Protocol Title:

An open-label observation of the Bivalent Enterovirus Vaccine (Vero Cell), Inactivated in healthy adults and children aged 6–12 years, and a randomized, double-blind, controlled Phase I/II clinical trial evaluating tolerability, safety, and immunogenicity in children aged 6–71 months.

Protocol Number: [redacted]

Version: 4.0

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Investigational Product: Bivalent Enterovirus Vaccine (Vero Cell), Inactivated

Trial Phase: Phase I/II

Sponsor: Sinovac Biotech Co., Ltd.

Clinical Trial Institution: Yunnan Provincial Center for Disease Control and Prevention

SINOVAC BIOTECH CO., LTD.

Protocol Approval - Sponsor Signature

Protocol Title	An open-label observation of the Bivalent Enterovirus Vaccine (Vero Cell), Inactivated in healthy adults and children aged 6–12 years, and a randomized, double-blind, controlled Phase I/II clinical trial evaluating tolerability, safety, and immunogenicity in children aged 6–71 months.
Protocol Number	[redacted]
Version Date	28 August 2024

Protocol Approver: [redacted]

Signature of Approver:

Date of Approval:

Investigator Signature

I agree to:

- Take responsibility for correctly directing this clinical trial in my region.
- Ensure that the trial is conducted in accordance with the protocol and the clinical trial standard operating procedures.
- Ensure that personnel involved in this project are fully informed about the investigational product and the other trial-related duties and obligations set out in the protocol.
- Make no changes to the protocol without review and written approval by the sponsor and the Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard to participants or to comply with requirements of the regulatory authority (e.g., administrative aspects of the project).
- Be fully familiar with the correct use of the investigational vaccine as described in the protocol and with the other information provided by the sponsor, including but not limited to the current Investigator's Brochure (IB) or equivalent document and any IB supplements (if any).
- Be familiar with and comply with the Good Clinical Practice (GCP) for pharmaceutical products, the Guiding Principles for Quality Management of Vaccine Clinical Trials (for Trial Implementation), and all current regulatory requirements.

Principal Investigator:

Signature:

Date:

Research Team

Sponsor

Institution: Sinovac Biotech Co., Ltd.

[redacted]

Clinical Trial Institution

Institution: Yunnan Provincial Center for Disease Control and Prevention

[redacted]

Sponsor Medical Expert

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Clinical Trial Site

Institution: Dayao County Center for Disease Control and Prevention

[redacted]

Clinical Trial Monitoring Organisation

[redacted]

Data Management Organisation

[redacted]

Statistical Analysis Organisation

[redacted]

Sample Testing Laboratory

Institution: National Institutes for Food and Drug Control (NIFDC), China

[redacted]

Protocol Amendment History

Serial Number	Previous version number/Version Date/Amended Section	Current version number/Version Date/Previous content/Change/Rationale
1	1.0 / 31 Jul 2023 / 1.1 Synopsis, 4.1 Description of Trial Design	2.0 / 24 Aug 2023 / Urine sample volume changed from 5-10 mL to approximately 2-10 mL / per investigator advice
2	1.0 / 31 Jul 2023 / 1.1 Synopsis, 4.1 Description of Trial Design	2.0 / 24 Aug 2023 / Pregnancy event collection added to overall design / per investigator advice
3	1.0 / 31 Jul 2023 / [redacted]	2.0 / 24 Aug 2023 / [redacted]
4	1.0 / 31 Jul 2023 / 1.3 Schedule of Activities	2.0 / 24 Aug 2023 / Contact card added and footnotes revised; visits for SAEs, concomitant vaccines/medications, and pregnancy events within 30-180 days post-full vaccination clarified; presentation of “visit date” row revised / per investigator advice
5	1.0 / 31 Jul 2023 / [redacted]	2.0 / 24 Aug 2023 / [redacted]
6	1.0 / 31 Jul 2023 / [redacted]	2.0 / 24 Aug 2023 / [redacted]
7	1.0 / 31 Jul 2023 / 4.5 Trial duration	2.0 / 24 Aug 2023 / Definitions for age calculation and timing added / per investigator advice
8	1.0 / 31 Jul 2023 / 5 Study population	2.0 / 24 Aug 2023 / Exclusion criteria (4)-(7): “combined with medical history and/or physical examination” revised to “combined with medical history and physical examination” / per ethics committee advice
9	1.0 / 31 Jul 2023 / 5 Study population	2.0 / 24 Aug 2023 / Exclusion criterion (10) expanded to include male participants planning conception within 90 days / per investigator advice
10	1.0 / 31 Jul 2023 / 5 Study population	2.0 / 24 Aug 2023 / Dose-2 exclusion/postponement criteria restructured: (1)-(3) prohibit vaccination, (4)-(6) postpone, (7) at investigator discretion / per investigator advice
11	1.0 / 31 Jul 2023 / 6.2.1 Product receipt and inventory	2.0 / 24 Aug 2023 / Five receipt-and-inventory rules simplified to four / per investigator advice
12	1.0 / 31 Jul 2023 / 6.2.4 Administration	2.0 / 24 Aug 2023 / Post-vaccination record-keeping procedures added, including entries on the child vaccination certificate and the immunisation information system / per ethics committee advice
13	1.0 / 31 Jul 2023 [redacted]	2.0 / 24 Aug 2023 / [redacted]

		[redacted]
14	1.0 / 31 Jul 2023 / 6.4 Intervention compliance	2.0 / 24 Aug 2023 / Contact card description added / per investigator advice
15	1.0 / 31 Jul 2023 / 7.1 Intervention suspension rules	2.0 / 24 Aug 2023 / Laboratory parameters added to the first suspension criterion and related wording revised / per investigator advice
16	1.0 / 31 Jul 2023 / 7.3 Participant discontinuation/withdrawal	2.0 / 24 Aug 2023 / Minor participant assent wording clarified / per investigator advice
17	1.0 / 31 Jul 2023 / 7.4 Loss to follow-up	2.0 / 24 Aug 2023 / Definitions of loss to follow-up and drop-out clarified / per investigator advice
18	1.0 / 31 Jul 2023 / 8.1 Trial procedures	2.0 / 24 Aug 2023 / Physical examination and vital signs specified; diary card review moved from D3 telephone visit to D7; follow-up wording aligned with 1.3; details on telephone visits for SAEs, concomitant vaccines/medications, and pregnancy events within 30-180 days post-full vaccination added / per investigator advice
19	1.0 / 31 Jul 2023 / 8.3.2 Vital signs	2.0 / 24 Aug 2023 / Contact card usage added; footnotes of Tables 8-10 annotated: “The above are the key biochemistry indicators observed in this study; for other indicators in the test report, if abnormal, the on-site investigator shall judge whether to record them as AEs based on the participant’s situation” / per investigator advice
20	1.0 / 31 Jul 2023 / 8.4.4 Severity grading	2.0 / 24 Aug 2023 / Laboratory evaluation flow and grading tables corrected / per internal review
21	1.0 / 31 Jul 2023 / 8.4.5.2 Safety follow-up	2.0 / 24 Aug 2023 / Contact card usage added / per investigator advice
22	1.0 / 31 Jul 2023 / 8.4.6.1 Management of general adverse events	2.0 / 24 Aug 2023 / Management of AEs requiring intervention clarified; laboratory re-testing required for out-of-range values not pre-specified in the protocol / per ethics committee advice
23	1.0 / 31 Jul 2023 / 8.4.6.2 Management of serious adverse events; 10.5.1 Sponsor	2.0 / 24 Aug 2023 / Compensation description refined / per ethics committee and investigator advice
24	1.0 / 31 Jul 2023 / [redacted]	2.0 / 24 Aug 2023 / [redacted]
25	1.0 / 31 Jul 2023 / 10.3 Participant protection	2.0 / 24 Aug 2023 / Protection measures for paediatric participants added / per ethics committee advice
26	1.0 / 31 Jul 2023 / 10.4 Sample storage and data use	2.0 / 24 Aug 2023 / Unique sample identifier rules and serum storage location clarified / per ethics committee advice

27	1.0 / 31 Jul 2023 / 10.9 Protocol deviations	2.0 / 24 Aug 2023 / Examples of minor deviations added; training material on major deviations removed, to be handled via site SOP / per investigator advice
28	1.0 / 31 Jul 2023 / 10.12 Protocol amendments	2.0 / 24 Aug 2023 / Wording on whether related documents are to be amended removed; revisions notified based on actual situation / per investigator advice
29	1.0 / 31 Jul 2023 / 1.1 Synopsis, 4.1 Description of Trial Design	2.0 / 24 Aug 2023 / Rule clarified: blood and urine sampling at D3 (V2), D30 (V5), D33 (V6) in the 24-71-month group is required only if ⩾10% of participants in the corresponding dose step of the 6-12-year group develop clinically significant vaccine-related abnormal results after dose 1 / per investigator advice
30	2.0 / 31 Jul 2023 / 1.1 Synopsis, 4.1 Description of Trial Design	2.0 / 24 Aug 2023 / Biochemistry sample volume increased from 3 mL to 3.5 mL to match collaborating hospital testing capability / per investigator advice
31	2.0 / 31 Jul 2023 / 8.1 Trial procedures	2.0 / 24 Aug 2023 / Source documents and EDC are no longer required to be completed at the end of each visit; completion follows site SOP / per investigator advice
32	2.0 / 31 Jul 2023 / 8.4.6.1 Management of general adverse events	2.0 / 24 Aug 2023 / Re-testing requirement extended to any out-of-range value, not only clinically significant findings / per investigator advice
33	2.0 / 31 Jul 2023 / 8.3.3 Clinical laboratory testing	2.0 / 24 Aug 2023 / Detailed evaluation flow for clinical laboratory results added
34	2.0 / 31 Jul 2023 / Terminology	2.0 / 24 Aug 2023 / “Subject” replaced by “participant”
35	2.0 / 24 Aug 2023 / 1.3 Schedule of Activities	3.0 / 22 Sep 2023 / In footnote b, the phrase “or judged by the investigator as no longer clinically significant” removed; 8.3.3 updated accordingly / typographical correction
36	2.0 / 24 Aug 2023 / [redacted]	3.0 / 22 Sep 2023 / [redacted]
37	2.0 / 24 Aug 2023 / 10.9 Protocol deviations	3.0 / 22 Sep 2023 / Examples of major and minor deviations refined to cover the key situations considered in this study / revised after discussion with investigator
38	3.0 / 22 Sep 2023 [redacted]	4.0 / 28 Aug 2024 / [redacted]

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Abbreviations

AE	Adverse Event
ALB	Albumin
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AR	Adverse Reaction
ASaT	All Subjects as Treated
AST	Aspartate Aminotransferase
CA16	Coxsackievirus A16
CBC	Complete Blood Count
CDC	Center for Disease Control and Prevention
CDE	Center for Drug Evaluation
CFDA	China Food and Drug Administration
CFDI	Center for Food and Drug Inspection
CI	Confidence Interval
CK	Creatine Kinase
CPE	Cytopathic Effect Assay
CPK	Creatine Phosphokinase
CR	Creatinine
CRF	Case Report Form
CSR	Clinical Study Report
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ELISPOT	Enzyme-Linked Immunospot Assay
EV71	Enterovirus 71
FAS	Full Analysis Set
GCP	Good Clinical Practice
Glu	Glucose
GMFR	Geometric Mean Fold Rise
GMI	Geometric Mean Increase
GMT	Geometric Mean Titre
HFMD	Hand, Foot and Mouth Disease
IB	Investigator's Brochure

ICF	Informed Consent Form
IEC	Independent Ethics Committee
ITT	Intention-to-Treat
LD50	Median Lethal Dose
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NMPA	National Medical Products Administration
NOAEL	No Observed Adverse Effect Level
PBS	Phosphate-Buffered Saline
PI	Principal Investigator
PPS	Per-Protocol Set
PT	Preferred Term
PV	Pharmacovigilance
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedure
SS	Safety Set
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBIL	Total Bilirubin
TEAE	Treatment-Emergent Adverse Event
TP	Total Protein

1. Protocol Summary

1.1 Synopsis

Protocol title	An open-label observation of the Bivalent Enterovirus Vaccine (Vero Cell), Inactivated in healthy adults and children aged 6–12 years, and a randomized, double-blind, controlled Phase I/II clinical trial evaluating tolerability, safety, and immunogenicity in children aged 6–71 months.
Protocol overview	The Phase I clinical trial is conducted in two parts. The first part adopts an open design, and the second part adopts a randomised, double-blind, active-controlled design. The first part is planned to enrol 36 healthy adults aged 18-59 years and 36 healthy children aged 6-12 years. Within each age group, participants will receive two doses of the investigational vaccine on a 0- and 1-month schedule, with sequential escalation from low dose [redacted] to medium dose [redacted] to high dose [redacted] Sequential enrolment proceeds from adults to children aged 6-12 years, with 12 participants per dose group in both adults and children aged 6-12 years. The second part is planned to enrol 72 healthy children aged 6-71 months, who will be vaccinated on a 0- and 1-month schedule with sequential escalation from low dose to medium dose, to high dose. Each dose step uses a randomised, double-blind, active-controlled design. Within each dose step, 12 participants in the 6-23-month subgroup and 12 participants in the 24-71-month subgroup are enrolled and randomly allocated in a 3:1 ratio to receive either the investigational vaccine or the control vaccine (EV71 vaccine). The principle for dose-escalation vaccination within each age group is: escalating from low dose, to medium dose, to high dose, proceeding to a higher dose level is permitted only after completing a 0-7 day safety observation following the first dose of the lower dose level and confirming safety, based on the incidence of AEs and results of Complete Blood Count (CBC), blood biochemistry, and urinalysis tests (if applicable). The principle for sequential enrolment between different age groups is enrolling in the order of adults → children aged 6-12 years → children aged 6-71 months. Specifically, participants in the same dose group of children aged 6-12 years can be enrolled only after a 0-7 day safety observation following the first dose administration in each adult dose group confirms safety;

	enrolment of the group of children aged 6-71 months can begin only after the medium-dose group of adults completes the 7-day safety observation following the second dose administration. Participants in the adult group and group of children aged 6-12 years will have approximately 5.5 mL of blood (approximately 2.0 mL anticoagulated and 3.5 mL non-anticoagulated) and approximately 2-10 mL of urine samples collected before each dose and on day 3 after each dose for Complete Blood Count (CBC), blood biochemistry, and urinalysis tests to evaluate vaccine safety. In the group of children aged 6-71 months, only participants aged 24-71 months undergo the above tests, and only before the first dose; whether testing is performed at D3 (V2), D30 (V5), and D33 (V6) depends on the relevant test results of the group of children aged 6-12 years. If 10% of participants in each dose step of the group of children aged 6-12 years develop vaccine-related abnormal and clinically significant test results after the first dose, then the corresponding dose step of the group of children aged 24-71 months needs to collect blood and urine samples at D3 (V2), D30 (V5), and D33 (V6) for testing. The Phase II clinical trial uses a randomised, double-blind, active-controlled design: A total of 600 paediatric participants aged 6 – 71 months are planned to be enrolled, including 360 participants aged 6 – 23 months and 240 participants aged 24 – 71 months. Participants will be randomly assigned in a 1:1:1:1 ratio to one of three investigational vaccine dose groups—low dose [redacted], medium dose [redacted] and high dose [redacted] or a control group. Following a 0- and 1-month vaccination schedule, participants will receive two doses of the investigational vaccine or control vaccine, respectively. In Phase II, approximately 3.0 mL of venous blood will be collected from all participants on Days 0, 60, and 210. Serum will be separated for the measurement of EV71 and CA16 neutralising antibodies to evaluate the immunogenicity and immune persistence of the vaccine. In both Phase I and Phase II, all participants will be observed for immediate reactions for 30 minutes after each vaccination. Solicited local and systemic AEs occurring within 0 – 7 days after vaccination, as well as unsolicited AEs occurring within 0 – 30 days after vaccination, will be collected. Serious adverse events (SAEs) will be monitored from the first vaccination

	until 6 months after completion of the vaccination schedule. In Phase I, pregnancy events occurring within 3 months (120 days) after vaccination will be collected based on spontaneous reporting. After safety data through 30 days following completion of the vaccination schedule have been obtained for all participants in Phase I, the results will be submitted to the Ethics Committee for review. If the safety profile is acceptable and approval is granted by the Ethics Committee, the Phase II clinical trial will be initiated.
[redacted]	[redacted]

Trial Objectives and endpoints

Phase I

Primary objective	**Primary endpoint**
• Based on AEs, evaluate the safety of the investigational vaccine in participants of different age groups.	• The incidence rate of Adverse Reactions (ARs) from the start of vaccination to 30 days after completion of full vaccination;
Secondary objectives	**Secondary endpoints**
• Based on AEs, evaluate the safety of the investigational vaccine in participants of different age groups. • Based on abnormalities in laboratory indicators, evaluate the safety of the investigational vaccine in participants of different age groups.	• The incidence rate of ARs within 0-7 days after each dose; • The incidence rate of SAEs from the start of vaccination to 6 months after completion of full vaccination; • The incidence rate of clinically significant abnormalities in blood biochemistry, CBC, and urinalysis indicators on day 3 after each dose.

