Sinovac Biotech Co., Ltd.

Clinical Master Protocol

Protocol No.: PRO-sIPV-4001

Protocol Title

A Multi-country, Multi-center, Open-labelled, Randomized, Controlled, Extended Phase III Clinical Trial to Evaluate the Immunogenicity and Tolerability of Sabin Strain Inactivated Poliovirus Vaccine Administered with or without Routine Infant Vaccines

Regulatory Agency Identifier Number:

Protocol version: 3.4

Date: March 27, 2024

Prepared by: Sinovac Biotech Co., Ltd.

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice and applicable regulatory requirements.

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LIST OF ABBREVIATION

AE	Adverse Event
AR	Adverse Reaction
ASaT	All Subjects as Treated
bOPV	Bivalent Oral Poliovirus Vaccine
CRO	Contract Research Organization
eCRF	Electronic Case Report Form
EPI	Expanded Programme on Immunization
FAS	Full Analysis Set
FHA	Filamentous Hemagglutinin
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titers
GMFR	Geometric Mean Fold Increase
GPEI	Global Polio Eradication Initiative
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IP	Investigational Product
IPV	Inactivated Poliovirus Vaccine
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
NMPA	National Medical Products Administration
OPV	Oral Polio Vaccine
PPS	Per-Protocol Set
PRN	Pertussis Antigen Pertactin
PT	Preferred Term
PT	Pertussis Toxin
QA	Quality Assurance
QC	Quality Control
VAPP	Vaccine-Associated Paralytic Poliomyelitis
VDPV	Vaccine-Derived Poliovirus
wIPV	Wild Strain Inactivated Poliovirus Vaccine
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
sIPV	Poliomyelitis Vaccine (Vero cells), Inactivated, Sabin Strains
SoA	Schedule of Activities
SOC	System Organ Class
SS	Safety Set
TEAE	Treatment-Emergent Adverse Events
tOPV	Trivalent Oral Poliovirus Vaccine

PROTOCOL APPROVAL–SPONSOR SIGNATORY

Study Title: A Multi-country, Multi-center, Open-labelled, Randomized, Controlled, Extended Phase III Clinical Trial to Evaluate the Immunogenicity and Tolerability of Sabin Strain Inactivated Poliovirus Vaccine Administered with or without Routine Infant Vaccines

Protocol Number: PRO-sIPV-4001

Protocol Version: 3.4

Protocol Version Date: March 27, 2024

Protocol accepted and approved by:

Gang Zeng Mar 27. 2024

Gang Zeng, Chief Medical Officer, Date

Sinovac Biotech Co., Ltd.

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DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled "A Multi-country, Multi-center, Open-labelled, Randomized Controlled, Extended Phase III Clinical Trial to Evaluate the Immunogenicity and Tolerability of Sabin Strain Inactivated Poliovirus Vaccine Administered with or without Routine Infant Vaccines" and the most recent version of the Investigator's Brochure (IB).

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the current Protocol, the International Council for Harmonisation (ICH) Technical Requirements for Registration of Pharmaceuticals for Human Use, E6(R2) Good Clinical Practice (GCP) Guidance, and all applicable government regulations. I will not make changes to the protocol before consulting with Sinovac Biotech Co. Ltd or implement protocol changes without IRB/IEC approval unless it is necessary to eliminate the immediate hazard to participants or as required by the registration authority.

I agree to administer study treatment only to participants under my personal supervision or the supervision of a sub-investigator. I will not supply study treatment to any person without authorization to receive it. I will not disclose confidential information contained in this document, including participants' information, to anyone other than the recipient study staffs and members of IRB/IEC. I will not disclose information or publish the results regarding this clinical investigation without authorization from Sinovac Biotech Co. Ltd.

March 27, 2024

Signature of Principal Investigator

Date

(National Principal Investigator Bangladesh:

Dr. Wasif Ali Khan)

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled "A Multi-country, Multi-center, Open-labelled, Randomized Controlled, Extended Phase III Clinical Trial to Evaluate the Immunogenicity and Tolerability of Sabin Strain Inactivated Poliovirus Vaccine Administered with or without Routine Infant Vaccines" and the most recent version of the Investigator's Brochure (IB).

