.

10.3.2 Administration

Low dose group (5×10^{10}vp/vial, 1 vial): take a vial of investigational vaccine, use a disposable syringe to extract 0.5ml vaccine and intramuscularly inject it into the middle of the lateral deltoid muscle of the participant's upper arm. The injection dose is 5×10^{10}vp for the participants in the low dose group.

Middle dose group (5×10^{10}vp/ vial, 2 vials): take 2 vials of investigational vaccine, use a disposable syringe to extract 1.0ml vaccine and intramuscularly inject it into the middle of the lateral deltoid muscle of the participant's upper arm. The injection dose is 1×10^{11}vp for the participants in the middle dose group.

High dose group (5×10^{10}vp/vials, 3 vials): take 3 vials of investigational vaccine, use two disposable syringes to extract 0.5ml and 1.0ml vaccine and intramuscularly inject

them into the middle of the lateral deltoid muscle of the participant's two upper arms, respectively. The injection dose is 1.5×10^{11}vp for the participants in the high dose group. 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.

In case any emergency situation may happen to the participants during the vaccination or during the 6-hour observation after vaccination, appropriate emergency medical equipment and doctors should be prepared.

10.3.3 Vaccine management

The sponsor should provide all the investigational vaccines, including the backup vaccines. The package of the investigational vaccines must comply with the requirements of clinical trials.

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

After vaccination, all participants are required to stay in the designated temporary lodgment for a safety observe of 14 days and then they are allowed to be back to their home for further safety observation since day 15 post-vaccination. The contents of safety observation during the study period are as follows:

(1) After vaccination, the participants will stay at the clinic for 6-hour observation and the temperature will be captured by both wireless remote continuous temperature measurement system and routine axillary thermometer.

(2) Within 14 days after vaccination, the participants are asked to complete the safety observation by themselves, and record the results on the "diary card". A designated doctor is responsible for visit the participants every day and instruct them to complete the diary card.

(3) From the day 15 to the day 28 after vaccination, the participants will be instructed

to record any adverse events on the "diary card" by themselves. On day 28, the investigators visited the participants, retrospectively investigated and verified the contents of the safety observation.

(4) During the whole study period (about 6 months after vaccination), the participants will be asked to report any serious adverse events following the vaccination.

10.4.2 Safety observation and grade of adverse reaction/event

10.4.2.1 Definition of adverse event and serious adverse event

An adverse event (AE) is any untoward medical occurrence in a participant administered an investigational product and which does not necessarily have a causal relationship with this treatment. An adverse reaction (AR) is all untoward and unintended responses to a medical product related to any dose administered.

A serious adverse event/reaction (SAE) is occurrence of any untoward medical during the whole study period that:

- Result in death.
- life-threatening (an event in which the participant is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe).
- Result in persistent or significant disability/incapacity.
- Require hospitalization or prolongation of an existing hospitalization.
- Congenital anomaly/birth defect.

10.4.2.2 Safety observation contents

Adverse events occurred 0-7 day after vaccination.

Adverse events occurred 0-28 day after vaccination.

Serious adverse events within 6 months after vaccination;

Changes of safety laboratory measures (hemoglobin, white blood cell count, total lymphocyte count, platelets, creatinine, alanine transaminase, neutrophil, glutamic oxaloacetic transaminase, total bilirubin, and fasting blood glucose) on day 7.

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	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	Abscess, exfoliative dermatitis, dermal or deep tissue necrosis

	daily life		drainage or seriously 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 Grading for laboratory testing index

Table 10-4-1-4 Grading for blood biochemical indicators

Index	Grade 1	Grade 2	Grade 3	Grade 4
Liver function (ALT, AST increase)	1.25～＜2.5 ×ULN	2.5～＜5.0×ULN	5.0～＜10×ULN	≥10×ULN
Increase of total bilirubin (mg/dL; μmol/L)	1.1～＜1.6×ULN	1.6～＜2.6×ULN	2.6～5.0×ULN	≥5.0×ULN
Hyperglycemia (fasting) (Glu,mmol/L)	6.11～＜6.95	6.95～＜13.89	13.89～＜27.75	≥27.75
Hypoglycemia (Glu, mmol/L)	3.05～＜3.55	2.22～＜3.05	1.67～＜2.22	＜1.67
Creatinine (μmol/L)	1.1～1.5×ULN	1.6～3.0×ULN	3.1～6×ULN	>6×ULN