Phase II

Primary objective	**Primary endpoint**
• Evaluate the immunogenicity of the investigational vaccine in the target population.	• The seroconversion rate of EV71 and CA16 neutralising antibodies 30 days after completion of full vaccination in children aged 6-71 months;
Secondary objectives	**Secondary endpoints**
• Evaluate other immunogenicity indicators of the investigational vaccine	• The seropositivity rate, GMT, and GMFR of EV71 and CA16 neutralising antibodies 30 days after completion of full vaccination;

• Based on AEs, evaluate the safety of the investigational vaccine.	• The incidence rate of ARs from the start of vaccination to 30 days after completion of full vaccination; • The incidence rate of ARs within 0-7 days after each dose; • The incidence rate of SAEs from the start of vaccination to 6 months after completion of full vaccination;
• Evaluate the immune persistence of the investigational vaccine.	• The seropositivity rate and GMT of EV71 and CA16 neutralising antibodies 6 months after completion of full vaccination.
Trial Design	Phase I, Part I (adults and children aged 6-12 years) used an open-label trial design. Phase I, Part II and Phase II (children aged 6-71 months) used a randomised, double-blind, and controlled trial design.
Trial Population	Phase I: 36 healthy adults aged 18-59 years; 36 healthy children aged 6-12 years; 72 healthy children aged 6-71 months. Phase II: 360 healthy children aged 6-23 months; 240 healthy children aged 24-71 months.
Trial phase	Phase I/II.
Participant Enrolment Institution(s)	Yunnan Provincial Center for Disease Control and Prevention.
Trial intervention	Investigational Vaccines: 1. Bivalent Enterovirus Vaccine (Vero Cell), Inactivated, Low Dose: [redacted] 2. Bivalent Enterovirus Vaccine (Vero Cell), Inactivated, Medium Dose: [redacted] 3. Bivalent Enterovirus Vaccine (Vero Cell), Inactivated, High Dose: [redacted] Control Vaccine: Enterovirus Type 71 Vaccine, Inactivated (Vero Cell) - Inlive®: [redacted]

	Eligible participants will receive a single intramuscular injection of 0.5 mL of the investigational vaccine (at different doses) or control vaccine into the deltoid muscle of the upper arm. All participants will receive two doses according to a 0- and 1-month schedule. The vaccine should be thoroughly shaken before administration.
Trial duration	Approximately 22 months.
Participant duration	Each participant is expected to be in the trial for at least 7 months

1.2 Trial Schema

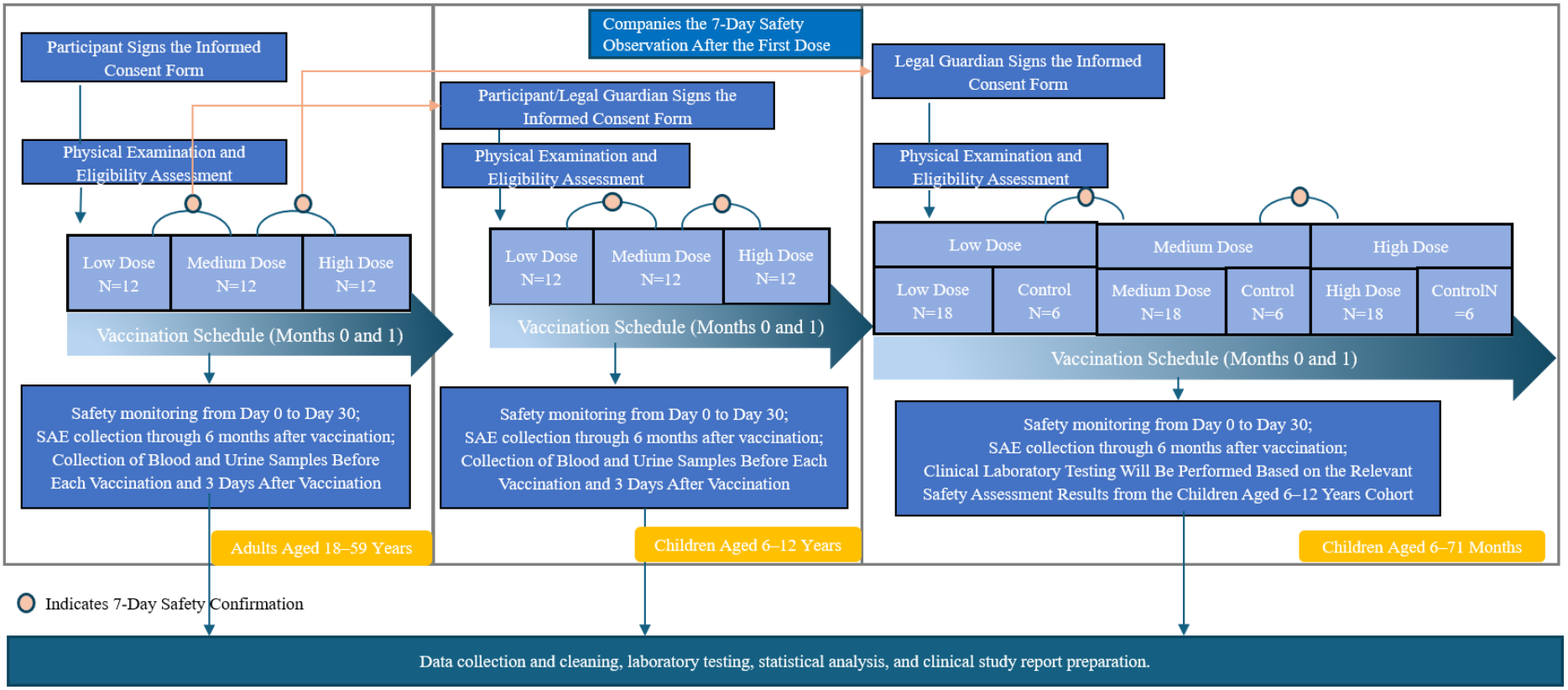


Figure 1. Phase I flowchart of the bivalent vaccine clinical trial

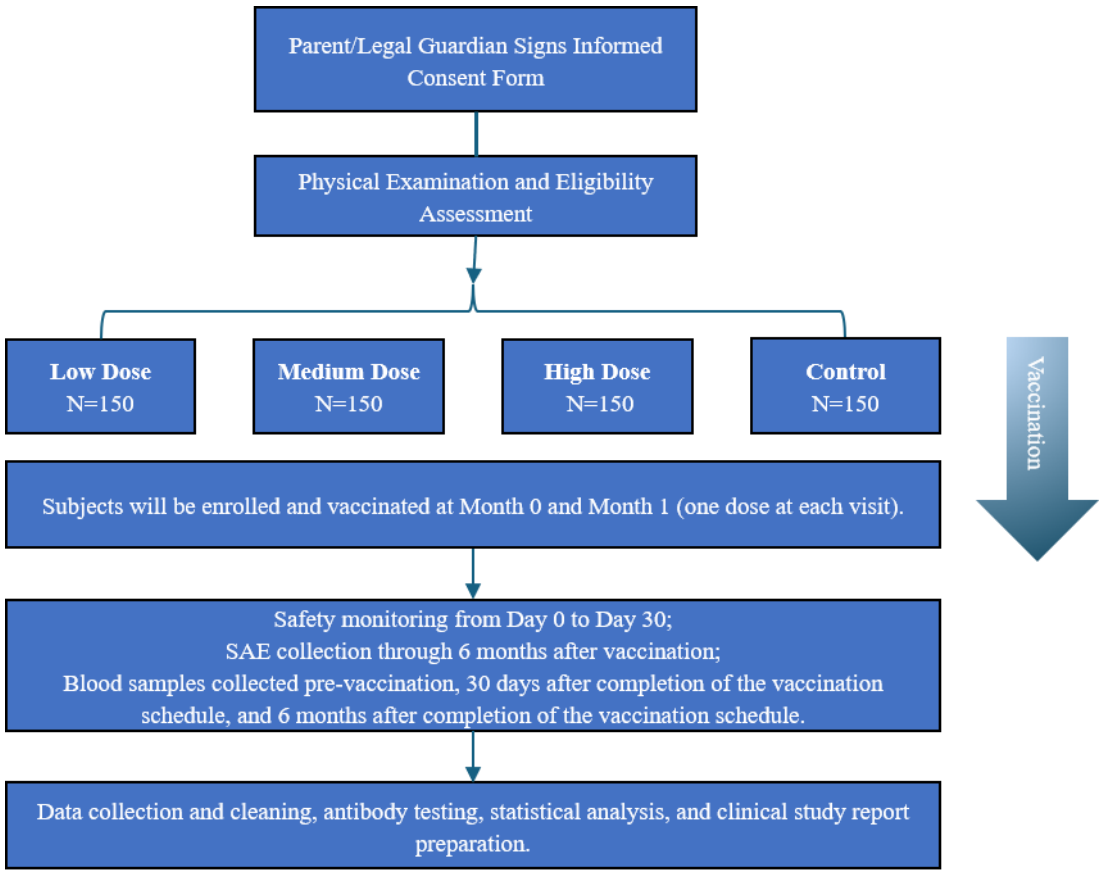


Figure 2. Phase II flowchart of the bivalent enterovirus inactivated vaccine clinical trial

1.3 Schedule of Activities

Table 1. Phase I visit schedule

Visit	D-21 to D0	V0a	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Visit date		D-7 to D0	D0	V1+3	V1+7	V1+14	V1+30	V5+3	V5+7	V5+14	V5+30	V5+90	V5+150	V5+180
Window Period				+1	+3	+3	+7	+1	+3	+3	+7	+10	+10	+30
Initial notification, participant recruitment	X													
Informed consent		X												
Demographics		X												
Medical history and relevant concomitant medications		X												
Haematology and blood biochemistry tests[b]		X		X			X	X						
Urinalysis testing[c]		X		X			X	X						
Female urine pregnancy test (adults from menarche to menopause)			X				X							
General examination			X											
Inclusion/exclusion screening			X				X							
Vaccination			X				X							
Participant/guardian diary card or contact card record the safety observation content on the diary/ contact card			X	X	X	X	X	X	X	X	X			
Adverse reaction/event monitoring (including grade ⩾3 AEs, SAEs)[d, e] / pregnancy events[f]			X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication/vaccine record[d, e]			X	X	X	X	X	X	X	X	X	X	X	X

a. Pre-enrolment screening will be conducted within 7 days before vaccination or on the day of vaccination.

b. Approximately 5.5ml of venous blood (approximately 2.0ml of anticoagulated blood and approximately 3.5ml of non-anticoagulated blood) is collected at each time point for routine blood and blood biochemistry testing. Whether hematology and blood biochemistry assessments will be performed in participants aged 24–71 months on Day 3 (V2), Day 30 (V5), and Day 33 (V6) will be determined based on the corresponding assessment results from the 6–12 years age group. If, within any

dose-escalation stage of the 6–12 years age group, vaccine-related and clinically significant laboratory abnormalities are observed in 10% of participants after the first vaccination, participants in the corresponding dose-escalation stage of the 24–71 months age group will undergo blood sample collection for hematology and blood biochemistry assessments on Day 3 (V2), Day 30 (V5), and Day 33 (V6). Any laboratory parameter with a result outside the reference range during the clinical trial shall be repeated, regardless of whether it is considered clinically significant. Participants shall undergo repeat biological sample collection and testing of the corresponding abnormal parameter(s) and shall be followed until the parameter returns to the normal range or becomes stable.

c. Approximately 2-10 mL of urine is collected for urinalysis testing at each time point. Whether urinalysis testing will be performed in participants aged 24–71 will be determined based on the assessment results from the 6–12 years age group. If, any clinically significant laboratory abnormalities are observed in participants aged 6–12 years, participants in 24–71 months age group will undergo urine sample collection for urinalysis testing on Day 3 (V2), Day 30 (V5), and Day 33 (V6).

d. Participants should record safety observation data in the Diary Card or Contact Card 30 days after each dose; axillary temperature should be measured daily within 0-7 days post-vaccination and whenever fever is suspected. Investigators will conduct face-to-face visits with participants in accordance with the visit plan in “8.1 Trial Procedures” to verify and record Adverse Events (AEs) as well as concomitant medications/vaccines.

e. During V9 (30 days after completion of full vaccination) to V12 (6 months after completion of full vaccination), only Serious Adverse Events (SAEs) and records of concomitant medication/vaccine use will be collected.

f. Pregnancy events will only be collected up to 3 months after the last vaccination (V10); see details in 8.4.7.

Table 2. Phase II visit schedule

Visit	D-21 to D0	V0[a]	V1	V2	V3	V4	V5	V6	V7	V8
Visit date		D-7 to D0	D0	V1+7	V1+30	V3+7	V3+30	V3+90	V3+150	V3+180
Window Period				+3	+7	+3	+7	+10	+10	+30
Pre-notification and recruitment	X									
Informed consent		X								
Demographics		X								
Medical history and relevant concomitant medication		X								
Venous Blood Collection (for Neutralising Antibody Testing)[b]			X				X			X
General examination			X							
Inclusion/exclusion screening			X		X					
Vaccination			X		X					
Participant/guardian diary card or contact card entriesc			X	X	X	X	X			
Adverse reaction/event monitoring (incl. grade ⩾ 3 AEs, SAEs)[c, d]			X	X	X	X	X	X	X	X
Concomitant medication/vaccine record[c, d]			X	X	X	X	X	X	X	X

a. Pre-enrolment screening will be conducted within 7 days prior to vaccination or on the day of vaccination.

b. Approximately 3.0 mL of venous blood will be collected for antibody testing at each time point.

c. Participants should record safety observation data in the Diary Card or Contact Card 30 days after each dose; axillary temperature should be measured daily within 0-7 days post-vaccination and whenever fever is suspected. Investigators will conduct face-to-face visits with participants in accordance with the visit plan in "8.1 Trial Procedures" to verify and record AEs as well as concomitant medications/vaccines.

d. During V5 (30 days after completion of full vaccination) to V8 (6 months after completion of full vaccination), only SAEs and records of concomitant medication/vaccine use will be collected.

2. Introduction

2.1 Purpose of Trial

The Bivalent Enterovirus Vaccine (Vero Cell), Inactivated (hereafter “bivalent vaccine”) developed by Sinovac Biotech Co., Ltd., (hereafter “Sinovac”) is a prophylactic biological product, [redacted] Its active ingredients are inactivated enterovirus 71 (EV71) and coxsackievirus A16 (CA16), and it is intended to prevent diseases caused by EV71 and CA16 infection, such as hand, foot and mouth disease (HFMD) and herpangina[1].

Enterovirus is a common virus that can cause acute infections in children.. The clinical symptoms and signs caused by it mainly include HFMD, herpangina, encephalitis, brainstem encephalitis, encephalomyelitis, and poliomyelitis-like syndromes; HFMD and herpangina are the most common manifestations.

HFMD predominantly affects children and infants under 5 years of age[1-2], with occasional cases in adults. Over the past 20 years, HFMD has frequently occurred worldwide, particularly in the Asia-Pacific region[3-4]. The main symptoms after infection include fever, anorexia, and vesicles and ulcers on the hands, feet, and oral cavity. A small number of children develop severe cases, with complications such as aseptic meningitis, brainstem encephalitis, neurogenic pulmonary edema, and acute flaccid paralysis[5], resulting in high mortality and disability rates, which seriously endanger the physical health and life safety of children. It is known as the "polio" of the 21st century. The main pathogenic serotypes of HFMD include Coxsackievirus (CV) group A serotypes 4-7, 9, 10, and 16; group B serotypes 1-3 and 5; some serotypes of Echovirus; and Enterovirus A71 (EV71), among others. Among these, Coxsackievirus A16 (CA16) and EV71 are the most common, with severe cases and deaths mostly caused by EV71[5]. Since HFMD was classified as a Class C Communicable Diseases in China in 2008, surveillance data show that: from 2008 to 2012, EV71 and CA16 were the main pathogens of HFMD, with EV71 predominating; 2013-2015 was a period of rapid growth of CA6; from 2016 to 2019, four main pathogens (CA6, CA16, EV71, and CA10) co-circulated; and from 2017 to 2019, CA6 and CA16 predominated[6].

Herpangina is an acute contagious pharyngoangina caused by enterovirus, characterized by acute fever and herpetic ulcers in the pharyngeal arch. A subset of children with HFMD present as herpangina in the early stage of onset. It has a high incidence rate, with fecal-oral and respiratory tract as the main transmission routes, and summer and spring as the main epidemic seasons. The main pathogenic serotypes of herpangina are Coxsackievirus A (CV-A) serotypes 2, 4, 5, 6, 8, 10, and 16, and Enterovirus A71 (EV71). Coxsackievirus B (CV-B) group serotypes 1-5 can also cause the disease, though less commonly. Echovirus serotypes 3, 6, 9, 16, 17, 25, and 30 can also cause this disease[7].

China-developed EV71 vaccine was the first to be approved in 2015. However, different serotypes of EV show no cross-reactivity[4]. Monovalent EV71 vaccines cannot prevent HFMD and related diseases caused by other pathogens, and there is an urgent need to develop multivalent

enterovirus vaccines. Because EV71 and CA16 are the main pathogens of HFMD epidemics, the development of combination vaccines should prioritize EV71 and CA16 as the primary targets. Currently, several companies and research institutions have progressively initiated research on multivalent HFMD vaccines. The vaccines under development mainly include bivalent EV71/CA16 vaccines, trivalent EV71/CA16/CA6 vaccines, and tetravalent EV71/CA16/CA6/CA10 vaccines, however, most of them are in the preclinical research stage[8]. In 2020, South Korean company HK inno.N registered a clinical trial for the bivalent EV71-CA16 vaccine (IN-B001) on clinical trial (NCT04637919), but its status shows "unknown" with results temporarily unavailable. On October 31, 2022, AIM Vaccine's investigational bivalent EV71-CA16 HFMD vaccine (human diploid cell) obtained a clinical trial approval from the Center for Drug Evaluation (CDE) of the National Medical Products Administration (NMPA). This is the first bivalent HFMD vaccine to obtain a clinical trial approval and also the world's first-in-class innovative vaccine[9].