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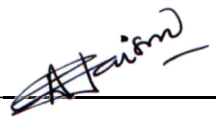

March 27 2024

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Protocol Revision Record

No.	Original version number/version date/revision part	Current version number/version date/revision description
1	Version3.0/03 January, 2023/1.1 Synopsis: Schema	Version3.1/09 February, 2023/ Added the missing word of "weeks" in S2
2	Version3.0/03 January, 2023/ 1.2 Schedule of Activities and Timeline	Version3.1/09 February, 2023/Deleted the "Demographic information and data collection" of "Screening-1 (for mothers) ",
3	Version3.0/03 January, 2023/ 4.2 Rationale for Study Design	Version3.1/09 February, 2023/Added Pakistan national immunization schedule description
4	Version3.0/03 January, 2023/ 5.2 Exclusion Criteria	Version3.1/09 February, 2023/ Added the "Bacillus Calmette–Guérin (BCG)" of 2) Prior vaccination with routine infant vaccines
5	Version3.0/03 January, 2023/6.3 Measures to Minimize Bias: Randomization and Blinding: Randomization	Version3.1/09 February, 2023/Revised Randomization method, using paper randomization cards instead of IWRS
6	Version3.0/03 January, 2023/8.6 Study Procedures	Version3.1/09 February, 2023/Deleted "Obtain the mother's demography (including full date of birth, sex)" of "Screening for mothers (~Day 0)"
7	Version3.0/03 January, 2023/ Table 9 Severity Grading Criteria for Unsolicited Symptoms	Version3.1/09 February, 2023/Changed Table No. as 10
8	Version3.0/03 January, 2023/ LIST OF ABBREVIATION	Version3.1/09 February, 2023/Added EPI abbreviation
9	Version3.1/09 February, 2023/5.2 Exclusion Criteria	Version3.2/13 February, 2023/ Added "only for Pakistan" of "1) History of polio vaccination (except the OPV at birth)"; Removed restrictions on BCG and Hepatitis B of 2) Prior vaccination with routine infant vaccines
10	Version3.1/09 February, 2023/ 8.6.2 Staggered administration group (group S1/S2)	Version3.2/13 February, 2023/ Deleted "Collect the Diary Card from participants" of "Visit 7- Follow up-V5+28 (+7) days"
11	Version3.1/09 February, 2023/13 ANNEX COUNTRY: PAKISTAN	Version3.2/13 February, 2023/ Removed the "Bangladesh" as "Pakistan" in the paragraph

12	Version3.1/09 February, 2023/1.1 Synopsis	Version3.2/13 February, 2023/ Deleted the “Estimated date first participant enrolled: March 1st, 2023; Estimated date last participant enrolled: October 31th, 2023”
13	Version3.1/09 February, 2023/1.2 Schedule of Activities and Timeline	Version3.2/13 February, 2023/ Added description of the three tables of “d”.
14	Version3.1/09 February, 2023/8.6 Study Procedures	Version3.2/13 February, 2023/ Adjusted the order of “Check inclusion and exclusion criteria” and “Obtain the participant’s randomization number” of “Visit 1-First Vaccination (Day 0)”
15	Version3.2/13 February, 2023/5.1 Inclusion Criteria	Version3.3/28 July, 2023/ Updated the criteria for "5)" by adding the need for a negative Hepatitis C test from the participant's mother. Revised sections 1.2 SOA, 8.6 Study Procedures, and Synopsis to reflect these updates.
16	Version 3.3/28 July, 2023/1.1 Synopsis	Version 3.4/ March 27, 2024/ Modified the IP name as ‘Poliomyelitis Vaccine (Vero cells), Inactivated, Sabin Strains’ to consistent with Investigator Brochure and IP label and modified the description in the relevant part.
17	Version 3.3/28 July, 2023/ 8.5.7 Safety Oversight	Version 3.4/ March 27, 2024/ Described the oversight scope and charter of DSMB.
18	Version 3.3/ 28 July, 2023/4.1. Overall Design	Version 3.4/ March 27, 2024/ PCV10 was modified to PCV and modified the description in the relevant part of the design. And modified the ‘infants of 6 weeks old (42-47 days)’ to the ‘infants of 6 weeks old (42-47 days) for Bangladesh and of 6-8 weeks old (42-56 days) for Pakistan’.
19	Version 3.3/28 July, 2023/ 13. ANNEX	Version 3.4/ March 27, 2024/ PCV10 was modified to PCV13 according to the Vaccination schedule for Pakistan and modified the description in the relevant part of the design. And modified HeB to HepB.
20	Version 3.3/28 July, 2023/ 5.1 Inclusion Criteria	Version 3.4/ March 27, 2024/ Amended the inclusion criteria 1): To enroll infants of 6-8 weeks old (42-56 days) from

		Pakistan, and modified the description in the relevant part.
21	Version 3.3/28 July, 2023/ 5.2 Exclusion Criteria	Version 3.4/ March 27, 2024/ Amended the exclusion criterion 1): Participants from Pakistan who have received the second dose of OPV > 14 days before are now permitted for inclusion. Amended the exclusion criterion 4): Participants from Pakistan, low birth weight is defined as < 2200g.
22	Version 3.3/28 July, 2023/ 5.3 Exclusion Criteria	Version 3.4/ March 27, 2024/ Added 'or factors' to the exclusion criterion 4).
23	Version 3.3/28 July, 2023/ 3 Objectives and endpoints	Version 3.4/ March 27, 2024/ Revised the Secondary Objectives and endpoints.
24	Version 3.3/28 July, 2023/ 8.1.1 Blood Collection and Laboratory Testing	Version 3.4/ March 27, 2024/ Revised the table 5 for Definition of immune response.
25	Version 3.3/28 July, 2023/ Study Team	Version 3.4/ March 27, 2024/ Added the missing information about National Principal Investigator Pakistan and Clinical trial monitoring (Bangladesh).
26	Version 3.3/28 July, 2023/ 4.2 rationale for study design	Version 3.4/ March 27, 2024/ Revised description of hypotheses based on secondary endpoints
27	Version 3.3/28 July, 2023/ 9.3.4 Immunogenicity Analysis	Version 3.4/ March 27, 2024/ Revised statistical methods based on secondary endpoints and definition of immune response.