Note: ULN means the upper limit of the normal value range

Table 10-4-1-5 Grading for blood routine indicators

Index	Grade 1	Grade 2	Grade 3	Grade 4
White blood cell increase(WBC,10^9/L)	11~＜13	13～＜15	15～＜30	≥30
White blood cell decrease (WBC, 10^9/L)	2.000～2.499	1.500～1.999	1.000～1.499	＜1.000
Lymphocyte decrease (LY, 10^9/L)	0.75～1.00	0.5～0.749	0.25～0.49	＜0.25

Neutrophils decrease (ANC, 10^9/L)	0.800～1.000	0.600～0.799	0.400～0.599	＜0.400
Platelets decrease (PLT, 10^9/L)	125～140	100～124	25～99	＜25
Low hemoglobin (g/dL)				
Male	10.0～10.9	9.0～＜10.0	7.0～＜9.0	＜7.0
Female	9.5～10.4	8.5～＜9.5	6.5～＜8.5	＜6.5

Note: ULN means the upper limit of the normal value range.

10.4.2.5 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, including death due to any cause, which occurs during this study, whether or not related to the investigational products, must be reported immediately (within 24 hours of the investigator's knowledge of the event) by

telephone or fax to the sponsors, principle investigator, JSCDC IRB, Health Bureau of Logistics Support Department of CMC, and Hubei Medical Products Administration, at the following number:

Principal Investigator: Feng-Cai Zhu, Tel: +86-25-83759418, Fax: +86-25-83759409

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

JSCDC IRB: Hui-Yuan Cai, Tel: +86-25-83759406; Fax: +86-25-83759406

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 Health Bureau of Logistics Support Department of CMC and 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 Health Bureau of Logistics Support Department of CMC and 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 Biological sample collection and examination

10.5.1 Detection of ELISA Antibody against SARS-CoV-2 's 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, month 3 and month 6 after immunization.

10.5.1.2 Blood sample processing and detection methods

The SOP for serum isolation is shown in Appendix 1, and the SOPs for storage and transportation by serum are shown in Appendix 2. The SOP for detecting SARS-CoV-2 antibody by ELISA is in Appendix 3.

10.5.1.3 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 14, day 28 and month 6 after immunization.

10.5.2.2 Blood sample processing and detection methods

The SOP for isolation of serum is shown in Appendix 1, and the details of SOP preserved and transported by serum are shown in Appendix 2.

The SOP of detecting SARS-CoV-2 antibody by pseudo virus neutralization test is detailed in Appendix 3.

10.5.2.3 Evaluation 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 specific CD4+ T cell and CD8+ T cell response

10.5.3.1 Detection time point

Specific CD4+ T cell and CD8+ T cell responses will be detected at day 0, day 14(main evaluation time point), day 28 and month 6 after immunization (IL-2, IFN- γ and TNF will be secreted by S protein overlapping peptide library will be detected by intracellular cytokine staining).

10.5.3.2 Blood sample processing and detection methods

PBMC isolation and cryopreserved SOP from human peripheral blood mononuclear cells are shown in Appendix 4. For SOP detection of T cell response by intracellular cytokine staining, see Appendix 5.

10.5.3.3 Evaluation content

The positive rate of T cell reaction on day 28 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.

10.5.4 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, day 14 (major evaluation time point), day 28 and month 6 after immunization.

10.5.4.2 Blood sample processing and detection methods

The SOP for the isolation and cryopreservation of human peripheral blood mononuclear

cells (PBMC) is shown in appendix 4. The SOP for the detection of T cell reaction by ELISpot method is shown in appendix 6.

10.5.4.3 Evaluation content

The positive rate of T cell reaction 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 Detection of neutralizing antibody to recombinant replication defective human type 5 adenovirus

10.5.5.1 Detection time point

Serum neutralizing antibody titers against recombinant replication defective human type 5 adenovirus will be detected at day 0, day 14, day 28, month 3 and month 6 after immunization.

10.5.5.2 Detection methods

The SOP of neutralization antibodies against human type 5 adenovirus will be detected by cell neutralization test is shown in appendix 7.