The preclinical animal trial results of the bivalent vaccine developed by Sinovac Biotech Co., Ltd. (hereinafter referred to as "Sinovac") have overall demonstrated good safety, immunogenicity, and compatibility between components. In accordance with the relevant requirements of the Measures for the Administration of Drug Registration[10], Good Clinical Practice (GCP) for Drug Clinical Trials[11], Technical Guidelines for Vaccine Clinical Trials[12], and Guiding Principles for Quality Management of Vaccine Clinical Trials (Trial Implementation)[13], a Phase I clinical trial is hereby conducted to primarily evaluate the tolerability and safety of this product in humans, and a Phase II clinical trial is conducted to explore the dosage of the investigational vaccine and evaluate its safety and immunogenicity in humans.

2.2 Background

2.2.1 Product summary

The bivalent vaccine is produced by respectively inoculating Vero cells with EV71 [redacted] and CA16 [redacted] The investigational vaccine has been tested and verified by the National Institutes for Food and Drug Control (NIFDC) [redacted]

The bivalent vaccine is a liquid injection, appearing as a milky white suspension liquid that may separate into layers due to precipitation and is easily resuspend able. Its main components are inactivated EV71 and CA16 viruses, [redacted] It is packaged in pre-filled syringes, with each syringe containing 0.5 mL. Each human dose is 0.5 mL,

[redacted]

This product is indicated for children aged 6-71 months who are susceptible to EV71 and CA16 virus infection. It is suitable for vaccination year-round. After vaccination with this product, it stimulates the body to produce immunity against EV71 and CA16, to prevent diseases caused by infection with EV71 and CA16 viruses, such as HFMD and herpangina.

2.2.2 Non-clinical data

[redacted]

2.2.2.1 Immunogenicity studies.

[redacted]

[redacted]

2.2.2.2 Safety studies.

[redacted]

2.2.3 Clinical data

No available.

2.3 Risk/benefit assessment

2.3.1 Known potential risks

Based on the product characteristics of the bivalent vaccine, preclinical study results, and vaccination experience, during this trial, hypersensitivity reactions, tenderness, induration, swelling, erythema, and other reactions at the injection site may occur. Additionally, theoretically, there exist safety risks unknown to the sponsor. To manage these potential risks, during vaccination in this trial, emergency

medical personnel with experience in managing allergic reactions will be arranged to be on standby at the clinical trial site to ensure timely management of any acute allergic reactions that occur.

Risks associated with venipuncture include pain upon needle insertion, dizziness or syncope that may occur in rare cases, and local infection at the venipuncture site with a very low probability. This trial aims to minimise venipuncture risks through close monitoring of participants, use of sterile disposable blood collection devices, and adherence to standard medical precautions. Meanwhile, considering ethical principles, the blood collection volume for children aged 24-71 months in Part II of the Phase I clinical trial is limited. Whether to perform Complete Blood Count (CBC), blood biochemistry, and urinalysis tests on Day 3 (V2), Day 30 (V5), and Day 33 (V6) will be determined based on the test results of the 6-12-year-old children group, and the test items have been appropriately reduced. The volume of blood collected in this trial will not cause harm to the health of participants.

2.3.2 Known potential benefits

In this trial, after participants are vaccinated with the investigational vaccine, it stimulates the body to produce immunity against EV71 and/or CA16, which is used to prevent diseases caused by EV71 and/or CA16 infection. However, like any vaccine, vaccination may not provide 100% protection to participants.

2.3.3 Assessment of potential risks and benefits

Although participants in this trial may experience the risks mentioned in Section 2.3.1, these risks will be well managed during the trial. Therefore, it is considered that the risks for participants in this trial are controllable, and the benefits outweigh the risks.

3. Objectives and Endpoints

3.1 Objectives and endpoints

Phase I	
Primary objective	**Primary endpoint**
• Based on AEs, evaluate the safety of the investigational vaccine in participants of different age groups.	• The incidence rate of Adverse Reactions (ARs) from the start of vaccination to 30 days after completion of full vaccination;
Secondary objectives	**Secondary endpoints**
• Based on AEs, evaluate the safety of the investigational vaccine in participants of different age groups. • Based on abnormalities in laboratory indicators, evaluate the safety of the investigational vaccine in participants	• The incidence rate of ARs within 0-7 days after each dose; • The incidence rate of SAEs from the start of vaccination to 6 months after completion of full vaccination; • The incidence rate of clinically significant

of different age groups.	abnormalities in blood biochemistry, CBC, and urinalysis indicators on day 3 after each dose.
Phase II	
Primary objective	**Primary endpoint**
• Evaluate the immunogenicity of the investigational vaccine in the target population.	• The seroconversion rate of EV71 and CA16 neutralising antibodies 30 days after completion of full vaccination in children aged 6-71 months;
Secondary objectives	**Secondary endpoints**
• Evaluate other immunogenicity indicators of the investigational vaccine	• The seropositivity rate, GMT, and GMFR of EV71 and CA16 neutralising antibodies 30 days after completion of full vaccination;
• Based on AEs, evaluate the safety of the investigational vaccine.	• The incidence rate of ARs from the start of vaccination to 30 days after completion of full vaccination; • The incidence rate of ARs within 0-7 days after each dose; • The incidence rate of SAEs from the start of vaccination to 6 months after completion of full vaccination;
• Evaluate the immune persistence of the investigational vaccine.	• The seropositivity rate and GMT of EV71 and CA16 neutralising antibodies 6 months after completion of full vaccination.

4. Trial Design

4.1 Description of Trial Design

The Phase I clinical trial is conducted in two parts. The first part adopts an open design, and the second part adopts a randomised, double-blind, active-controlled design.

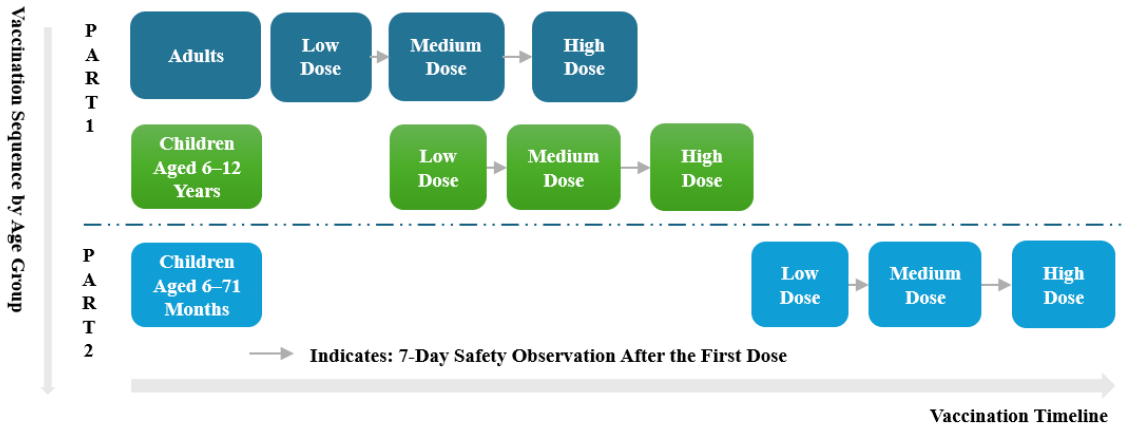
The first part is planned to enrol 36 healthy adults aged 18-59 years and 36 healthy children aged 6-12 years. Within each age group, participants will receive two doses of the investigational vaccine on a 0- and 1-month schedule, with sequential escalation from low dose [redacted] to medium dose [redacted], to high dose [redacted] Sequential enrolment proceeds from adults to children aged 6-12 years, with 12 participants per dose group in both adults and children aged 6-12 years.

The second part is planned to enrol 72 healthy children aged 6-71 months, who will be vaccinated on

a 0- and 1-month schedule with sequential escalation from low dose to medium dose, to high dose. Each dose step uses a randomised, double-blind, active-controlled design. Within each dose step, 12 participants in the 6-23-month subgroup and 12 participants in the 24-71-month subgroup are enrolled and randomly allocated in a 3:1 ratio to receive either the investigational vaccine or the control vaccine (EV71 vaccine).

The principle for dose-escalation vaccination within each age group is: escalating from low dose, to medium dose, to high dose, proceeding to a higher dose level is permitted only after completing a 0-7 day safety observation following the first dose of the lower dose level and confirming safety, based on the incidence of AEs and results of CBC, blood biochemistry, and urinalysis tests (if applicable). The principle for sequential enrolment between different age groups is enrolling in the order of adults → children aged 6-12 years → children aged 6-71 months. Specifically, participants in the same dose group of children aged 6-12 years can be enrolled only after a 0-7 day safety observation following the first dose administration in each adult dose group confirms safety; enrolment of the group of children aged 6-71 months can begin only after the medium-dose group of adults completes the 7-day safety observation following the second dose administration. Participants in the adult group and group of children aged 6-12 years will have approximately 5.5 mL of blood (approximately 2.0 mL anticoagulated and 3.5 mL non-anticoagulated) and approximately 2-10 mL of urine samples collected before each dose and on day 3 after each dose for CBC, blood biochemistry, and urinalysis tests to evaluate vaccine safety. In the group of children aged 6-71 months, only participants aged 24-71 months undergo the above tests, and only before the first dose; whether testing is performed at D3 (V2), D30 (V5), and D33 (V6) depends on the relevant test results of the group of children aged 6-12 years. If 10% of participants in each dose step of the group of children aged 6-12 years develop vaccine-related abnormal and clinically significant test results after the first dose, then the corresponding dose step of the group of children aged 24-71 months needs to collect blood and urine samples at D3 (V2), D30 (V5), and D33 (V6) for testing.

The specific vaccination sequence is as shown in the figure below:



Note: The enrolment principle for participants in the group of children aged 6-71 months requires that enrolment of the group of children aged 6-71 months can begin only after the medium-dose group of adults completes the 7-

day safety observation following the second dose administration.

Figure 3. Schematic of sequential enrolment in the phase I trial.

The Phase II clinical trial uses a randomised, double-blind, active-controlled design:

A total of 600 paediatric participants aged 6–71 months are planned to be enrolled, including 360 participants aged 6–23 months and 240 participants aged 24–71 months. Participants will be randomly assigned in a 1:1:1:1 ratio to one of three investigational vaccine dose groups—low dose [redacted] medium dose [redacted] and high dose [redacted]—or a control group. Following a 0- and 1-month vaccination schedule, participants will receive two doses of the investigational vaccine or control vaccine, respectively.

In Phase II, approximately 3.0 mL of venous blood will be collected from all participants on Days 0, 60, and 210. Serum will be separated for the measurement of EV71 and CA16 neutralising antibodies to evaluate the immunogenicity and immune persistence of the vaccine.

In both Phase I and Phase II, all participants will be observed for immediate reactions for 30 minutes after each vaccination. Solicited local and systemic AEs occurring within 0 – 7 days after vaccination, as well as unsolicited AEs occurring within 0 – 30 days after vaccination, will be collected. Serious adverse events (SAEs) will be monitored from the first vaccination until 6 months after completion of the vaccination schedule. In Phase I, pregnancy events occurring within 3 months (120 days) after vaccination will be collected based on spontaneous reporting.

After safety data through 30 days following completion of the vaccination schedule have been obtained for all participants in Phase I, the results will be submitted to the Ethics Committee for review. If the safety profile is acceptable and approval is granted by the Ethics Committee, the Phase II clinical trial will be initiated.The overall plans for phase I and phase II are summarised below.

Table 3. Phase I overall plan

Design	Age group	Total	Control vaccine	Investigational vaccine (/dose)			Schedule (months)	Urinalysis / CBC / blood biochemistry timepoints*
				Low	Medium	High		
Part 1 (open-label)	18-59 y	36	-	12	12	12	0, 1	D0, 3, 30, 33
	6-12 y	36	-	12	12	12		
Part 2 (Randomised, double-blind, controlled design)	6-23 mo	36	9	9	9	9		-
	24-71 mo	36	9	9	9	9		D0, 3, 30, 33
Total		144	18	42	42	42	-	-

*For the 6–71 months age group, laboratory assessments will only be conducted in participants aged 24–71 months. Whether testing will be performed on Day 3 (V2), Day 30 (V5), and Day 33 (V6) will be determined based on the corresponding assessment results from the 6–12 years age group. If, within any dose-escalation stage of the 6–12

years age group, vaccine-related and clinically significant laboratory abnormalities are observed in 10% of participants after the first vaccination, participants in the corresponding dose-escalation stage of the 24–71 months age group will undergo blood and urine sample collection for laboratory testing on Day 3 (V2), Day 30 (V5), and Day 33 (V6).

Table 4. Phase II overall plan

Age group (months)	Total	Control vaccine	Investigational vaccine (/dose)			Schedule (months)	Blood sampling (days)
			Low	Medium	High		
6-23	360	90	90	90	90	0, 1	D0, D60, D210
24-71	240	60	60	60	60		
Total	600	150	150	150	150	-	-

4.2 Rationale for trial design

The Phase I clinical trial aims to preliminarily evaluate the tolerability and safety of the investigational vaccine. Meanwhile, as the target population for the investigational vaccine is children aged 6-71 months, and to maximise participant safety, this trial also enrolled adult and children aged 6-12 years age groups to gradually explore the vaccine's safety in different populations. Enrolment was conducted in a sequential order of adults → children aged 6-12 years → children aged 6-71 months. Simultaneously, vaccination was administered using a dose-escalation approach: from low dose to high dose in adults and children aged 6-12 years, and from low, medium to high doses in children aged 6-71 months. Within each age group, higher doses could be administered only based on favorable safety data following vaccination with a lower dose. Additionally, younger age groups could be enrolled only based on favorable safety data following vaccination in older age groups.

To reduce potential bias in the safety evaluation among the target population, vaccination in each dose step for children aged 6-71 months adopts a randomised, double-blind, controlled design, with the control vaccine being the commercially available EV71 vaccine from Sinovac. This is to preliminarily evaluate the tolerability and safety of the bivalent vaccine with the newly added CA16 antigen.

The Phase II clinical trial aims to explore the dose of the investigational vaccine and evaluate its safety and immunogenicity in the target population. To reduce potential bias in the safety and immunogenicity evaluation among the target population, this trial also adopts a randomised, double-blind, controlled design, with the control vaccine being the commercially available EV71 vaccine from Sinovac, to evaluate the appropriate dose of the investigational vaccine as well as its safety and immunogenicity.

[redacted]

[redacted]

4.4 Definition of trial completion

If a participant has completed all visits in this trial, they are considered to have completed the trial. The trial end date is defined as the date of the last visit of the last participant.

4.5 Trial duration

Age Calculation and Related Definitions

1. Reference Date: The reference date is the date on which the participant signs the Informed Consent Form (ICF).

2. Method for Age Calculation: Adults and children aged 6-12 years: Age is calculated in years. Children aged 6-71 months: Age is calculated in months. The age of a participant at the reference date is calculated based on their date of birth, followed by unit conversion. A decimal representation of age is used (e.g., 6.5 years represents 6 years and 6 months).

3. Trial Observation Time Unit "Month": The trial observation time unit "month" is defined as a 30-day month. In this trial, a 30-day month is assumed for all months to simplify time calculations.

4. Month of Age: For children aged 6-71 months, "month of age" is used, which refers to the number of months elapsed since their date of birth.

4.5.1 Expected duration of the trial

Table 5 Clinical Trial Duration

Item	Duration
Trial preparation (protocol, forms, site selection, IEC review, Human Genetic Resources Administration application, etc.)	3 months
Database setup and participant recruitment	1 month
On-site implementation, data collection, and long-term safety observation	14 months
Antibody testing	2 months
Statistical Analysis	1 month
Complete the Clinical Study Report (CSR)	1 month
Total	22 months

4.5.2 Expected participant duration

Each participant is expected to be in the trial for at least 7 months.

5. Trial population

5.1 Inclusion criteria

(1) Healthy participants aged 18-59 years, children aged 6-12 years, and children aged 6-71 months;

(2) Participants and/or their guardians can understand and voluntarily sign the ICF (for participants aged 8-12 years, dual signatures from both the participant and their guardian are required);

(3) Willing and able to comply with all visit schedules, sample collection, vaccination, and other trial procedures;

(4) Provide legal identity proof of the participant and/or their guardian.

5.2 Exclusion criteria

(1) History of hand, foot, and mouth disease or EV71 vaccination;

(2) Known severe allergy to the vaccine or its components (e.g., urticaria, dyspnea, angioedema);

(3) Congenital abnormalities or developmental disorders, genetic defects (such as Down syndrome, thalassemia, or G6PD deficiency), severe malnutrition, etc.

(4) Based on medical history and physical examination, the presence of severe chronic diseases, severe cardiovascular diseases, uncontrolled hypertension or diabetes, liver or kidney diseases, etc;

(5) Based on medical history and physical examination, the presence of autoimmune diseases, immunodeficiency diseases, and/or blood diseases (including but not limited to systemic lupus erythematosus, ankylosing spondylitis, thyroidectomy, autoimmune thyroid disease, any form of malignancy, asplenia, functional asplenia).