1. PROTOCOL SUMMARY

1.1 Synopsis

Name of the Sponsor: Sinovac Biotech Co., Ltd.

Name of Investigational Product:

Poliomyelitis Vaccine (Vero cells), Inactivated, Sabin Strains (hereinafter as "sIPV")

Name of Active Ingredients: Inactivated Polioviruses of serotype I, II, III

Title of Study: A Multi-country, Multi-center, Open-labelled, Randomized, Controlled, Extended Phase III Clinical Trial to Evaluate the Immunogenicity and Tolerability of Sabin Strain Inactivated Poliovirus Vaccine Administered with or without Routine Infant Vaccines

Protocol Number: PRO-sIPV-4001

Study Period (years/months)	**Phase of Development:**
Estimated duration of the trial: 14 months	**extended phase** III

Objectives and Endpoints

The objectives and endpoints of this clinical trial are as follows:

	Objectives	Endpoints
Primary	To evaluate the non-inferiority of immune response to polio vaccination, when administered concomitantly with routine vaccines	• Seroconversion rates of neutralizing antibody against polioviruses of three serotypes, at 28 days after three doses of vaccination
	To evaluate the safety in terms of ARs (Vaccine-related AEs)	• Incidence of adverse reactions within 7 days after each dose of vaccination
Secondary	To evaluate non-inferiority of immune response to diphtheria and tetanus antigens, when routine vaccines are administered concomitantly with sIPV	• Sero-protection rate of IgG antibodies against diphtheria (DT) and tetanus (TT), at 28 days after vaccination
	To evaluate non-inferiority of immune response to acellular pertussis antigens, when routine vaccines are administered concomitantly with sIPV	• Seropositivity rate of IgG antibodies against pertussis toxin (PT), Filamentous hemagglutinin (FHA), Pertactin (PRN), at 28 days after vaccination
	To evaluate other immunogenicity against diphtheria, tetanus, acellular pertussis antigens	• GMC/GMFR of IgG antibodies against DT, TT, PT, FHA, PRN, at 28 days after vaccination

	To evaluate other immunogenicity of sIPV, when administered concomitantly with routine vaccines	• Sero-protection rate of neutralizing antibody against polioviruses of three serotypes, at 28 days after three doses of vaccination • GMT/GMFR of neutralizing antibodies against polioviruses of three serotypes, at 28 days after three doses of vaccination
	To evaluate the immunogenicity against hepatitis B and Hib, when routine vaccines are administered concomitantly with sIPV	• Sero-protection rate of IgG antibodies against hepatitis B and Hib, at 28 days after vaccination • GMC/GMFR of IgG antibodies against hepatitis B and Hib, at 28 days after vaccination
	To evaluate the immunogenicity against pneumococcal, when routine vaccines are administered concomitantly with sIPV	• Sero-protection rate of IgG antibodies against pneumococcal, at 28 days after vaccination • GMC/GMFR of IgG antibodies against pneumococcal, at 28 days after vaccination
	To evaluate other safety in terms of ARs (Vaccine-related AEs)	• Incidence of adverse reactions since first dose until 28 days after the last dose
	To evaluate the safety in terms of SAEs	• Incidence of SAEs throughout the study

DT= Diphtheria, TT= Tetanus, PT=Pertussis toxin, FHA=Filamentous hemagglutinin, PRN=Pertactin, Hib= Haemophilus influenzae type b, GMC=Geometric Mean Concentration, GMT=Geometric Mean Titer, GMFR=Geometric Mean Fold Rise, SAE=Serious Adverse Events.

Overall Design

This is a multi-country, multi-center, open-labelled, randomized, controlled, extended phase III clinical trial. Totally 1440 healthy infants of 6 weeks old (42-47 days) for Bangladesh and of 6-8 weeks old (42-56 days) for Pakistan are planned to be enrolled, and then randomized in a 1:1:1:1 ratio into four groups, i.e., co-administration group 1 (group C1), co-administration group 2 (group C2), staggered administration group 1 (group S1) and staggered administration group 2 (group S2). Participants in group C1 and C2 will receive sIPV at 6,10, 14 weeks of age (at 4-week intervals), administered concomitantly with routine infant vaccine (may include DTP-HepB-Hib vaccine, PCV or rotavirus vaccine in accordance with the local routine vaccination schedule). Participants in group S1 will receive sIPV at 6,10,14 weeks of age, and receive routine infant vaccines at 8,12,16 weeks of age. Participants in group S2 will receive routine infant vaccines at 6,10,14 weeks of age, and receive sIPV at 8,12, 16 weeks old (at 4-week intervals, respectively).