10.5.5.3 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.

10.5.6 Surveillance and laboratory diagnosis of SARS-CoV-2 infection during

clinical trials

During the observation period of the clinical trial, the participants with fever, cough and other respiratory symptoms should immediately go to the designated hospital (Guanggu Hospital affiliated to Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology) and inform the investigators. The doctor or investigator will collect the pharyngeal swabs (or sputum) and anal swabs and to performe CT and other imaging examinations to analyze whether it is caused by SARS-CoV-2 infection. In the event of SARS-CoV-2's infection during the clinical trial, it is necessary to conduct a case investigation, and the critically ill or dead cases need to continue to conduct a special investigation of critical or dead 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 pharyngeal swabs or 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 project 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 subject 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 subjects 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 Rehabilitation 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 initial analysis and the final analysis.

10.7.1.1 Initial analysis

After the last participant complete the Visit 6 (28 days after vaccination), the research database has been entered, audited and locked, initial analysis will be done by the statistical party. The initial statistical analysis report shall first be reviewed by the DSMB and determined that the report shall be carried out in strict accordance with the initial 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 8 (month 6 after vaccination), all the data of serious adverse events from Visit 6 (day 28) to Visit 8 (month 6), and the data of humoral and cellular immunity will be analyzed and summarized.

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 "Initial 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) for immunogenicity analysis: 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, were included in the FAS set for immunogenicity.

Per-protocol set (PPS): It is a subset of FAS. The participants in the data set were more compliant to the scheme, with no significant deviation or violation of protocol, all met the selection/exclusion criteria and completed vaccination within the vaccination time window according to the requirements of the scheme, and the participants who collected blood at day 0, day 7, day14, day 28 day, month 3 and month 6 month were included in the PPS set. This method of analysis does not include participants who violate the protocol, and confirmed as COVID-19 cases within 14 days after vaccination.

In this study, the FAS are 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 criteria: did not meet the selected case criteria; failed to 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 initial statistical analysis plan and the final statistical analysis plan for details).

11. CLINICAL MONITORING AND CONTROLLING OF EXPERIMENTS

11.1 Responsibility

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.

The China Institute for Food and Drug Control is responsible for the detection of various indicators of immunogenicity and issues a test report.

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, vaccine 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%.

The serum samples used for other detection are collected, processed and preserved in strict accordance with the requirements of SOPs.

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 8 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	18 days
2.Reviewed and Approved by Ethics Committee	3 days
3.The first participant recruited into the group	1 month
4.The last participant complete Visit 5	
5. Initial analysis	10 days
6. Initial analysis report	
7. The last participant complete Visit 8	6 months
8.Final Analysis	7 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)
- Case Report Form (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
- Notification of drug clinical trial of the National Medical Products Administration or approval of clinical study of special drugs of the Health Bureau of Logistics Support Department of CMC
- 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)

14. APPENDIX

Appendix 1 Standard Operating Procedures (SOP) for serum separation and cryopreservation

Appendix 2 Standard Operating Procedures (SOP) for serum preservation and transport

Appendix 3 Standard Operating Procedures (SOP) for detection of SARS-CoV-2 antibodies by chemiluminescence, ELISA, neutralization test with SARS-CoV-2 virus or/and its pseudovirus

Appendix 4 Standard Operating Procedures (SOP) for isolation of human peripheral

blood mononuclear cells (separation solution method)

Appendix 5 Standard Operating Procedures (SOP) for detection of T cell response by intracellular cytokine staining

Appendix 6 Standard Operating Procedures (SOP) for detection of T cell response by ELISpot method

Appendix 7 Standard Operating Procedures (SOP) for detection of neutralizing antibody against human type 5 adenovirus

15. ACCESSORY

Accessory1 recombinant novel coronavirus vaccine (adenovirus type 5 vector); Phase I Clinical Trial Participant Informed Consent Form (Low dose group)

Accessory2 recombinant novel coronavirus vaccine (adenovirus type 5 vector); Phase I Clinical Trial Participant Informed Consent Form (middle dose group)

Accessory3 recombinant novel coronavirus vaccine (adenovirus type 5 vector); Phase I Clinical Trial Participant Informed Consent Form (High dose group)