(6) Based on medical history and physical examination, abnormal coagulation function (e.g., coagulation factor deficiency, coagulopathy, platelet abnormalities) or obvious bruising/bleeding disorders, based on medical history and physical examination;

(7) Based on medical history and physical examination, the presence of severe neurological diseases (epilepsy, convulsions, or seizures), mental illness, or corresponding family history.

(8) Long-term use (more than 14 days) of corticosteroids or other immunosuppressive agents (excluding corticosteroid sprays for allergic rhinitis and surface corticosteroid treatment for acute non-complicated dermatitis) or cytotoxic therapy or planning to receive such treatment during the trial;

(9) History of chronic alcoholism or drug abuse;

(10) Females who are breastfeeding, pregnant, or planning to become pregnant within 90 days, or females with positive pregnancy test results. Note: male participants whose spouse plans to become pregnant within 90 days are also included;

(11) Receipt of immunoglobulin and/or other blood products within the past 3 months, or planned receipt during the trial;

(12) Receipt of other investigational drugs or vaccines within the past 30 days, or planned receipt during the trial;

(13) Receipt of live attenuated vaccines within the past 14 days, or subunit/inactivated vaccines within the past 7 days;

(14) Suspected or confirmed fever within 72 hours prior to vaccination, or axillary temperature >37.0°C on the day of vaccination;

(15) Clinically significant laboratory abnormalities, defined as laboratory test results outside the reference range and considered clinically meaningful (applicable only to adult participants, children aged 6–12 years, and children aged 24–71 months in the Phase I clinical trial):

A. Routine blood tests: White blood cell count, hemoglobin, platelet count;

B. Blood biochemistry: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), creatinine (CR), fasting blood glucose (Glu);

C. Urinalysis: Proteinuria (PRO);

(16) Any acute illnesses (moderate or severe, with or without fever) within the past 7 days, or acute exacerbation of chronic diseases;

(17) In the investigator's judgment, the participant has any other condition or factor that would make them unsuitable for participation in the clinical trial.

5.3 Exclusion/postponement criteria for the second dose

If the following events (1) to (3) occur, vaccination is prohibited, but other trial steps can be continued according to the investigator's judgment; if the following events (4) to (6) occur, vaccination can be postponed within the time window specified in the plan; if (7) other events that are not suitable for vaccination occur, the investigator will judge whether to vaccinate or postpone the vaccination.

(1) Any serious adverse reaction causally related to the investigational vaccine;

(2) Severe hypersensitivity reactions after vaccination with investigational vaccines (including urticaria/rash occurring within 30 minutes of vaccination);

(3) Other ARs as judged by the investigator (including severe pain, severe swelling, severe limitation of activity, persistent high fever, severe headache, or other systemic or local ARs);

(4) Acute illness (moderate or severe, with or without fever) or acute exacerbation of chronic diseases at the time of vaccination;

(5) Axillary temperature >37.0℃ on the day of vaccination;

(6) Have received subunit vaccine or inactivated vaccine within 7 days, and have received live attenuated vaccine within 14 days;

(7) Have any other factors that make them unsuitable for vaccination, as determined by the investigator.

5.4 Lifestyle restrictions

All requirements during the trial that participants must agree to comply with are as described in the inclusion/exclusion criteria.

Medications (vaccines)/treatments prohibited during the trial are detailed in Section 6.5.

5.5 Screening failure

Participants who agree to participate in the clinical trial but fail to meet one or more criteria for participation during the screening process are considered screening failures. For participants with screening failures, at least the following information is required to ensure transparent reporting of the screening failure to regulatory authorities: demographic information, details of the screening failure, and compliance with the inclusion/exclusion criteria.

6. Trial Intervention

6.1 Trial Intervention Management

6.1.1 Trial Intervention Description

(1) Investigational vaccine

Group Name	**Low Dose Group**
Intervention Name	Bivalent Enterovirus Vaccine (Vero Cell), Inactivated
Dosage Form	Pre-filled syringe, 0.5 mL per syringe
Antigen Content per Dose	[redacted]
Route of Administration	Intramuscular injection into the deltoid muscle of the upper arm
Intended Use	For clinical trial use
Whether it is an Investigational Medicinal Product (IMP)	Yes
Source	Provided by Sinovac
Packaging and Labeling	The vaccine for each participant will be packaged in a separate small box, with each box containing only one pre-filled syringe

Group Name	**Medium Dose Group**
Intervention Name	Bivalent Enterovirus Vaccine (Vero Cell), Inactivated
Dosage Form	Pre-filled syringe, 0.5 mL per syringe
Antigen Content per Dose	[redacted]
Route of Administration	Intramuscular injection into the deltoid muscle of the upper arm
Intended Use	For clinical trial use
Whether it is an Investigational Medicinal Product (IMP)	Yes
Source	Provided by Sinovac
Packaging and Labeling	The vaccine for each participant will be packaged in a separate small box, with each box containing only one pre-filled syringe

Group Name	**High Dose Group**
Intervention Name	Bivalent Enterovirus Vaccine (Vero Cell), Inactivated
Dosage Form	Pre-filled syringe, 0.5 mL per syringe
Antigen Content per Dose	[redacted]
Route of Administration	Intramuscular injection into the deltoid muscle of the upper arm
Intended Use	For clinical trial use
Whether it is an Investigational Medicinal Product (IMP)	Yes
Source	Provided by Sinovac
Packaging and Labeling	The vaccine for each participant will be packaged in a separate small box, with each box containing only one pre-filled syringe

(2) Control vaccine

Group Name	**Control Group**
Intervention Name	Enterovirus Type 71 Vaccine, Inactivated (Vero Cell) – Inlive®
Dosage Form	Pre-filled syringe, 0.5 mL per syringe
Antigen Content per Dose	[redacted]
Route of Administration	Intramuscular injection into the deltoid muscle of the upper arm
Intended Use	For clinical trial use
Whether it is an Investigational Medicinal Product (IMP)	Yes
Source	Provided by Sinovac
Packaging and Labeling	The vaccine for each participant will be packaged in a separate small box, with each box containing only one pre-filled syringe

6.1.2 Dose and administration

Eligible participants will each receive a single intramuscular injection of 0.5 mL of the investigational

vaccine or control vaccine (with different antigen doses) into the deltoid muscle of the upper arm. All participants will receive two doses according to a 0- and 1-month schedule, and the vaccine should be thoroughly shaken before administration.

6.2 Preparation, Storage, Handling and Accountability of Investigational Trial Intervention

6.2.1 Product receipt and inventory

1. The Sponsor will deliver the investigational vaccine to the clinical trial site under cold chain conditions of 2°C to 8°C. The investigator must sign the vaccine receipt records, and this receipt certificate should briefly describe the information of the received vaccine (e.g., name, quantity, specification, intact packaging, normal cold chain system indicators, etc.).

2. If the investigator discovers damage, deterioration, or lumps that cannot be dispersed by shaking in the vaccine, or if the vaccine has been frozen, do not use it; return it to the Sponsor.

3. Only participants enrolled in the trial can be vaccinated with the investigational vaccine, and only authorised on-site staff can provide and administer the investigational vaccine for the clinical trial.

4. Use a vaccine inventory record form to document the quantity of vaccine received, the quantity administered to participants, the remaining quantity, and the lost quantity. Upon completion of on-site research work, the remaining investigational vaccine should be counted and returned to the Sponsor, or the Sponsor may entrust the investigator to destroy it on-site and maintain corresponding records.

6.2.2 Dosage form, appearance, packaging, and labelling

In this trial, all investigational vaccines are in the dosage form of pre-filled syringes. The inner and outer packaging of the control vaccine is consistent with that of the investigational vaccine; it is a milky white suspension liquid that may separate into layers due to precipitation and is easy to re-disperse by shaking. Each vaccine will be packaged in a separate small package box, with each box containing only one pre-filled syringe. Blinded vaccines are all equipped with a unique blind label. The label does not allow identification of the investigational vaccine or control vaccine at different doses. This label is affixed to the barrel of the pre-filled syringe and the body of the small package box, and an additional movable label is placed inside the small package box.

6.2.3 Product storage and stability

After the investigator receives the investigational vaccine, the vaccine should be stored and transported at 2°C to 8°C protected from light. If a cold chain interruption occurs, a report should be sent to the Sponsor to confirm whether the affected investigational vaccine can continue to be used or needs to be replaced. All affected investigational vaccines should be placed in a separate area until further instructions are received from the Sponsor.

6.2.4 Administration

The investigational vaccine should be prepared and distributed by an investigator authorised by the

PI (Principal Investigator), and another staff member should be assigned to verify the allocation.

The vaccinator retrieves the vaccine labeled with the corresponding number matching the participant's number, opens the small package box, and verifies the information on the label of the pre-filled syringe, the label on the small package box, and the movable label inside the box. Only proceed with vaccination after confirming consistency. After vaccination, tear off the movable label inside the box and affix it to the corresponding position in the source document, and record the vaccination information in the source document.

Disinfect the injection site with 75% alcohol before vaccination, and allow the skin to dry before injection. Refer to "6.1.2 Dosage and Administration" for the vaccination method and schedule.

After vaccination, fill out the Child Vaccination Record(adults receive a vaccination voucher). After unblinding, enter the vaccination information of the marketed EV71 vaccine into the immunisation programme information management system.

6.3 Randomisation and blinding

6.3.1 Randomisation

Part 1 of the Phase I clinical trial (adult group and group of children aged 6-12 years) uses an open-label design, with 12 doses of the investigational vaccine set at each dose level.

Part 2 of the Phase I clinical trial (group of children aged 6-71 months) and the Phase II clinical trial both adopt a randomised double-blind design. An independent third-party randomisation statistician will use SAS software (version 9.4 or above) and apply a stratified block randomisation method (with age [6-23 months, 24-71 months] as the stratification factor) to allocate participants to the investigational vaccine groups and control group according to the protocol requirements, generating a participant randomisation code list. Vaccines will be labelled according to the participant randomisation code list (each vaccine has a unique identifier). The randomisation blind code will be kept by the third-party randomisation statistician for unblinding the trial.

At each clinical trial site, in addition to the vaccines required for vaccination, numbered reserve vaccines will be placed. Considering approximately 10% reserve vaccines, the reserve vaccine numbers are: Phase I: [redacted] (30 doses in total, 2 doses each of investigational vaccines at different dose levels and control vaccine); Phase II: [redacted] (120 doses in total, 2 doses each of investigational vaccines at different dose levels and control vaccine).

When the investigational vaccine is damaged, has insufficient volume, shows abnormal appearance, or is administered incorrectly during the trial (requiring reserve vaccine use), the vaccinator should report to the site supervisor and the principal investigator, initiate the reserve vaccine activation procedure, obtain the reserve vaccine number through the online reserve vaccine acquisition system, and use the reserve vaccine to replace the investigational vaccine.

6.3.2 Blinding

Part 1 of the Phase I clinical trial (adult group and group of children aged 6-12 years) uses an open-label design.

Part 2 of the Phase I clinical trial and the Phase II clinical trial both adopt a blinded design. The Sponsor or independent third-party personnel not involved in the conduct of the trial shall print vaccine labels according to the randomisation code list generated by the randomisation statistician. The blinding process shall be coordinated by the Sponsor and carried out under the supervision of the randomisation statistician to ensure that it is conducted in accordance with the protocol and appropriately documented. The printed labels shall be affixed to the designated location on each vaccine package. The entire blinding process shall be documented in writing. Personnel involved in the blinding process shall sign confidentiality agreements, shall not participate in any trial-related activities, and shall not disclose treatment assignments or other blinding information to any personnel involved in the conduct of the trial.

6.3.3 Emergency unblinding

If an emergency occurs during on-site implementation (for example, when it is necessary to know the vaccine allocation status of participants in order to provide corresponding medical treatment to the participants), emergency unblinding can be performed when necessary, and the ethics committee should be informed after the emergency unblinding.

In an emergency, the investigator determine whether it is necessary to unblind the participant group. If the investigator thinks it is necessary to unblind, the sponsor should be notified in time;

. Investigators should evaluate the relationship between AEs and investigational vaccines before unblinding.

Participants who have been urgently unblinded will only have a safety visit, and the investigator will also need to record the time and reason for unblinding in the Case Report Form (CRF).

6.3.4 SUSAR unblinding

When an unexpected serious adverse event (SAE) occurs, to facilitate the judgment of the correlation between the SAE and the investigational vaccine and determine whether rapid reporting is required, the Sponsor needs to unblind the individual case report for Suspected Unexpected Serious Adverse Reaction (SUSAR).

The second part of the Phase I and the Phase II adopt a blinding design. If unblinding is required for the evaluation of a SUSAR, authorised Sponsor Pharmacovigilance (PV) personnel shall request the treatment assignment for the relevant participant from the randomisation statistician via email. [redacted] Following unblinding, if the SUSAR is determined to have occurred in a participant assigned to the investigational vaccine group, the SUSAR shall be reported in accordance with the expedited reporting requirements and procedures. Details of the reporting process are provided in Section 8.4.6.4, “Sponsor Reporting Procedures to Regulatory Authorities”. This unblinding process shall be performed only by specifically authorised personnel on an individual case basis. Personnel responsible for the analysis and interpretation of efficacy results shall remain blinded to treatment assignment. Unblinding for an individual SUSAR case shall not affect the conduct of the clinical trial or the analysis of the final study results.

6.3.5 Study Unblinding

[redacted]

6.4 Intervention compliance

Develop a concise and clear volunteer recruitment brochure and ICF in accordance with the clinical protocol.

Train physicians are responsible for informed explanation to communicate with volunteers using plain and understandable language to ensure full understanding.

Screen participants strictly in accordance with the inclusion and exclusion criteria.

Follow-up personnel should possess a high sense of responsibility and professionalism, and their communication skills and affinity should be enhanced through training. After each vaccination, issue a diary card to the participant and/or their guardian. On the 7th day after each vaccination, collect and review the diary card, and issue a contact card to ensure effective communication between the

participant and/or guardian and the investigator, timely manage identified AEs, and provide relevant health consultations to the participant and/or guardian.

For participants who fail to comply with the visit schedule and miss the second dose of the investigational vaccine not due to safety reasons, the investigator should contact the participant to complete subsequent vaccinations and visits in accordance with the vaccination procedure and visit schedule specified in the trial protocol.

The clinical trial site is responsible for ensuring that each participant's visit complies with the allowed time window. If a participant misses a visit, the participant and/or guardian should be contacted as much as possible, and the visit should be completed within the specified visit window. If the participant fails to complete the visit within the window, the visit will be classified as a missed visit, and the participant will continue to receive subsequent planned visits.

6.5 Concomitant therapy

Permitted concomitant medications/vaccines/treatments.

- If an adverse event (AE) occurs during the trial, the use of necessary medications and medical treatments is permitted.
- In case of a severe allergic reaction or life-threatening situation, immediate first aid measures should be taken.
- The investigator should record information on any concomitant medications, including name, dosage form, dose, time of use, etc.
- During the trial, participants who receive routine immunisations can be vaccinated according to the product instructions, but there needs to be a certain time interval between the vaccination time and the investigational vaccine. After receiving the investigational vaccine, there must be an interval of at least 7 days before receiving other vaccines.
- If any vaccine other than the investigational vaccine for the clinical trial is administered during the trial, detailed records should be made of the following information: name, dose, administration method, vaccination date, etc.

Prohibited concomitant medications/vaccines/treatments.

- Use of the investigational EV71 vaccine or other marketed EV71 vaccines is prohibited.
- Other prohibited concomitant medications (vaccines)/treatments are detailed in Section 5. Study Population

7. Intervention Suspension/Termination and Participant Discontinuation /Withdrawal

7.1 Intervention suspension rules

The Sponsor and Principal Investigator (PI) monitor the safety situation during the clinical trial, including whether the rules for suspending vaccination with the investigational vaccine are met:

- In each age group of each phase of the clinical trial, if 15% of participants experience Grade 3 or higher AEs (including local AEs, systemic AEs, vital signs abnormalities, and clinically significant abnormal laboratory test indicators), the Sponsor and investigators will decide whether to suspend vaccination.
- If 1 case of a vaccine-related Grade ≥4 AR or a fatal/life-threatening SUSAR occurs, vaccination will be suspended.

7.2 Intervention termination rules

Any of the following situations will lead to the termination of the trial:

- After the suspension of vaccination, the investigator and the Sponsor jointly discuss whether to terminate the trial;
- The Sponsor requests the termination of the trial and provides reasons;
- The Ethics Committee requests the termination of the trial and provides reasons;
- The regulatory authority requests the termination of the trial and provides reasons.

Suspension of the trial intervention does not mean the termination of the trial; the subsequent trial procedures shall be completed in accordance with the provisions of the trial protocol.

7.3 Participant discontinuation/withdrawal

Participants may withdraw from the trial unconditionally at their own and/or guardian's discretion. The investigator may request the participant to suspend/withdraw from the trial based on the following reasons:

- Intolerable AEs, regardless of whether they are related to the investigational vaccine;
- The participant's health condition does not permit them to continue participating in this clinical trial;
- Any other reason deemed by the investigator.