For all the Participants, the immediate reactions within 30 minutes after each dose of vaccination will be observed on site. Guardians of participants will utilize the diary card to record solicited adverse events from the time of vaccination for 7 days post-vaccination of each dose. From the time of the first vaccination and 28 days post-vaccination of the last dose, unsolicited adverse events and any SAEs will be required to recorded in the diary card.

About 3 ml venous blood will be collected before the first vaccination and 28 days (+7) days after the last vaccination of sIPV or routine vaccines. Antibodies level will be determined using the collected sera for immunogenicity evaluation. Group C1 and S1 will be compared in terms of immunogenicity against polio; Group C2 and S2 will be compared in terms of immunogenicity

against diphtheria, Tetanus, Pertussis, Hepatitis B, Hib and Pneumococcal.

Investigational Product, Dosage and Mode of Administration:

Poliomyelitis Vaccine (Vero cells), Inactivated, Sabin Strains (sIPV); Dosage 15DU/45DU/45DU per 0.5ml for type I/II/III; Mode of administration: Intramuscular injection (preferably in anterolateral thigh muscles)

Criteria for Inclusion/Exclusion

Inclusion Criteria

In order to be eligible to participate in this study, any individual must meet the following criteria:

1. Infants of 6 weeks old (42-47 days) for Bangladesh and of 6-8 weeks old (42-56 days) for Pakistan;
2. For whom a parent/legal guardian has given written informed consent after the study has been explained.
3. Be able to provide the vaccination records after birth;
4. Negative results in SARS-CoV-2 rapid antigen testing, within 24 hours before enrollment;
5. The participant's mother was tested negative for HIV, Syphilis, Hepatitis A, Hepatitis B, Hepatitis C infection during or before (during pregnancy) her child's enrollment to this study (the test result should be provided, and that obtained during pregnancy period is acceptable).

Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. History of polio vaccination (except the OPV at birth, and the second dose OPV > 14 days before for Pakistan);
2. Prior vaccination with routine infant vaccines against Diphtheria, Tetanus, Pertussis, Haemophilus influenzae type b (Hib), Pneumococcal or Rotavirus;
3. History of severe allergic reaction after previous vaccinations or hypersensitivity to any vaccine component;
4. Infants with premature labor (delivery before week 37 of gestation) and low body weight (In Bangladesh birth body weight is <2,500 g, while in Pakistan, set at <2200g);
5. Infants with difficult labor at birth, asphyxiation rescue and history of nervous system injury;
6. Congenital malformation or development disorder, genetic defect, severe malnutrition, etc.;
7. Autoimmune disease or immunodeficiency/immunosuppression;
8. Patients with serious chronic diseases (such as Down's syndrome, diabetes, sickle cell anemia, or neurological disorders);
9. Abnormal coagulation functions (such as coagulation factor deficiency, blood coagulation disease and blood platelet disorders) or obvious bruise or blood coagulation disorders diagnosed by the doctors;
10. Those who have received immunosuppressant therapy, cytotoxic drug therapy and inhaled corticosteroid therapy (excluding the corticosteroid aerosol therapy for allergic rhinitis and surface corticosteroid therapy for acute non-complicated dermatitis);
11. The volunteer has received blood products before inoculation of the trial vaccine;
12. The volunteer has received other study drugs within 30 days before inoculation of the trial vaccine;
13. The volunteer has received live attenuated vaccines within 14 days before inoculation of the trial vaccine;
14. The volunteer has received subunit or inactivated vaccines within 7 days before inoculation of the trial vaccine;
15. Various acute diseases or acute exacerbation of chronic diseases within recent 7 days;
16. Significant acute disease or chronic infection within the previous 7 days or axillary temperature ≥ 37.3℃ prior to vaccination in the present study;
17. The volunteer has any other factors which are unsuitable for participation in the clinical trial

as judged by the investigator.

Immunogenicity Evaluations

Serum samples from all the participants will be obtained for immunogenicity testing. Microneutralization method will be used to determine the neutralizing antibodies against polioviruses of all serotypes, and Enzyme Linked Immunosorbent assay (ELISA) will be used to determine IgG antibodies against diphtheria, tetanus, pertussis, Hepatitis B, Hib and pneumococcal.