The investigator should attempt to contact the participant and/or guardian who miss scheduled visits or follow-ups and record the reason for the participant's withdrawal in the case report form (CRF). If the participant withdraws due to an adverse event (AE) after vaccination, with the participant's consent, appropriate follow-up or medical care should be arranged until the AE is resolved. In any case, every effort should be made to track and record the outcome of the AE. If a participant who withdraws/suspends from the trial has already received the investigational vaccine, their clinical trial data will be used for safety analysis. Data and blood samples collected before the participant's withdrawal should continue to be used for the analysis of this trial, unless the participant specifically requests otherwise.

7.4 Loss to follow-up

If a participant consecutively misses multiple scheduled visits and cannot be contacted by the site investigator or their guardian, the participant will be considered lost to follow-up. For participants who miss scheduled visits, the following measures may be taken:

- The clinical trial site must attempt to contact the participant and/or their guardian, reschedule the missed visit as soon as possible, inform the participant and/or guardian of the importance of attending visits at the designated time, and confirm whether the participant voluntarily agrees or the participant's guardian agrees for their child to continue the trial.
- The investigator or designated personnel must make every effort to re-establish contact with the participant/participant's guardian and record this in the participant's source documents.
- If the participant/participant's guardian still cannot be contacted, the participant may be considered dropped out.

8. Trial Procedures and Assessments

Before the start of the clinical trial, all materials required for the collection, processing, storage, and transportation of biological samples shall be sent to the clinical trial site. Before performing any trial procedures, the ICF must be voluntarily signed by the participant and/or their guardian. Participants will complete the trial procedures at the time points specified in "1.3 Planned Visit Schedule", and no exemptions are allowed.

The investigator may enrol the participant only after completing the participant screening assessment and confirming that the participant meets the inclusion criteria and does not meet the exclusion criteria. The investigator should maintain a screening log to record detailed information of all screened participants, in order to confirm their eligibility for enrolment or record the reasons for screening failure (if applicable).

Every effort should be made to ensure that all trial procedures and tests are completed in accordance with the protocol. When a test required by the protocol cannot be completed, the investigator should record the reason, as well as the preventive and corrective measures taken to ensure the test is completed as much as possible as required by the protocol. Preventive measures include, for example, providing a detailed introduction to the trial procedures during recruitment and informed consent, following the participant's wishes, and strictly adhering to the trial procedures during execution.

8.1 Trial procedures

8.1.1 Phase I

Screening visit (V0) - Day -7 to Day 0.

Screening should be conducted within 7 days before or on the day of Visit 1 (Vaccination). The procedures for the screening visit are as follows:

- Sign the ICF;
- Assign a screening number to the participant;
- Obtain the participant's demographic information (including date of birth, gender, ethnicity, etc.);
- Collect the participant's medical history and relevant concomitant medication information;
- Collect blood and urine samples from the participant for routine blood tests, blood biochemistry, and urinalysis indicator tests.

Visit 1 (V1) - Day 0.

If the screening visit is conducted on the same day as vaccination, the screening visit and Visit 1 will be combined into a single visit. All procedures of the screening visit will be conducted during Visit 1.

The procedures are as follows:

- Sign the ICF (which may also be done during the screening visit);
- Assign a screening number to the participant (which may also be done during the screening visit);
- Obtain the participant's demographic information (including date of birth, gender, ethnicity, etc.) (which may also be done during the screening visit);
- Collect the participant's medical history and relevant concomitant medication information (which may also be done during the screening visit);
- Female participants who have reached menarche and are premenopausal undergo a urine pregnancy test;
- Conduct physical examination and vital signs measurement (for adults: skin, throat, height, weight, temperature, heart rate, blood pressure, respiratory rate; for children aged 6-12 years and children aged 6-71 months: skin, throat, height, weight, temperature);
- Collect approximately 5.5 mL of venous blood (about 2.0 mL anticoagulated and 3.5 mL non-anticoagulated) and approximately 2-10 mL of urine from the participant for routine blood tests, blood biochemistry, and urinalysis indicator tests (which may also be done during the screening visit);
- Evaluate compliance with the inclusion/exclusion criteria;
- Assign a trial number to the participant;
- Clinical trial site staff assign the vaccine and administer the vaccination;
- Provide the participant with a diary card and train them on how to complete it;
- Clinical trial site staff conduct a 30-minute on-site safety observation of the participant after

vaccination to identify any immediate reactions, record any AEs in the diary card; if a serious adverse event (SAE) occurs, complete the SAE report form;

- Inform the participant of the time of the next visit.

Visit 2 (V2) - V1 + 3.

- Verify the occurrence of AEs through face-to-face visits (for participants requiring clinical laboratory tests) or telephone visits;
- Verify the use of the participant's concomitant vaccines (non-investigational vaccines) and/or concomitant medications;
- Based on self-report, confirm whether the participant or their partner (a female who has reached menarche and is premenopausal) has had a pregnancy event;
- Collect approximately 5.5 mL of venous blood (about 2.0 mL anticoagulated and 3.5 mL non-anticoagulated) for routine blood tests and blood biochemistry tests, and collect approximately 2-10 mL of urine for urinalysis. Among these, whether children aged 24-71 months will undergo routine blood tests, blood biochemistry, and urinalysis will be determined based on the test results of the group of children aged 6-12 years;
- Inform the participant of the time of the next visit.

Visit 3 (V3) - V1 + 7.

- Through face-to-face visits, collect and review the completeness of the diary card entries, and verify the occurrence of AEs;
- Verify the use of the participant's concomitant vaccines (non-investigational vaccines) and/or concomitant medications;
- Based on self-report, confirm whether the participant or their partner (a female who has reached menarche and is premenopausal) has had a pregnancy event;
- Issue a contact card and inform the participant of the time of the next visit.

Visit 4 (V4) - V1 + 14.

- Verify the occurrence of AEs through telephone visits;
- Verify the use of the participant's concomitant vaccines (non-investigational vaccines) and/or concomitant medications;
- Based on self-report, confirm whether the participant or their partner (a female who has reached menarche and is premenopausal) has had a pregnancy event;
- Inform the participant of the time of the next visit.

Visit 5 (V5) - V1 + 30.

- Through face-to-face visits, collect and review the completeness of the contact card entries, and verify the occurrence of AEs;
- Verify the use of the participant's concomitant vaccines (non-investigational vaccines) and/or concomitant medications;
- Verify the participant's use of concomitant medications (vaccines)/treatments prohibited by the protocol;
- Collect approximately 5.5 mL of venous blood (about 2.0 mL anticoagulated and 3.5 mL non-anticoagulated) for routine blood tests and blood biochemistry tests, and collect approximately 2-10 mL of urine for urinalysis;
- Female participants who have reached menarche and are premenopausal undergo a urine pregnancy test;
- Measure body temperature;
- Verify whether the participant meets the exclusion criteria for the second dose vaccination;
- Clinical trial site staff assign the vaccine and administer the vaccination;
- Provide the participant with the diary card for after the second dose vaccination and train them on how to complete it;
- Clinical trial site staff conduct a 30-minute on-site safety observation of the participant after vaccination to identify any immediate reactions, record any AEs in the diary card; if a serious adverse event (SAE) occurs, complete the SAE report form;
- Inform the participant of the time of the next visit.

Visit 6 (V6) - V5 + 3.

- Verify the occurrence of AEs through face-to-face visits (for participants requiring clinical laboratory tests) or telephone visits;
- Verify the use of the participant's concomitant vaccines (non-investigational vaccines) and/or concomitant medications;
- Based on self-report, confirm whether the participant or their partner (a female who has reached menarche and is premenopausal) has had a pregnancy event;
- Collect approximately 5.5 mL of venous blood (about 2.0 mL anticoagulated and 3.5 mL non-anticoagulated) for routine blood tests and blood biochemistry tests, and collect approximately 2-10 mL of urine for urinalysis. Among these, whether children aged 24-71 months will undergo routine blood tests, blood biochemistry, and urinalysis will be determined based on the test results of the group of children aged 6-12 years;
- Inform the participant of the time of the next visit.

Visit 7 (V7) - V5 + 7.

- Through face-to-face visits, collect and review the completeness of the diary card entries, and verify the occurrence of AEs;
- Verify the use of the participant's concomitant vaccines (non-investigational vaccines) and/or concomitant medications;
- Based on self-report, confirm whether the participant or their partner (a female who has reached menarche and is premenopausal) has had a pregnancy event;
- Issue a contact card and inform the participant of the time of the next visit.

Visit 8 (V8) - V5 + 14.

- Verify the occurrence of AEs through telephone visits;
- Verify the use of the participant's concomitant vaccines (non-investigational vaccines) and/or concomitant medications;
- Based on self-report, confirm whether the participant or their partner (a female who has reached menarche and is premenopausal) has had a pregnancy event;
- Inform the participant of the time of the next visit.

Visit 9 (V9) - V5 + 30.

- Through face-to-face visits, collect and review the completeness of the contact card entries, and verify the occurrence of AEs;
- Verify the use of the participant's concomitant vaccines (non-investigational vaccines) and/or concomitant medications;
- Based on self-report, confirm whether the participant or their partner (a female who has reached menarche and is premenopausal) has had a pregnancy event;
- Inform the participant of the time of the next visit.

Visit 10 (V10) - V5 + 90.

- Verify the occurrence of serious adverse events (SAEs) through telephone visits;
- Verify the use of the participant's concomitant vaccines (non-investigational vaccines) and/or concomitant medications;
- Verify whether the participant or their partner (a female who has reached menarche and is premenopausal) has had a pregnancy event.

Visit 11 (V11) - V5 + 150.

- Verify the occurrence of serious adverse events (SAEs) through telephone visits;

- Verify the use of the participant's concomitant vaccines (non-investigational vaccines) and/or concomitant medications;

Visit 12 (V12) - V5 + 180.

- Verify the occurrence of serious adverse events (SAEs) through telephone visits;
- Verify the use of the participant's concomitant vaccines (non-investigational vaccines) and/or concomitant medications;
- Complete the filling of the source document and Electronic Data Capture (EDC).

8.1.2 Phase II

Screening visit (V0) - Day -7 to Day 0.

Screening should be conducted within 7 days before or on the day of Visit 1 (Vaccination). The procedures for the screening visit are as follows:

- Sign the ICF;
- Assign a screening number to the participant;
- Obtain the participant's demographic information (including date of birth, gender, ethnicity, etc.);
- Collect the participant's medical history and relevant concomitant medication information;

Visit 1 (V1) - Day 0.

If the screening visit is conducted on the same day as vaccination, the screening visit and Visit 1 will be combined into a single visit. All procedures of the screening visit will be conducted during Visit 1. The procedures are as follows:

- Sign the ICF (which may also be done during the screening visit);
- Assign a screening number to the participant (which may also be done during the screening visit);
- Obtain the participant's demographic information (including date of birth, gender, ethnicity, etc.) (which may also be done during the screening visit);
- Collect the participant's medical history and relevant concomitant medication information (which may also be done during the screening visit);
- Female participants who have reached menarche and are premenopausal undergo a urine pregnancy test;
- Conduct physical examination and vital signs measurement (for adults: skin, throat, height, weight, temperature, heart rate, blood pressure, respiratory rate; for children aged 6-12 years and children aged 6-71 months: skin, throat, height, weight, temperature);

- Collect approximately 5.5 mL of venous blood (about 2.0 mL anticoagulated and 3.5 mL non-anticoagulated) and approximately 2-10 mL of urine from the participant for routine blood tests, blood biochemistry, and urinalysis indicator tests (which may also be done during the screening visit);
- Evaluate compliance with the inclusion/exclusion criteria;
- Assign a trial number to the participant;
- Clinical trial site staff assign the vaccine and administer the vaccination;
- Provide the participant with a diary card and train them on how to complete it;
- Clinical trial site staff conduct a 30-minute on-site safety observation of the participant after vaccination to identify any immediate reactions, record any AEs in the diary card; if a serious adverse event (SAE) occurs, complete the SAE report form;
- Inform the participant of the time of the next visit.

Visit 2 (V2) - V1 + 7.

- Through face-to-face visits, collect and review the completeness of the diary card entries, and verify the occurrence of AEs;
- Verify the use of the participant's concomitant vaccines (non-investigational vaccines) and/or concomitant medications;
- Issue a contact card and inform the participant of the time of the next visit.

Visit 3 (V3) - V1 + 30.

- Through face-to-face visits, collect and review the completeness of the contact card entries, and verify the occurrence of AEs;
- Verify the use of the participant's concomitant vaccines (non-investigational vaccines) and/or concomitant medications;
- Measure body temperature;
- Verify whether the participant meets the exclusion criteria for the second dose vaccination;
- Clinical trial site staff assign the vaccine and administer the vaccination;
- Provide the participant with the diary card for after the second dose vaccination and train them on how to complete it;
- Clinical trial site staff conduct a 30-minute on-site safety observation of the participant after vaccination to identify any immediate reactions, record any AEs in the diary card; if a serious adverse event (SAE) occurs, complete the SAE report form;
- Inform the participant of the time of the next visit.

Visit 4 (V4) - V3 + 7.

- Through face-to-face visits, collect and review the completeness of the diary card entries, and verify the occurrence of AEs;
- Verify the use of the participant's concomitant vaccines (non-investigational vaccines) and/or concomitant medications;
- Issue a contact card and inform the participant of the time of the next visit.

Visit 5 (V5) - V3 + 30.

- Through face-to-face visits, collect and review the completeness of the contact card entries, and verify the occurrence of AEs;
- Verify the use of the participant's concomitant vaccines (non-investigational vaccines) and/or concomitant medications;
- Collect approximately 3.0 mL of venous blood for neutralising antibody testing;
- Inform the participant of the time of the next visit.

Visit 6 (V6) - V3 + 90.

- Verify the occurrence of serious adverse events (SAEs) through telephone visits;
- Verify the use of the participant's concomitant vaccines (non-investigational vaccines) and/or concomitant medications.

Visit 7 (V7) - V3 + 150.

- Verify the occurrence of serious adverse events (SAEs) through telephone visits;
- Verify the use of the participant's concomitant vaccines (non-investigational vaccines) and/or concomitant medications.

Visit 8 (V8) - V3 + 180.

- Verify the occurrence of serious adverse events (SAEs) through face-to-face visits;
- Verify the use of the participant's concomitant vaccines (non-investigational vaccines) and/or concomitant medications;
- Collect approximately 3.0 mL of venous blood for neutralising antibody testing;

8.2 Immunogenicity evaluation

Phase II clinical trial will collect blood samples from participants at the time points specified in "1.3 Planned Visit Schedule". EV71 and CA16 neutralising antibodies will be detected using the micro cytopathic effect assay at the National Institutes for Food and Drug Control (NIFDC). Based on the test results, the seropositivity rate of neutralising antibodies, seroconversion rate, GMT, and GMI will be calculated.

Definition of seroconversion: Pre-vaccination neutralising antibodies are negative and post-vaccination neutralising antibodies are positive; or pre-vaccination neutralising antibodies are positive and post-vaccination neutralising antibodies show a four-fold or greater increase.

8.3 Safety evaluation

"1.3 Planned Visit Schedule" provides the planned visit time points for all safety evaluations. In addition, unscheduled visits may be arranged at any time during the trial to follow up on any known safety issues. Any clinically relevant changes occurring during the trial should be recorded in the case report form (CRF). The collection, recording, and reporting of AEs/SAEs are detailed in Section 8.4. For any significant clinical abnormalities (including abnormal laboratory test indicators) that are ongoing at the end of the clinical trial/early withdrawal, investigators should continuously follow up until they return to normal or reach a clinically stable state.

The following safety assessments should also be conducted at the time points specified in "1.3 Planned Visit Schedule".

8.3.1 Physical examination

A physical examination will be performed on the day of vaccination by the investigator or a designated clinician who has received appropriate medical training. The physical examination will include assessment of the skin, throat, height, and weight. Any clinically relevant abnormalities observed during the examination of body systems will be recorded in the case report form (CRF).

8.3.2 Vital signs

During the physical examination, the following vital signs will be assessed. For adults, body temperature, heart rate, blood pressure, and respiratory rate will be measured. For children aged 6 – 12 years and 6 – 71 months, body temperature will be measured. In addition, all participants will be observed on site for 30 minutes after each vaccination for immediate post-vaccination ARs, and body temperature will be measured for each participant at the end of the observation period. Participants or their legal guardians will use diary cards to record solicited and unsolicited AEs (including vital sign abnormalities) occurring from vaccination through 7 days after vaccination. Contact cards will be used to record unsolicited AEs (including vital sign abnormalities) occurring from Day 8 through Day 30 after vaccination. Body temperature will be measured daily during the first 7 days after vaccination and recorded in the diary card. Any fever occurring between Days 8 and 30 after vaccination will be recorded in the contact card, together with the highest axillary temperature observed.

8.3.3 Clinical laboratory testing

Laboratory test indicators include:

A. Routine blood tests: White blood cell count, hemoglobin, platelet count;

B. Blood biochemistry: Alanine aminotransferase (ALT), aspartate aminotransferase (AST),

total bilirubin (TBIL), creatinine (CR), fasting blood glucose (Glu);

C. Urinalysis: Proteinuria (PRO);

The investigator must review the results of routine blood tests, blood biochemistry tests, and urinalysis, and record them in the source document. Any clinically significant laboratory indicator changes occurring during the trial shall be recorded in the source document as AEs. Laboratory test results must be retained in accordance with source documents.

Laboratory test indicator grading is detailed in 8.4.4 Severity of AEs.