The primary hypothesis of this clinical trial is:
The seroconversion rate of polio vaccination when administered concomitantly with routine vaccines, is non-inferior to that when administered staggered from other routine vaccines

The secondary hypothesis of this clinical trial is:
The seropositivity rate of diphtheria, tetanus, and pertussis when routine vaccines are administered concomitantly with sIPV, is non-inferior to that administered staggered from sIPV

The following non-inferiority criteria should be met:

The lower bound of the 95% confidence interval around the difference in seroconversion rates (test group-control group) should not exceed -10%.

Safety Evaluations

Physical Examinations

Physical examination will be performed at screening by the investigator or designated medically trained physician. A physical examination will be performed during a screening visit by the investigator or designated medically trained physician (or a trained healthcare practitioner, if allowed per local regulations). Any clinically relevant abnormalities or changes in severity observed during the review should be documented in the electronic case report form.

Vital Signs including height and weight, body temperature, heart rate, and breathing rate will be measured during Visit 1. At all visits, temporal temperature (axillary temperature) will be measured. Guardians of participants will be required to utilize the diary cards to record body temperature (axillary temperature) measurements from the time of vaccination until 7 days post-vaccination.

Indicators for safety observation

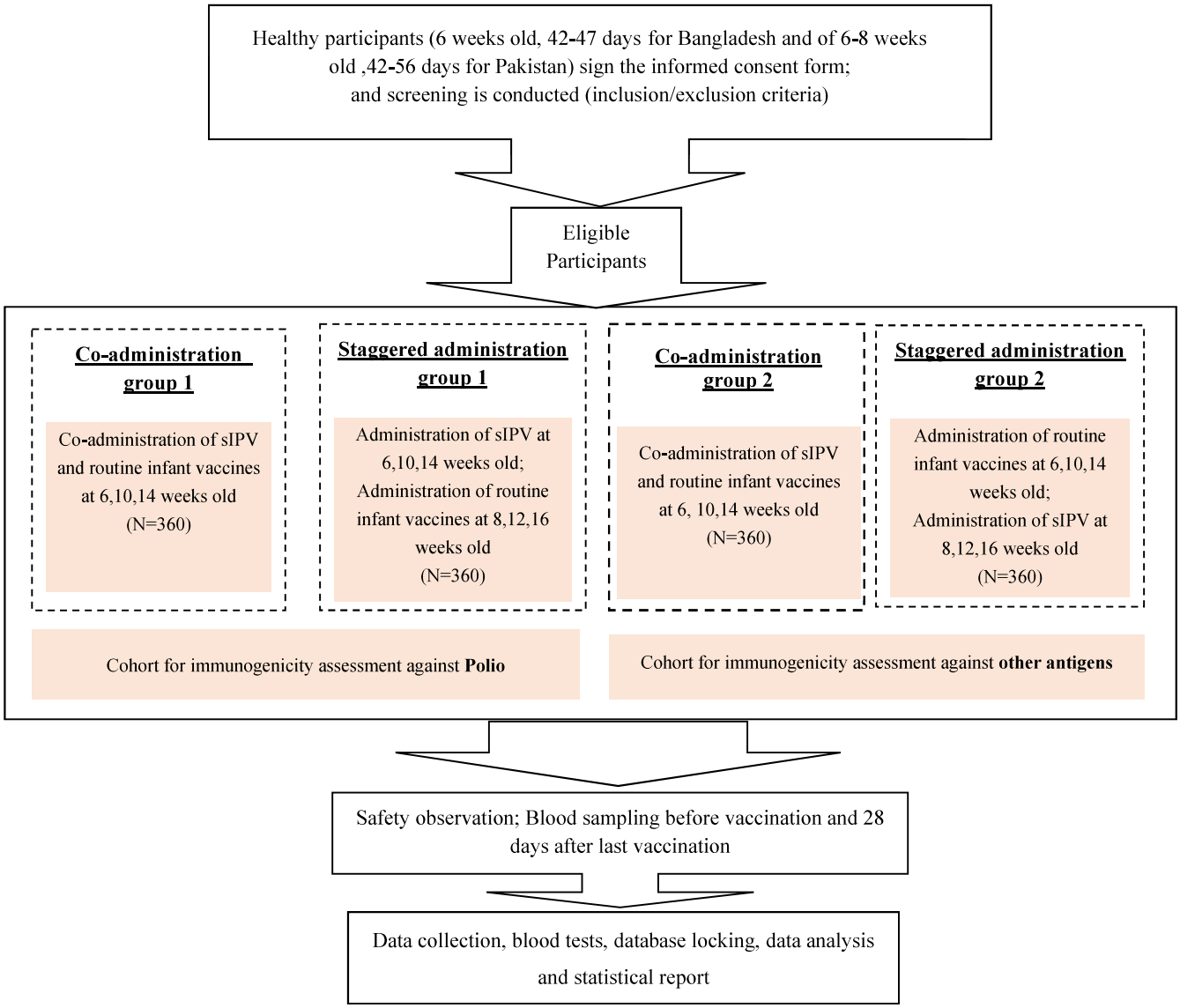
Solicited local (injection site) symptoms: redness, swelling, rashes, induration, and pruritus

Solicited systemic symptoms (including vital signs): fever (axillary temperature will be measured), acute allergic reaction, diarrhea, decreased appetite, irritability, decreased activity.