Determination of clinical significance includes:

(1) Within the reference range, normal;

(2) Outside the reference range, abnormal without clinical significance;

(3) Outside the reference range, abnormal with clinical significance.

The investigator shall grade the results according to the grading standards specified in the protocol, then refer to the normal ranges provided by the testing laboratory to make a medical judgment on the post-vaccination blood biochemistry, routine blood test, and urinalysis results: If the result is within the normal range, it is classified as "Within the reference range, normal." If the result is outside the normal range and does not meet the criteria for a Grade 1 AE, comprehensively assess its clinical significance based on the participant's specific condition. If clinically insignificant, classify it as "Abnormal outside the reference range but clinically insignificant, " and simultaneously arrange re-testing and follow-up until the indicator returns to normal or stabilizes. If clinically significant, classify it as "Abnormal outside the reference range and clinically significant, " further determine the relatedness of the AE, and simultaneously arrange re-testing and follow-up until the indicator returns to normal or stabilizes. That is, all laboratory test indicators outside the reference range during the clinical trial shall be re-tested regardless of clinical significance. The participant shall have biological samples re-collected to test the corresponding items with abnormal indicators, and follow-up shall continue until the indicator returns to normal or stabilizes.

8.3.4 Pregnancy test

A urine pregnancy test is performed before vaccination in women of childbearing potential (post-menarche, pre-menopausal, or per local criteria).

8.4 Adverse events, serious adverse events, and other safety reporting

8.4.1 Definitions

Adverse event (AE)

An AE is defined as any untoward medical occurrence in a participant following administration of the investigational vaccine during the clinical trial, regardless of whether it is considered causally related to the vaccine or vaccination. An AE could include any unfavorable and unintended sign,

symptom, disease, or abnormal laboratory finding.

Adverse reaction (AR)

An AR is any noxious and unintended response occurring during the clinical trial that is considered to be related to the investigational vaccine. A causal relationship between the investigational vaccine and the AE is at least a reasonable possibility; that is, a relationship cannot be ruled out.

Solicited and unsolicited AEs

In this study, the period from Day 0 through Day 7 after vaccination will be defined as the solicited period, and all remaining observation periods will be considered unsolicited periods. Solicited symptoms occurring during the solicited period will be classified as solicited AEs. Unsolicited symptoms occurring during the solicited period, as well as any symptoms occurring during the unsolicited periods, will be classified as unsolicited AEs. Details of solicited symptoms and vital signs are provided in Section 8.4.5, “Assessment of AEs and Follow-up Duration and Frequency”.

Serious adverse event (SAE)

Refers to an event that occurs in a clinical trial participant after receiving the investigational vaccine and meets one of the following criteria:

- Results in death;
- Is life-threatening: The participant is at risk of death at the time the AE occurs, rather than an AE that may lead to death after the event has progressed to a more severe stage;
- Results in permanent or serious illness or functional impairment: If the AE causes serious disruption to the participant's normal daily functioning - i.e., the AE causes significant, persistent, or permanent changes, damage, or impairment to the participant's physical function/structure, physical activities, and/or quality of life - it should be reported;
- Requires hospitalisation or prolongs existing hospitalisation: The AE necessitates the participant's hospitalisation for treatment, or extends the hospital stay when the participant was already prepared for discharge but experienced the AE. It must be confirmed that the cause of this situation is the AE itself, rather than hospitalisation due to elective surgery, non-therapeutic reasons, etc.;
- Results in congenital anomaly or birth defect;
- Other important medical events: An AE that may not immediately threaten life, cause death, or require hospitalisation at the time of onset but may harm the participant; or requires active intervention to prevent the persistence of the above situations. Examples include anaphylactic bronchospasm requiring emergency rescue in the emergency room or at home, hematological cachexia or convulsions that have not yet led to hospitalisation, or the development of drug dependence or abuse. These situations should all be recorded and handled as important medical events.

Suspected unexpected serious adverse reaction (SUSAR)

A suspected and unexpected serious adverse reaction whose nature or severity is inconsistent with the information available in the Investigator's Brochure, the approved product label, the Summary of Product Characteristics, or equivalent (see the Reference Safety Information section of the vaccine Investigator's Brochure).

8.4.2 AE outcomes

The outcome of an AE shall be classified as one of the following categories: (1) recovered/resolved; (2) recovering/resolving (improved); (3) not recovered/not resolved (ongoing); (4) recovered/resolved with sequelae; (5) fatal; or (6) unknown.

8.4.3 Causality assessment

The investigator shall make every effort to explain the adverse event (AE) and assess its possible causality, i.e., the causal relationship with the investigational vaccine versus alternative causes (such as history of underlying diseases or concomitant treatments). This applies to all AEs, including both serious and non-serious ones.

The causality assessment will be determined by the extent to which the event can be reasonably explained in one or more of the following aspects:

- Whether there is a reasonable temporal relationship between the administration of the investigational vaccine and the onset of the AE;
- Whether similar reactions of a similar nature have been observed previously with this type of preparation;
- Whether the same event has been reported in the literature for similar types of preparations;
- Whether the event occurs temporally associated with the administration of the investigational vaccine and reoccurs after re-administration of the investigational vaccine;
- Whether the event can be explained by the effects of concomitant medications (vaccines) or other treatments.

The causality of the AE shall be assessed by the investigator based on the following question: Is there a reasonable possibility that the AE was caused by the vaccination:

(1) Definitely unrelated: The AE is caused by other factors, such as the participant's clinical condition, other treatments, or concomitant medications.

(2) Possibly unrelated: The AE may be caused by other factors (e.g., the participant's clinical condition, other treatments, or concomitant medications) and is inconsistent with known information about the investigational vaccine.

(3) Possibly related: The AE is consistent with known information about the investigational vaccine and has a causal relationship with the investigational vaccine, but may also be related to other factors.

(4) Probably related: The AE is consistent with known information about the investigational vaccine and has a causal relationship with the investigational vaccine, and cannot be explained by other factors (e.g., the participant's clinical condition, other treatments, or concomitant medications).

(5) Definitely related: The AE is consistent with known information about the investigational vaccine and has a causal relationship with the investigational vaccine, and this relationship cannot be explained by other factors (e.g., the participant's clinical condition, other treatments, or concomitant medications). Additionally, the AE reoccurs when the participant is re-exposed to the investigational vaccine.

8.4.4 Severity grading

Solicited local symptoms, systemic symptoms, and vital signs: The grading standards for solicited AEs primarily refer to the Guidelines for Grading Standards of AEs in Clinical Trials of Prophylactic Vaccines(2019) issued by the National Medical Products Administration (NMPA) [14], as shown in the table below. Both solicited AEs and unsolicited AEs with the same symptoms shall be graded according to the following standards:

Table 6. Grading of injection-site (local) AEs

Type	Grade 1	Grade 2	Grade 3	Grade 4
Pain (≥24 months)	Does not affect or only mildly affects limb activity	Affects limb activity	Affects daily activities	Loss of basic self-care; hospitalisation
Tenderness (<23 months)	Withdraws or resists on touch	Cries on touch but can be consoled	Persistent inconsolable crying	Requires emergency care or hospitalisation
Induration*# swelling #				
>14 y	Diameter 2.5-<5 cm or area 6.25-<25 cm² and no/mild effect on daily activities	Diameter 5-<10 cm or area 25-<100 cm² or affects daily activities	Diameter ≥10 cm or area ≥100 cm² or ulceration, secondary infection, phlebitis, sterile abscess, wound drainage, or severe effect on daily activities	Abscess, exfoliative dermatitis, dermal or deep tissue necrosis
≤14 y	Diameter <2.5 cm	Diameter ≥2.5 cm and area <50% of the vaccinated limb	Area ≥50% of the vaccinated limb or ulceration, secondary infection, phlebitis, wound drainage	Abscess, exfoliative dermatitis, dermal or deep tissue necrosis
Rash*#erythema #				
>14 y	Diameter 2.5-<5 cm or area 6.25-<25 cm² and	Diameter 5-<10 cm or area 25-<100 cm² or affects daily activities	Diameter ≥10 cm or area ≥100 cm² or ulceration, secondary	Abscess, exfoliative dermatitis, dermal or deep tissue necrosis

	no/mild effect on daily activities		infection, phlebitis, sterile abscess, wound drainage, or severe effect on daily activities	
≤14 y	Diameter <2.5 cm	Diameter ≥2.5 cm and area <50% of the vaccinated limb	Area ≥50% of the vaccinated limb or ulceration, secondary infection, phlebitis, wound drainage	Abscess, exfoliative dermatitis, dermal or deep tissue necrosis
Pruritus	Self-limited or resolves within 48 h after treatment	Does not resolve within 48 h after treatment	Affects daily activities	NA

* For induration and rash, in addition to grading evaluation by direct measurement of diameter, the progression of measurement results should also be recorded.
# Induration and swelling, rash and erythema should be measured using the maximum diameter or area. For evaluation and grading, based on the functional grade and actual measurement results, the indicator with the higher grade should be selected.

Table 7. Grading of non-injection-site (systemic) AEs and vital signs

Type	Grade 1	Grade 2	Grade 3	Grade 4
Acute allergic reaction*	Localised urticaria, no treatment required	Localised urticaria requiring treatment or mild angioedema not requiring treatment	Generalised urticaria, or angioedema requiring treatment, or mild bronchospasm	Anaphylactic shock, life-threatening bronchospasm, or laryngeal oedema
Anorexia	Reduced appetite without reduced food intake	Reduced appetite and reduced food intake, without marked weight loss	Reduced appetite with marked weight loss	Requires intervention (NG feeding, parenteral nutrition)
Vomiting	1-2 episodes / 24 h, no impact on activities	3-5 episodes / 24 h or limits activities	>6 episodes / 24 h or requires IV fluids	Shock from hypotension requiring hospitalisation or alternative nutrition
Irritability	Mild	Increased irritability	Inconsolable	NA
Lethargy	Mild	Drowsiness	Decreased responsiveness	NA
Diarrhoea	Mild or transient, 3-4 times/day, abnormal stool or	Moderate or persistent, 5-7 times/day, abnormal stool	>7 times/day, abnormal consistency, bloody diarrhoea,	Hypotensive shock requiring hospitalisation

Type	Grade 1	Grade 2	Grade 3	Grade 4
	mild diarrhoea <1 week	or diarrhoea >1 week	orthostatic hypotension, electrolyte imbalance, IV fluids >2 L	
Nausea	Transient (<24 h) or intermittent with near-normal intake	Persistent with reduced food intake for 24-48 h	Persistent with almost no intake for >48 h or IV fluids needed	Life-threatening (e.g., hypotensive shock)
Cough	Transient, no treatment	Persistent cough responsive to treatment	Paroxysmal cough not controlled by treatment	ER visit or hospitalisation
Fatigue	Does not affect daily activities	Affects daily activities	Severely affects daily activities and prevents work	ER visit or hospitalisation
Myalgia (non-injection site)	Does not affect daily activities	Mildly affects daily activities	Severe pain, severely affects daily activities	ER visit or hospitalisation
Headache	Does not affect daily activities, no treatment	Transient, mildly affects daily activities, may require treatment	Severely affects daily activities, requires treatment or intervention	Refractory, requires ER visit or hospitalisation
Vital signs-fever (axillary, °C)				
>14 y	37.3-<38.0	38.0-<38.5	≥38.5	≥39.5 lasting >3 days
≤14 y	37.5-<38.0	38.0-<39.5	≥39.5	≥39.5 lasting >5 days

*Type I hypersensitivity.

Laboratory parameters. After results are obtained, grading is applied first, then clinical-meaning judgement, following the 2019 NMPA guidance[14] and (for creatinine) the 2005 guidance[15].

Table 8. Haematology grading

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Elevation of white blood cell (WBC) (10^9/L)	11-<13	13-<15	15-<30	≥30
Reduction of white blood cell (WBC) (10^9/L)	2.000-2.499	1.500-1.999	1.000-1.499	<1.000
Low hemoglobin (g/dL)				
Adult males	10.0-10.9	9.0-<10.0	7.0-<9.0	<7.0
Adult females	9.5-10.4	8.5-<9.5	6.5-<8.5	<6.5
Children aged 6 months to 12 years (boys and girls)	9.5-10.4	8.5-<9.5	6.5-<8.5	<6.5
Thrombocytopenia (10^9/L)				
Adults	125-140	100-124	25-99	<25
Children aged 6 months to 12 years	NA	50-75	25-49	<25

Note: these are the key haematology parameters observed in this study. For any other parameters on the test report, the on-site investigator judges on a case-by-case basis whether an abnormal result should be recorded as an AE.

Table 9. Biochemistry grading

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Liver function (ALT, AST)	1.25-<2.5 ×ULN	2.5-<5.0 × ULN	5.0-<10 × ULN	≥10 × ULN
Elevation of total bilirubin (mg/dL; μmol/L)	1.1-<1.6 × ULN	1.6-<2.6 × ULN	2.6-5.0 × ULN	≥5.0 × ULN
Creatinine (CR)	1.1-1.5 × ULN	1.6-3.0 × ULN	3.1-6 × ULN	>6 × ULN
Hyperglycemia (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

Note: ULN refers to the upper limit of the normal range; blood glucose is measured in the fasting state.
The above are the key blood biochemistry indicators observed in this study. For other indicators on the test report, if abnormal results occur, the on-site investigators shall determine whether to record them as adverse events (AEs) based on the participant's specific condition.

Table 10. Urinalysis grading

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Urine protein (dipstick)	1+	2+	3+ or more	NA

Note: The above are the key Urinalysis indicators observed in this study. For other indicators on the test report, if abnormal results occur, the on-site investigators shall determine whether to record them as adverse events (AEs) based on the participant's specific condition.

For AEs not covered in the grading table above, the severity grading assessment of AEs shall be performed according to the following standards:

Grade 1 Mild: Short-term (<48h) or mild discomfort, no impact on activity, no treatment required;

Grade 2 Moderate: Mild or moderate limitation of activity, may require medical consultation, no or only mild treatment needed;

Grade 3 Severe: Significant limitation of activity, requires medical consultation and treatment, hospitalisation may be required;

Grade 4 Critical: Potentially life-threatening, severe limitation of activity, requires intensive care treatment;

Grade 5: Death.

8.4.5 AE assessment, follow-up duration, and frequency

8.4.5.1 Safety observation parameters

Table 11. Solicited symptoms by age group

Age group	Local (injection-site) symptoms	Systemic (non-injection-site) symptoms
6-23 months	Tenderness, induration, swelling, erythema, rash, pruritus	Acute allergic reaction, diarrhoea, anorexia, vomiting, irritability, lethargy, fever (axillary)

24-71 months	Pain, induration, swelling, erythema, rash, pruritus	Acute allergic reaction, diarrhoea, anorexia, vomiting, nausea, cough, fatigue, fever (axillary)
6-12 y / 18-59 y	Pain, induration, swelling, erythema, rash, pruritus	Acute allergic reaction, diarrhoea, anorexia, vomiting, nausea, fatigue, myalgia (non-injection-site), headache, cough, fever (axillary)

8.4.5.2 Safety follow-up

The investigator explains to the participant and/or their guardian the judgment, measurement methods, recording procedures, precautions, and reporting methods for adverse events (AEs). They will issue diary cards (for use from 0 to 7 days after each dose vaccination)/contact cards (for use from 8 to 30 days after each dose vaccination), a ruler, and a thermometer. The investigator trains the participant or guardian to use the thermometer, observe AEs, complete the diary card/contact card, and schedules the return time for these cards.

After each dose vaccination, the diary card is issued to the participant or guardian. The investigator conducts on-site observation of AEs within 30 minutes after vaccination and performs systematic observation for 7 days post-vaccination. The participant and/or guardian is required to observe the participant's symptoms and signs daily, and record solicited local and systemic AEs, unsolicited AEs, and concomitant medications or vaccines from 0 to 7 days post-vaccination. The investigator visits to collect and verify the 0-7-day safety observation data and retrieves the diary card during the visit on Day 7.

On Day 7 after each dose vaccination, the contact card is issued to the participant or guardian. From Day 8 to 30, a combination of proactive recording/reporting by the participant/guardian on the contact card and regular follow-up by the investigator is used to record and verify AE occurrences, as well as concomitant medications or vaccines. The contact card is retrieved during the visit on Day 30.

Inform the participant and/or guardian to record any occurring AEs at any time. If an acute allergic reaction, Grade 3 or higher AEs, or serious adverse event (SAE) occurs, they should report to the investigator immediately. See details in "8.4.6 Procedures for Handling and Reporting of Adverse Reactions/Events".

The severity grading standards for AEs are detailed in "8.4.4 Severity of AEs".

8.4.6 Management and reporting of adverse events and reactions

8.4.6.1 Management of general adverse events

Reactions such as erythema, swelling, pain, and/or fever, general malaise of Grade 2 or lower that occur after vaccination generally resolve spontaneously without special treatment. For Grade 2 or lower fever, special treatment is not required in principle but increased rest is needed; however, this may vary depending on individual heat tolerance. Local ARs of Grade 2 or lower can also be alleviated by cold or hot compresses. AEs of Grade 3 or higher require timely medical diagnosis and treatment.

For AEs where routine blood test, blood biochemistry, and urinalysis indicators (including those not

collected in the protocol) are detected outside the reference range, follow-up with necessary re-testing of laboratory indicators should be conducted until the indicator returns to normal or stabilizes.

The investigator shall investigate and conduct medical follow-up for Grade 3 or higher adverse reactions/events occurring in participants from the start of immunisation to 30 days after completion of the full vaccination course. This includes medical history, physical examination, necessary laboratory tests and management, and tracking until the event is resolved, and completing a detailed investigation record. The investigation record shall include symptoms, signs, diagnosis, and laboratory test results.

8.4.6.2 Management of serious adverse events

The clinical trial site shall establish an emergency plan for the management of serious adverse events (SAEs) in the clinical trial and train all relevant personnel. If a participant experiences a serious adverse event, the investigator shall immediately take appropriate measures for the participant and document them. The investigator must have measures to promptly learn of any clinically significant disease/event occurring in the participant after vaccination, and in accordance with relevant national regulations, ensure the participant receives appropriate treatment at a designated hospital in a timely manner.

Throughout the entire observation period, if a participant experiences trial-related injury or death confirmed by an expert investigation panel, the sponsor will, with reference to relevant requirements such as Good Clinical Practice (GCP), bear the medical expenses for the trial-related injury to the participant and provide corresponding compensation.

The investigator at the clinical trial site shall conduct follow-up for SAEs until: the symptoms disappear, the symptoms stabilize, the participant returns to baseline status, the event is otherwise explained, or the participant is lost to follow-up. The investigator shall document the progress and outcome of all SAEs in detail, and all drug treatments and medical management will be recorded during each follow-up. The investigator shall truthfully record the SAEs on the SAE report form and, after the trial is completed or terminated, evaluate and discuss them in the final report.

8.4.6.3 Investigator reporting procedure for SAEs

The clinical trial institution shall establish an emergency plan for the management of serious adverse events (SAEs). For any SAE, regardless of whether it is related to the investigational vaccine, the investigator must, immediately upon learning of it (within 24 hours), complete the Serious Adverse Event Report Form and send the initial report to the sponsor [redacted]. Subsequently, follow-up supplementary information/reports shall be submitted as soon as possible until the event concludes.

If a SAE involves death, the investigator shall immediately report to the sponsor and the ethics committee, and provide other medical materials such as the autopsy report and final medical report.

When completing the SAE Report Form, the investigator shall report the full situation in the form of

a written report, including but not limited to: the name and relevant description of the AE, time and type of SAE occurrence, duration, severity, causal relationship with vaccination, outcome, measures taken (symptomatic treatment), and other relevant clinical and laboratory data. If the SAE report submitted by the investigator has missing key data related to the integrity and accuracy of AE data, the sponsor's PV personnel may send a query form to the investigator. The investigator shall reply to the query, sign for confirmation, and feedback to the sponsor's PV personnel via email as soon as possible after receiving the query form.

The clinical trial institution/investigator of the clinical trial shall promptly forward the sponsor's latest safety information report regarding the clinical trial to the ethics committee.

8.4.6.4 Sponsor reporting procedure to regulatory authorities

The day the sponsor first learns of a valid serious adverse event (SAE) report is designated as Day 0.

Upon receiving the SAE report submitted by the investigator, the sponsor's PV personnel shall immediately review it and, if necessary, send a query to the reporter/investigator. Meanwhile, the sponsor's PV personnel shall analyse and assess the report, including the severity of the AE, its causal relationship with the investigational product, and whether it is an expected event. If it is determined to be a Suspected Unexpected Serious Adverse Reaction (SUSAR), the sponsor's PV personnel shall submit the SUSAR report to the drug regulatory authorities and health authorities in accordance with the relevant requirements of the Measures for the Administration of Drug Registration, Good Clinical Practice (GCP), and the Standards and Procedures for Rapid Reporting of Safety Data During Drug Clinical Trials. Meanwhile, the sponsor will deliver the SUSAR report to the investigator for review and sign-for-receipt, and the investigator shall forward the signed report to the ethics committee.

For fatal or life-threatening unexpected serious adverse reactions (SUSARs), the sponsor shall report as soon as possible after first learning of them, but no later than 7 calendar days, and report and complete/supplement follow-up information within the subsequent 8 calendar days. For non-fatal or non-life-threatening unexpected serious adverse reactions, the sponsor shall report as soon as possible after first learning of them, but no later than 15 calendar days. After the initial report, the sponsor shall continue to follow up on the serious adverse reactions and timely submit relevant new information or updates to previous reports in the form of follow-up reports, with the reporting deadline being 15 calendar days from the date the new information is obtained. When the sponsor and investigator cannot reach a consensus on the judgment of the causal relationship between the SAE and the vaccine, if either party determines that a relationship with the investigational drug cannot be ruled out, rapid reporting shall also be conducted.

For other potential serious safety risk information, the sponsor shall also report it to the national drug evaluation authority as soon as possible, while making medical and scientific judgments for each case.

8.4.7 Pregnancy events

Pregnancy is an exclusion criterion for participant enrolment. Women of childbearing potential (those

who have reached menarche and are premenopausal) must use contraception and continue to do so for 30 days after completion of the full vaccination course. However, participants or their partners may still experience unintended pregnancy during participation. The investigator shall collect pregnancy-related events within 3 months after vaccination. Upon learning of a participant's or their partner's pregnancy, the investigator must complete the Pregnancy Event Report Form and report it via email to the sponsor's PV personnel and monitor, with the reporting time limit requirements being the same as for serious adverse event (SAE) reporting. The investigator shall closely follow up on the participant's or their partner's pregnancy event, obtain information on pregnancy outcomes (e.g., delivery and newborn conditions, or details of pregnancy termination), and update the Pregnancy Event Report Form. If the pregnancy continues, regular follow-ups shall be conducted (at the time of first learning of the pregnancy, and then at least once every 3 months thereafter) until the pregnancy ends or 1 month after delivery.

Pregnancy itself is not considered a SAE. However, any complications during pregnancy or abnormal pregnancy outcomes will be considered AEs, and those meeting the definition of a SAE (e.g., spontaneous abortion, stillbirth, fetal death, and congenital anomalies in the infant) shall be treated as SAEs. The investigator shall report these to the sponsor in accordance with the reporting procedures and time limits for SAEs. An induced abortion decided by the participant or their spouse, when no abnormal conditions are found in the fetus, is not considered an AE.

9. Statistical considerations

9.1 Sample size

In accordance with the relevant requirements of the Measures for the Administration of Drug Registration[8], Good Clinical Practice (GCP)[9], Technical Guidelines for Vaccine Clinical Trials[10], Guiding Principles for Quality Management of Vaccine Clinical Trials (Trial Implementation)[11], etc., and comprehensively considering the pharmaceutical process characteristics of the vaccine and preclinical evaluation results.

Phase I clinical trial is a small-scale trial (20-30 participants) focusing on evaluating the safety of the vaccine. The sample size of this trial was not calculated based on any statistical hypothesis, but based on the general requirements for sample size in Phase I clinical trials. A total of 144 participants were enrolled in the Phase I clinical trial, with 36 adult participants and 36 participants aged 6-12 years, 36 children aged 6-23 months and 36 children aged 24-71 months. The sample size for children aged 6-71 months in each dose group was 24, and the total sample size for children aged 6-71 months in the control vaccine group was 18.

Phase II clinical trial is designed to demonstrate the immunogenicity and safety of the vaccine in the target population, with a minimum sample size of 300 cases. The sample size of this trial is 600 cases, including 450 cases in the three trial dose groups and 150 cases in the control group.

9.2 Analysis sets

9.2.1 Safety Set (SS).

Includes all participants who were randomised and completed at least one dose of vaccination. In safety evaluation, participants with vaccination errors shall be included in the statistical analysis according to the actual vaccine group they received, in accordance with the All Subjects as Treated (ASaT) principle.

The Safety Analysis Set is divided into the Total Safety Analysis Set, the First-Dose Safety Analysis Set, and the Second-Dose Safety Analysis Set. The safety analysis for each dose is conducted based on the actual number of participants vaccinated for that dose. The First-Dose Safety Analysis Set includes all participants who completed the first dose of vaccination, denoted as SS1; The Second-Dose Safety Analysis Set includes all participants who completed the second dose of vaccination, denoted as SS2.

9.2.2 Immunogenicity Analysis Set

Full Analysis Set (FAS)

Following the Intention-to-Treat (ITT) principle, it includes all participants who were randomised, completed at least one dose of vaccination, completed at least one pre-vaccination and one post-vaccination blood collection, and have valid antibody titre values. Among them, participants with vaccination errors shall undergo immunogenicity evaluation according to their original randomised group in accordance with the ITT principle.

Per-Protocol Set (PPS)

A subset of the corresponding Full Analysis Set (FAS), including all participants who: meet the inclusion criteria, do not meet the exclusion criteria, are randomised, have completed vaccination, completed vaccination within the time window as required by the protocol, completed blood sample collection at corresponding pre-vaccination and post-vaccination time points, and have valid neutralising antibody titre values; while excluding participants with protocol deviations that may significantly affect the immunogenicity analysis.

Immune Persistence Set (IPS)

Includes all participants who completed two doses of vaccination, completed blood collection 6 months after the second dose vaccination within the specified time window, and have valid antibody titre values.

9.3 Statistical analysis plan

The statistician will prepare the Statistical Analysis Plan (SAP) and finalise it before database lock for the first analysis.

9.3.1 General principles.

Unless otherwise stated, continuous variables are summarised as mean, standard deviation, median, maximum, and minimum; categorical or ordinal variables as frequencies and proportions. All analyses will be performed in SAS version 9.4 or higher.

9.3.2 Participant disposition

Separately summarize the number of participants enrolled in and completing the trial in each trial group, as well as the number of participants in each analysis set, and analyse the dropout participants and their reasons for dropout.

9.3.3 Demographics and baseline characteristics

Descriptive statistics for demographics (sex, age, ethnicity) and baseline characteristics (height, weight) shall be performed.

9.3.4 Immunogenicity analysis

Separately calculate the seroconversion rate of post-vaccination neutralising antibodies and the pre-vaccination and post-vaccination seropositivity rates for the different dose-level investigational vaccine groups and the control group. The two-sided 95% Confidence Interval (CI) shall be calculated using the Clopper-Pearson method, and statistical tests for inter-group differences shall be performed using the chi-square test or Fisher's exact test.

Separately calculate the Geometric Mean Titre (GMT) of neutralising antibodies at different pre-vaccination and post-vaccination time points, the Geometric Mean Fold Rise (GMFR) of post-vaccination neutralising antibodies and their 95% CIs for the different dose-level investigational vaccine groups and the control group. Statistical tests for inter-group differences shall be performed using analysis of variance (ANOVA) after logarithmic transformation.

9.3.5 Safety analysis

Adverse events (AEs) and serious adverse events (SAEs) shall be medically coded using Medical Dictionary for Regulatory Activities (MedDRA), and classified and statistically analysed by System Organ Class (SOC) and Preferred Term (PT). In addition, solicited adverse events shall be classified and statistically analysed based on the injection site AEs, non-injection site (systemic) AEs, and vital signs specified in the protocol. This trial will primarily perform statistical analysis on Treatment Emergent Adverse Events (TEAEs) (i.e., AEs occurring after vaccination), while AEs occurring before vaccination will be listed in a tabular form. Unless otherwise specified, the term "adverse events" in the following text refers to TEAEs.

Separately calculate the incidence counts, number of cases, and incidence rates of the following for the trial group and control group: all AEs, AEs related to the investigational vaccine, AEs unrelated to the investigational vaccine, AEs of Grade 3 or higher, and AEs of Grade 3 or higher related to the vaccine. Statistical comparison of inter-group differences in the incidence rates of the above AEs shall

be performed using Fisher's exact test. Conduct statistical description of the onset time and severity of AEs. List the list of AEs related to the investigational vaccine and the list of AEs unrelated to the investigational vaccine.

Separately calculate the incidence counts, number of cases, and incidence rates of the following for the trial group and control group: all SAEs, SAEs related to the investigational vaccine, and SAEs unrelated to the investigational vaccine. Statistical comparison of inter-group differences in the incidence rates of the above SAEs shall be performed using Fisher's exact test. List the list of SAEs.

9.3.6 Subgroup analyses

This trial is designed to analyse the safety of different age subgroups (adults, children aged 6-12 years, children aged 6-23 months, and children aged 24-71 months). The Phase II clinical trial will also conduct subgroup analyses on the immunogenicity and immune persistence of EV71/CA16 pre-vaccination antibody-negative and -positive populations.

9.3.7 Handling of missing data

In the immunogenicity analysis of the Full Analysis Set (FAS), for participants with missing serum antibody results at 30 days after the second dose vaccination, data imputation shall be performed using the LOCF (Last Observation Carried Forward) method, and the corresponding immunogenicity endpoints shall be derived. For participants with post-vaccination serum results but missing pre-vaccination serum results, the participant's pre-vaccination antibody shall be imputed using the maximum pre-vaccination serum antibody value of that type from all participants. This trial will not handle missing data in the immunogenicity durability evaluation and safety evaluation endpoints.

10. Supporting information and operational considerations

10.1 Informed consent

10.1.1 Informed consent form.

The Informed Consent Form (ICF) for this trial will describe the trial background, trial objectives, trial treatment, the possibility of random allocation to each group, basic participation criteria, trial procedures (including the volunteer's obligations), other optional preventive measures, potential risks and benefits of participation, information confidentiality, voluntary participation, circumstances under which the trial may be terminated, and other content. It will clarify that the participant and/or their guardian decides whether to participate and can withdraw at any time (including suspending/terminating participation). Before the trial officially starts, a signed written informed consent document from the participant and/or their guardian must be obtained first.

The ICF will be submitted to the Ethics Committee together with the clinical trial protocol and can be used only after obtaining approval from the Ethics Committee.

10.1.2 Consent process

Informed consent is a step that begins before an individual participates in a clinical trial and is an

ongoing process throughout the entire participation in the trial. The participant and/or their guardian are required to read the Informed Consent Form (ICF), while the investigator will verbally explain the trial to them in a manner suitable for their understanding, covering: trial objectives, content, procedures, potential risks, and the participant's rights.

Before signing the written informed consent document, the participant and/or their guardian shall have sufficient time to read it carefully and raise questions. Before agreeing to participate, the participant shall have the opportunity to discuss the trial with family members or representatives or consider it on their own. The investigator shall answer all questions that may be raised by the participant and/or their guardian. Before conducting any procedure in this trial, the signed informed consent document from the participant and/or their guardian must be obtained. The investigator will provide a copy of the informed consent document to the participant and/or their guardian for retention.

The informed consent process should be conducted before the participant undergoes any procedure related to the trial. The process (including the date) shall be recorded in the source document, and the signed informed consent document shall be retained. The investigator must specifically inform the participant that the decision to join this trial by the participant and/or their guardian is entirely voluntary, they may withdraw at any time unconditionally during the trial, and regardless of their choice, their medical treatment and rights will not be affected, nor will they be discriminated against or retaliated against.

10.2 Confidentiality and privacy

The Principal Investigator (PI) shall manage all personnel involved in the clinical trial and assign clear responsibilities. The investigator must maintain confidentiality of the participant's personal information. Documents provided to the sponsor shall identify participants only by participant code and participant ID. The investigator shall retain an identification list of participants in the investigator's files. In accordance with GCP principles, the source documents of each participant are accessible for monitoring, auditing, and inspection.

All information identifying the participant's identity will be kept confidential, and names will not appear in any publications or reports related to this trial. Trial records will be made available to the sponsor's representative for collecting medical data in the presence of study staff. Additionally, monitors, auditors, representatives of the Ethics Committee, and representatives of drug regulatory authorities may review the participant's original trial documents related to this trial as required to verify the accuracy of the data collected. The original data obtained in this trial will be used solely for publications or presentations of papers or results related to the project.

The trial protocol, documents, data, and all other information generated by the trial will be kept strictly confidential. No trial data or information shall be disclosed to unauthorised third parties without the sponsor's written permission.

Participant trial data for statistical analysis and scientific reports will be transferred and stored with

the data management party, excluding the participant's contact information or identifying details. Instead, individual participants and their trial data will be identified by a unique trial identification code. The trial data entered and the trial management system used by investigators at the clinical research centre and the data management party will be secured and password-protected. At the end of the trial, all trial databases will be de-identified and stored with the data management party.

10.3 Participant protection

The clinical trial will be conducted at county/municipal Centers for Disease Control and Prevention (CDCs) qualified for vaccination. The sponsor shall assess the clinical trial site in strict accordance with Good Clinical Practice (GCP) requirements before the trial begins. The environmental facilities of the clinical trial site must meet the requirements of the Guiding Principles for Quality Management of Vaccine Clinical Trials (Trial Implementation). The clinical trial site shall formulate emergency plans for participant injury and emergencies. Physical examination rooms and blood collection rooms shall be staffed with qualified and experienced physicians and nurses to strictly adhere to inclusion/exclusion criteria and successfully complete blood collection. The emergency room shall be equipped with appropriate emergency facilities, equipment, and medications, and emergency physicians must possess the corresponding qualifications and capabilities. If a participant experiences an adverse event (AE) at the clinical trial site, timely treatment shall be provided in the on-site emergency room. If emergency hospitalisation is required, after on-site treatment and stabilisation of the condition, the participant will be transported to the agreement hospital (a designated hospital) by the on-site ambulance, which is equipped with necessary emergency facilities and medications. The clinical trial site shall sign a green channel agreement with a county-level or above general hospital in the local area. During participant enrolment, the agreement hospital shall be notified to ensure timely treatment. The agreement shall specify personnel responsibilities, contact numbers, ambulance routes, and other details to guarantee rapid reporting and handling of sudden AEs. The agreement hospital shall provide green channel services for medical consultation, hospitalisation, and medical security to ensure participants receive timely treatment. The investigator shall track the progress over time and complete investigation records until the serious adverse event (SAE) concludes.