Safety Follow-up

Diary cards will be distributed to guardians of participants to record the local and systemic solicited AEs within 7 days after each dose vaccination and record unsolicited AEs up to 28 days after the last dose vaccination. For all participants, the immediate reactions within 30 minutes after the last injection in each vaccination visit will be observed on site, and the collection of SAEs will be monitored up to 28 days after the last dose vaccination. In addition, acute allergic reactions, severity level 3 and above AEs and SAEs should be reported to the investigators in a timely manner.

1.2 Trial Schema



1.3 Schedule of Activities and Timeline

Table 1 Schedule of Activities _Group C1/C2

Procedure	Screening-1 (for mothers) [a]	Screening-2 (for infants) [a]	V1	V2	V3	V4	V5	V6	V7
Date of Visit	~D0	D-14~D0	D0	V1+14 (+3 days)	V1+ 28 (+7 days)	V3+14 (+3 days)	V3+ 28 (+7 days)	V5+14 (+3 days)	V5+28 (+7 days)
Preliminary notification and recruitment	X								
Participant enrolment		X							
Informed consent [b]	X	X							
Demographic information and data collection		X							
HIV, syphilis, hepatitis A, hepatitis B, hepatitis C infection testing for mothers	X								
Physical examination and consultation for infants			X						
Collection of medical history			X						
Collection of concomitant medicine			X						
Health status confirmation			X						
Vital signs measurement [c]			X						
SARS-CoV-2 rapid antigen testing			X						
Inclusion/exclusion criteria screening			X						
Randomization			X						
Vaccination discontinue or postpone rules screening					**X**		**X**		
Vaccination			**X**		**X**		**X**		
Blood samples for humoral immunogenicity [d]			**X**						**X**
Participant self-recording of the safety observation on diary card			**X**	**X**	**X**	**X**	**X**	**X**	**X**
Monitoring of SAE, information of concomitant use of drug/vaccine			**X**	**X**	**X**	**X**	**X**	**X**	**X**

SAE: Serious adverse event
a. Infant Screening will be performed within 14 days prior to the study vaccination or on the day of vaccination. Screening must be completed, and all eligibility criteria must be fulfilled prior to randomization and vaccination. Mother screening could be performed coincide with the infant screening or before that.
b. Signing the informed consent form should be done before any study-related procedure. This procedure should be conducted following the regulatory requirements in each country.
c. Measure vital signs including height and weight, body temperature, heart rate and breathing rate at the first visit. Body temperature will be measured in every visit preferably via axillary temperature
d. Before the first vaccination and 28 days (+7) days after the last vaccination of sIPV or routine vaccines, a 3 ml blood sample for humoral immunogenicity evaluation needed to be collected.

Table 2 Schedule of Activities Group S1

Procedure	Screening-1 (for mothers) [a]	Screening-2 (for infants) [a]	V1	V2	V3	V4	V5	V6	V7	V8
Date of Visit	~D0	D-14~D0	D0	V1+14 (+3 days)	V2+ 14 (+3 days)	V3+14 (+3 days)	V4+14 (+3 days)	V5+14 (+3 days)	V5+28 (+7 days)	V6+28 (+7 days)
Preliminary notification and recruitment	X									
Participant enrollment		X								
Informed consent [b]	X	X								
Demographic information and data collection		X								
HIV, syphilis, hepatitis A, hepatitis B, hepatitis C infection testing for mothers	X									
Physical examination and consultation for infants			X							
Collection of medical history			X							
Collection of concomitant medicine			X							
Health status confirmation			X							
Vital signs measurement [c]			X							
SARS-CoV-2 rapid antigen testing			X							
Inclusion/exclusion criteria screening			X							
Randomization			X							
Vaccination discontinue or postpone rules screening				**X**	**X**	**X**	**X**	**X**		
Vaccination of sIPV			**X**		**X**		**X**			
Vaccination of routine vaccines				**X**		**X**		**X**		
Blood samples for humoral immunogenicity [d]			**X**						**X**	
Participant self-recording of the safety observation on diary card			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Monitoring of SAE, information of concomitant use of drug/vaccine			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

SAE: Serious adverse event

a. Infant Screening will be performed within 14 days prior to the study vaccination or on the day of vaccination. Screening must be completed, and all eligibility criteria must be fulfilled prior to randomization and vaccination. Mother screening could be performed coincide with the infant screening or before that.

b. Signing the informed consent form should be done before any study-related procedure. This procedure should be conducted following the regulatory requirements in each country.

c. Measure vital signs including height and weight, body temperature, heart rate and breathing rate at the first visit. Body temperature will be measured in every visit preferably via axillary temperature.

d. Before the first vaccination and 28 days (+7) days after the last vaccination of sIPV, a 3 ml blood sample for humoral immunogenicity evaluation needed to be collected.