Protective Measures for Child Participants:

Establish strict inclusion criteria: Ensure that participating children meet the trial requirements in terms of health status and specific conditions.

Sequential trial design: Enrol participants sequentially from adults to older children aged 6-12 years, then to younger children aged 6-71 months.

Ethical review and informed consent: All clinical trials must undergo rigorous review and approval by the Ethics Committee. For children aged 8-12 years capable of providing written consent, a child-friendly version of the Informed Consent Form (ICF) shall be used to obtain their own written informed consent. The language for explanation shall be appropriate for the child’s perspective and comprehension ability, and the consent process shall take place in a quiet, private location with

sufficient time for the child and guardian to consider. If the child participant disagrees to participate or decides to withdraw midway, their decision shall prevail even if the guardian has agreed to participate or continue.

Guardian involvement: Guardians must fully understand the trial's nature, objectives, potential risks, and benefits before deciding whether to allow their child to participate, and provide necessary support and supervision.

Vaccination practices: Select experienced vaccinators for on-site vaccination, pay attention to the child's experience, protect the child's privacy, avoid separation from guardians, and equip the site with paediatric medical facilities and emergency safety equipment.

Safety monitoring: Establish an independent Data Monitoring Committee (DMC) to periodically review trial data and ensure compliance with ethical and safety requirements. Conduct close safety monitoring of child participants during the trial, establish criteria for withdrawal and study termination, and promptly identify and address any potential issues.

Risk/benefit analysis: Perform a detailed risk-benefit analysis during the trial to ensure that potential risks do not outweigh possible benefits.

10.4 Sample storage and data use

Blood and urine samples collected in the Phase I clinical trial for routine blood test, blood biochemistry, urinalysis, and urine pregnancy test shall be disposed of as medical waste by the testing unit after testing is completed.

Serum specimens collected in the Phase II clinical trial shall be used solely for antibody testing for immunogenicity evaluation in this trial. Use for other trials requires the consent of the participant and/or their guardian and approval from the Ethics Committee.

For all participants, approximately 3.0 mL of venous blood will be collected on Days 0, 60, and 210. After blood collection, the serum shall be promptly separated and divided into two tubes: Tube A [redacted] and Tube B (backup serum). The samples shall be stored at -20°C or below for neutralising antibody testing for EV71 and CA16.

Each sample will have a unique identification number, and records shall be maintained for sample handover, separation, and storage. For all samples submitted for testing, a specimen submission record shall be completed, and temperature control records during submission shall be preserved.

Serum for antibody testing for immunogenicity evaluation shall be promptly sent to the National Institutes for Food and Drug Control (NIFDC) for neutralising antibody testing. [redacted]

10.5 Key roles and trial management

10.5.1 Sponsor

The sponsor of this clinical trial is Sinovac Biotech Co., Ltd., and its main responsibilities include:

- Providing the preliminary clinical trial protocol, and signing and stamping to approve the final protocol;
- Providing on-site application documents such as communication opinions with the Center for Drug Evaluation (CDE) and the Investigator's Brochure (IB) (containing preclinical safety information of the product);
- Being responsible for providing the investigational vaccine that meets the clinical trial requirements, and issuing a qualified test report or batch release certificate;
- Assessing and selecting the clinical trial institutions and sites for the clinical trial, assigning monitors to assess and approve the clinical trial sites, performing monitoring duties in accordance with Good Clinical Practice (GCP) requirements, and bearing ultimate responsibility for the quality of the clinical trial;
- Participating in the investigation and handling of vaccine AR cases. In accordance with GCP and other relevant regulations, bearing the medical expenses and corresponding compensation for trial-related injuries to participants. Handling of other situations is specified in the work agreement;
- Being responsible for providing funding for the clinical trial and organising the writing of the CSR.

10.5.2 Clinical trial institution

The clinical trial institution for this clinical trial is Yunnan Provincial Center for Disease Control and Prevention, and its main responsibilities include:

- Undertaking risk and feasibility assessment of the clinical trial;
- Participating in the development of the vaccine clinical trial protocol and the tables and cards required for the trial;
- Participating in drafting the vaccination Informed Consent Form (ICF), formulating Standard Operating Procedures (SOPs) for on-site clinical trial operations, and applying for approval from the Ethics Committee; being responsible for organising the implementation of selection of clinical trial sites that meet Good Clinical Practice (GCP) requirements, organising assessment of the clinical trial sites, and registering on the "Drug Clinical Trial Institution Filing Management Information Platform" of the National Medical Products Administration (NMPA);
- Organising and implementing the clinical trial, and conducting Quality Control (QC) over the implementation process;

- Guiding the site to report serious adverse events (SAEs) occurring during the trial to the sponsor in a timely manner, and conducting investigation and handling of such events;

- Participating in database lock and saving a backup of the locked database for verification purposes;

- Reporting the implementation progress of the clinical trial to relevant administrative departments and participating in writing the CSR.

10.5.3 Clinical trial site

The clinical trial site for this study is Dayao County, and the clinical trial site is Dayao County Center for Disease Control and Prevention. Its main responsibilities include:

- Cooperate in the assessment and filing work of the clinical trial site;

- Organise personnel with corresponding professional skills and rich clinical research experience to participate in the work of the clinical trial site. All investigators involved in the trial shall read and understand the content of the trial protocol in detail, strictly implement the protocol, and ensure sufficient time to complete the clinical trial within the period specified in the protocol;

- Organise on-site implementation, including: organisation and selection of participants, obtaining the signed Informed Consent Form (ICF) from participants, screening and enrolment, vaccination, safety follow-up visits, sample collection, serum separation, sample freezing, storage, and submission;

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

- Accept monitoring and auditing by monitors or auditors dispatched by the sponsor, as well as inspections by drug regulatory authorities, to ensure the quality of the clinical trial;

- Ensure that participants receive appropriate treatment when adverse reactions/events occur during the trial. In case of a serious adverse event (SAE), immediately take appropriate treatment measures for the participant and report to the sponsor simultaneously;

- Be responsible for the preservation of relevant clinical trial materials during the clinical trial.

10.5.4 Monitoring organisation

The monitoring unit for this clinical trial is [redacted] and its main responsibilities include:

- Conducting clinical trial monitoring in accordance with Good Clinical Practice (GCP), the trial protocol, and Standard Operating Procedures (SOPs);

- Undertaking tasks such as screening, training, and organising kick-off meetings for clinical trial institutions;

- Verifying the trial processes and progress;

- Verifying the signing status of informed consent;
- Confirming the qualifications of investigators and the effectiveness of implementation equipment;
- Verifying the transportation, storage, distribution, use, return, and disposal of the investigational vaccine for the clinical trial;
- Verifying the collection, storage, and transportation of biological samples;
- Verifying the handling of AEs;
- Verifying the logical consistency between source documents and reported documents in the trial;
- Completing post-trial monitoring work and other related tasks.

10.5.5 Testing laboratories

[redacted] and its main responsibilities include:

- Being responsible for routine blood test, blood biochemistry, urinalysis, and urine pregnancy test.

National Institutes for Food and Drug Control (NIFDC), and its main responsibilities include:

- Neutralising antibody testing for EV71 and CA16.

10.5.6 Data management organisation

The data management responsible unit for this clinical trial is [redacted] and its main responsibilities include:

- Developing the data management plan and data validation plan in accordance with the protocol requirements;
- Providing relevant online services such as Electronic Data Capture (EDC);
- Conducting data management work during the trial process in accordance with the Guidelines for Technical Work of Clinical Trial Data Management, and ensuring the reporting and recording of all data are correct and complete;
- Performing data cleaning, raising queries about the trial data, and assisting investigators in verification and clarification;
- Writing the data management report.

10.5.7 Statistical analysis organisation -

The statistical analysis responsible unit for this clinical trial is [redacted] and its main responsibilities include:

- Being responsible for drafting the sample size and statistical analysis sections in the clinical trial protocol;
- Drafting the Statistical Analysis Plan (SAP) based on the clinical trial protocol;

- Conducting statistical analysis in accordance with the drafted SAP and writing the statistical analysis report.

10.6 Safety monitoring

Safety oversight will be undertaken by the Data Monitoring Committee (DMC), which consists of at least 3 members with relevant professional expertise. DMC members shall not participate in the implementation of the clinical trial and shall have no conflict of interest with the trial; if a foreseeable conflict of interest exists, measures shall be taken to minimise it. The DMC shall meet regularly to ensure the scientific integrity of the trial and the credibility of the data, maximise the protection of trial participants' interests, and maintain the rigor of the trial design for the sponsor while ensuring maximum protection of participants. The DMC will also provide the sponsor with recommendations on whether the clinical trial should continue, be terminated, or be temporarily suspended, and may propose modifications to the clinical trial protocol. The DMC shall adhere to the bylaws established and approved at the time of its formation. Recommendations made by the DMC will be submitted to the sponsor, who has the right to decide whether to accept them.

10.7 Quality assurance and quality control

The sponsor shall implement and maintain Quality Assurance (QA) and QC systems, prepare quality management documents to ensure the trial is conducted as required, and ensure that data, records, and reports comply with Good Clinical Practice (GCP), other regulations, and the protocol requirements.

The Principal Investigator (PI) shall manage all personnel involved in the clinical trial and assign clear responsibilities. Before the trial starts, the sponsor and PI shall train the trial personnel in a meeting format. The training content shall include: brief clinical trial protocol, trial implementation procedures, schedule, operational precautions, and completion of trial documents. During the trial, if there are newly added monitors or investigators, they shall receive separate training. Retraining may be conducted if deemed necessary by the sponsor or PI. Each training session shall have training records.

Each clinical trial site shall implement internal quality management for the trial process, data and biological sample collection, document archiving, and completion status. Personalized quality management plans shall be developed for each institution.

The Data Manager shall perform QC on the generated data in the database. Any missing or abnormal data will be reported to the clinical trial institution for clarification or judgment.

Monitors shall, in accordance with written Standard Operating Procedures (SOPs), verify that the trial is conducted in compliance with the protocol, GCP, and relevant applicable regulations, including the trial process, generation/collection, archiving (recording), and reporting of data and biological samples.

Clinical trial institutions shall provide direct access rights to all relevant trial units, source data/documents, and reports for activities such as sponsor monitoring, auditing, or inspections by

local regulatory authorities.

10.8 Data recording and archiving

10.8.1 Source documents

Source documents shall include the Informed Consent Form (ICF), diary cards, contact cards, source document folders, etc., and record the following basic data:

- Trial name, participant ID;
- Demographic data;
- Inclusion/exclusion criteria;
- Vaccination records;
- Dates of follow-up and the date the participant withdrew from the trial;
- AEs/reactions, their management, and outcomes;
- Concomitant medications and concomitant vaccines.

All data must have original records. The investigator shall properly store them in a dedicated space. Source documents are archived at the research centre and serve as the basis for evaluating the participant's participation in the clinical trial and the authenticity and integrity of the data.

The investigator shall make original records conscientiously, accurately, and promptly. All collected raw data shall be recorded on the same day. It is required to fill them out with a black pen. Errors in filling shall not be erased; instead, a line shall be drawn through the error, the correct content shall be written beside it, and the investigator shall sign and date it.

10.8.2 Case report form

This trial uses the Electronic Data Capture (EDC) system to establish an electronic Case Report Form (eCRF). The eCRF is used to record clinical trial data (including participant ID, informed consent and demographic information, screening information for inclusion/exclusion criteria, vaccination records, AEs, their management, and outcomes, concomitant medications and concomitant vaccines, etc.). It is an important component of the clinical trial and trial report, and data must be entered using standardized terminology in accordance with the EDC system operation guidelines.

All data on the eCRF are derived from source documents and consistent with the source documents. Any process involving the entry, verification, modification, cleaning, and QC of eCRF data will be recorded in the EDC system. After data cleaning is completed, the investigator shall confirm the data in each eCRF and apply an electronic signature.

During the trial, only investigators and authorised staff are permitted to access the EDC system.

10.8.3 Data collection and management responsibilities

Trial staff are responsible for collecting data. The investigator shall supervise them and ensure the accuracy, completeness, legibility, and timeliness of the reported data.

All source documents shall be kept clear and neat to ensure data can be accurately identified.

Permanent copies of trial visit records will be regarded as source documents to record data of enrolled participants. Data recorded in the eCRF shall be derived from source documents and ensure consistency with the source data.

Clinical data (including adverse events (AEs), concomitant medications, and data on expected adverse drug reactions) and laboratory data will be entered into the EDC system. The data system has password protection and internal quality check functions, such as automated range checks that can identify inconsistent, incomplete, or inaccurate data. Clinical data will be directly entered based on source documents.

10.8.4 Database lock

After all data entry, verification, and cleaning are completed, final data verification will be performed. According to the evaluation criteria, determine the analysed population, identify the circumstances of protocol deviations, and assess their impact on the analysis dataset. Then, the database will be locked.

10.9 Protocol deviations

Protocol deviations refer to any changes or failures to follow the design or procedures of the clinical trial protocol. The protocol deviations of concern in this study include, but are not limited to:

- Informed Consent aspects: Failure to obtain adequate informed consent from the participant and/or their guardian, or the informed consent process not complying with protocol requirements.
- Eligibility aspects: Inclusion of participants who do not meet inclusion criteria or meet any exclusion criterion; or exclusion of participants who meet all inclusion criteria and none of the exclusion criteria.
- Study procedures: Failure to perform randomisation as required, missed visits, missed examinations, visits outside the time window, unintentional unblinding during the trial, or non-compliance with protocol requirements for distribution/collection of diary cards.
- Sample collection and management: Temperature excursions during sample storage/transportation, insufficient or excessive sample collection, or absence of temperature records for sample storage/transportation as required by the protocol/related documents.
- Use of investigational product: Including but not limited to: Continuing vaccination with the investigational vaccine when suspension or delay is required for safety reasons; Vaccination type, site, route, or dose not complying with protocol requirements; Use of vaccines with compromised cold

chain, abnormal color, broken packaging, or expired.

- Concomitant medications/vaccines: Use of drugs or vaccines prohibited by the protocol; Interval between other vaccines and the investigational vaccine not meeting protocol requirements.
- Safety events: Failure to handle, follow up on, or record adverse events (AEs) as per protocol requirements; Failure to report serious adverse events (SAEs) or pregnancy events within the specified timeframe.
- Qualification and authorisation management: Qualifications of on-site research staff not meeting requirements; Failure to receive relevant training for the clinical trial; Lack of authorisation by the Principal Investigator (PI).
- Suspension/termination of trial intervention or participant withdrawal/exit: Participants continuing to receive trial intervention after meeting the criteria for suspension/termination of intervention; Participants remaining in the trial after meeting the criteria for withdrawal/exit; The clinical trial continuing after meeting the criteria for suspension/termination.
- Source document management: Loss, damage, or incompleteness of source documents.

Actions that do not affect the participant's rights, safety, and benefits, or the integrity, accuracy, and reliability of trial data, or the evaluation of safety or primary endpoints, are considered Minor Protocol Deviations. Actions that affect the participant's rights, safety, and benefits, or the integrity, accuracy, and reliability of trial data, or the evaluation of safety or primary endpoints, are considered Major Protocol Deviations.

Participants with Major Protocol Deviations should be closely monitored, with safety information collected to ensure their safety. For protocol deviation events, the investigator shall document details and report to the Principal Investigator (PI) and sponsor, and submit to the Ethics Committee as required. The PI and sponsor shall determine whether participants with protocol deviations should continue the subsequent trial.

10.10 Publication and data-sharing policy

With the prior written consent of the sponsor, the investigator may publish papers. All data generated from the clinical trial and the corresponding intellectual property rights shall belong to the sponsor.

This clinical trial will be registered on the Drug Clinical Trial Registration and Information Disclosure Platform (https://www.chinadrugtrials.org.cn) and the ClinicalTrials.gov (https://clinicaltrials.gov) after approval by the Ethics Committee. After the completion of this clinical trial, if the trial results need to be disclosed and/or published, both positive and negative results will be disclosed and/or published together.

10.11 Conflict-of-interest policy

This clinical trial shall not be influenced by any existing or foreseeable factors. Therefore, for any personnel involved in any stage of the trial (including design, conduct, analysis, publication, or other

aspects), their actual conflicts of interest related to the trial shall be disclosed and managed. Furthermore, during the trial design and conduct, personnel who may have potential conflicts of interest shall be required to control the occurrence of such situations by appropriate methods.

10.12 Protocol amendments

After the sponsor and investigator sign the clinical trial protocol, if any amendments are made to the protocol, all amended protocols shall be re-signed and dated by the Principal Investigator (PI) and the sponsor.

Before the implementation of protocol amendments, the sponsor shall, based on the different nature of the amendment and its impact on participant safety risks, conduct supplemental applications, communication applications, or ethics reviews/filing in accordance with the Technical Guidelines for Protocol Amendments During Drug Clinical Trials (Trial Implementation).

During the clinical trial, protocol amendments shall also strictly comply with relevant regulations and requirements for ethics review and can only be implemented after approval by the Ethics Committee.

11. References

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