Table 3 Schedule of Activities _Group S2

Procedure	Screening-1 (for mothers)[a]	Screening-2 (for infants)[a]	V1	V2	V3	V4	V5	V6	V7	V8
Date of Visit	~D0	D-14~D0	D0	V1+14 (+3 days)	V2+ 14 (+3 days)	V3+14 (+3 days)	V4+14 (+3 days)	V5+14 (+3 days)	**V5**+28 (+7 days)	**V6**+28 (+7 days)
Preliminary notification and recruitment	X									
Participant enrolment		X								
Informed consent [b]	X	X								
Demographic information and data collection		X								
HIV, syphilis, hepatitis A, hepatitis B, hepatitis C infection testing for mothers	X									
Physical examination and consultation for infants			X							
Collection of medical history			X							
Collection of concomitant medicine			X							
Health status confirmation			X							
Vital signs measurement [c]			X							
SARS-CoV-2 rapid antigen testing			X							
Inclusion/exclusion criteria screening			X							
Randomization			X							
Vaccination discontinue or postpone rules screening				**X**	**X**	**X**	**X**	**X**		
Vaccination of sIPV				**X**		**X**		**X**		
Vaccination of routine vaccines			**X**		**X**		**X**			
Blood samples for humoral immunogenicity [d]			**X**						**X**	
Participant self-recording of the safety observation on diary card			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Monitoring of SAE, information of concomitant use of drug/vaccine			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

SAE: Serious adverse event
a. Infant Screening will be performed within 14 days prior to the study vaccination or on the day of vaccination. Screening must be completed, and all eligibility criteria must be fulfilled prior to randomization and vaccination. Mother screening could be performed coincide with the infant screening or before that.
b. Signing the informed consent form should be done before any study-related procedure. This procedure should be conducted following the regulatory requirements in each country.
c. Measure vital signs including height and weight, body temperature, heart rate and breathing rate at the first visit. Body temperature will be measured in every visit preferably via axillary temperature.
d. Before the first vaccination and 28 days (+7) days after the last vaccination of routine vaccines, a 3 ml blood sample for humoral immunogenicity evaluation needed to be collected.

2. INTRODUCTION

In the first year of life, infant immunization programs may include vaccines against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, disease caused by Haemophilus influenza type b (Hib), pneumococcal, rotavirus gastroenteritis etc. Multiple antigens may be administered at the same site as a combination vaccine or co-administered during the same medical visit at different injection sites. Both strategies minimize the required number of vaccine visits to achieve full coverage, improve timeliness of vaccination and allow for a programmatic fit across different vaccine regimens used in the respective country. These benefits are crucial to increase protection of infants [1].

The sIPV developed by Sinovac Biotech Co., Ltd. (hereinafter as "Sinovac"), was approved for marketing use by China National Medical Products Administration (NMPA) in July 2021 based on the favorable immunogenicity and safety results in both IPV-only and IPV-OPV sequential vaccination schedule [2-4], and subsequently passed the WHO Pre-qualification in June 2022.

2.1 Study Rationale

Sinovac sIPV will be supplied to multiple countries in the near future for the polio prevention. However, data on concomitant vaccination of sIPV and other routine infant vaccines are still lacking. Thus, this study is designed to fill this gap.

2.2 Background

Polio is an infectious disease, contracted predominantly by children, that can lead to the permanent paralysis of various body parts and can ultimately cause death immobilizing the patients' breathing muscles. No cure exists for the symptoms, but in the 1950s effective vaccines, including inactivated polio vaccine (IPV) or oral polio vaccine (OPV), were developed and have been used around the world since then. In the early 1980s, there were an estimated 300,000 to 400,000 cases worldwide per year and the disease was still prevalent in 125 countries. As a response, the "Global Polio Eradication Initiative" (GPEI) was founded in 1988 to fight the virus's spread and disease burden with a global vaccination campaign. Since then, the world has made rapid progress against the disease and until 2016 the number of paralytic cases was reduced by 99.99% with 42 cases in that year worldwide. As of 2021, the virus has been found to circulate in only two countries in the world-Afghanistan and Pakistan [5].

Both IPV and OPV have played a major role in the reduction of global poliomyelitis disease burden, while they all have their own advantages and disadvantages. OPV can be conveniently administered especially to children because there is no need of injecting the vaccine via a needle. It's also known to induce a better mucosal immunity in the intestines against the virus which predominantly uses the gastrointestinal tract as its portal of entry into the human body. However, in rare cases, the OPV was reported to cause the vaccine-derived poliovirus (VDPV) and vaccine-associated paralytic poliomyelitis (VAPP), which is a major concern regarding the use of OPV in the battle of the worldwide polio eradication. In contrast, one of the major advantages of using IPV is there is no risk of developing VDPV or VAPP, though the immunity induced by IPV is lower than that is induced by OPV.

To eliminate all poliomyelitis including VAPP and VDPV, the GPEI recommended withdrawal of OPV in a phased manner. By 2016, 155 OPV-using countries discontinued use of Sabin poliovirus type 2 and replaced trivalent oral polio vaccine (tOPV) with bivalent oral polio vaccine (bOPV)[6]. Furthermore, developed countries that had eliminated wild poliovirus (WPV) transmission shifted toward all IPV-immunization to prevent VAPP/VDPV. Nevertheless, the feasibility of switching to the all-IPV schedule depends on multiple factors, including the existing population's immunity level, the financial burden, and the IPV supply. The wild-strain IPV (wIPV) production can pose concern for poliovirus transmission due to the potential release of vaccine strain virus, especially in developing countries where population immunity is seldom sufficiently high [7]. On the other hand, the high production cost, owning to the strict safety requirements, makes wild-strain IPV production unaffordable for developing countries, which was a barrier for production scale-up. Due to the above restrictions, the conventional IPV supply remains a serious issue, and many countries are still using fractional IPV with OPV. Thus, several manufactures mainly in developing countries developed Sabin strain IPV (sIPV) to fill the gap of IPV supply with sIPV, which has a higher biosafety and reduced production cost.

2.2.1 Product Summary

The studied sIPV, developed by Sinovac Biotech, is a liquid trivalent vaccine (0.5ml/dose) for intramuscular injection. It was generated from Sabin poliovirus type 1, 2 and 3 strains grown on Vero cells. The antigen contents are 15, 45 and 45 D antigen units for type 1, 2 and 3 Sabin polioviruses, respectively. The vaccines were prepared in a good manufacturing practice-accredited facility and were approved by the National Institute for Food and Drug Control (NIFDC) of China. The validity period is 24 months from the date of configuration of the semi-finished product. All study participants will concomitantly receive other vaccines as per National Immunization Programme except for any other polio vaccine (oral or inactivated).

2.2.2 Summary of Existing Immunogenicity Data

2.2.2.1 Immunogenicity data for sIPV-only vaccination schedule

Immunogenicity of the Primary Vaccination

In the phase III pivotal clinical study, after three-doses primary vaccination, the maternal-antibody adjusted seroconversion rates of experimental and control group against type I, II, and III were 99.5%vs 99.3% (P=0.72), 98.6%vs 97.0% (P=0.08), and 99.6% vs 99.6% (P=0.99) respectively. The investigational sIPV was demonstrated to be non-inferior to the control wIPV when the influence of maternal antibodies was adjusted. The post-vaccination GMTs of experimental and control group against type I, II, and III were 4149.7 vs 493.5 (P<0.0001), 392.4 vs 158.8 (P<0.0001), 1372.3 vs 550.8 (P<0.0001), respectively. The GMTs of neutralizing antibodies against all serotypes of the experimental group were statistically higher than those of the control group.

Immune Persistence of the Primary Vaccination

In the phase III pivotal clinical study, the immune persistence of the primary vaccination was evaluated in 1082 Participants (540 in experimental group and 542 in control group) who received the three-dose primary vaccination and blood collection before the booster dose at 18 months of age. Fourteen months after the primary vaccination, the seropositive rates (≥1:8) of the experimental and control groups were 99.6% vs 99.5% against type I, 98.5% vs 95.4% against type II, and 100.0% vs 97.8% against type III. The seropositivity rates in both groups was equivalent. However, neutralizing antibody titers in experimental group were statistically significantly higher than that in control group with GMTs against serotype I, II, III of 750.5 vs 177.4 (P<0.0001), 108.4 vs 50.8 (P<0.0001), 411.7 vs 154.0 (P<0.001) respectively. Similar immune persistence profiles are found in the susceptible population whose base line Nab titers <1:8.

Immune response of the Booster Dose Vaccination

In the phase III pivotal clinical study, among the participants who received the complete infant immunization series, after the booster dose all participants in both experimental and control groups were seropositive (≥1:8) against serotypes I, II, III, and GMTs were 11176.8 vs 4524.2 (P<0.0001) for serotype I, 4871.2 vs 2057.9 (P<0.0001) for serotype II, and 10907.2 vs 7538.2 (P<0.0001) for serotype III, respectively in experimental and control group. The booster dose in the second year of life increased significantly in participants included in both vaccine groups the neutralizing antibody titers to all the three serotypes. However, antibody titers in participants of experimental group were statistically significantly higher than that in participants of control group for all the three serotypes.

2.2.2.2 Immunogenicity data for sIPV & bOPV sequential vaccination schedule

In the clinical trial with "IPV+2bOPV" sequential schedule, the maternal–antibody adjusted seroconversion rates of experimental and control group were 100% vs. 99.1% (P=0.3229) against serotype I, 100% vs 100% (P=1.00) against serotype III, 83.2% vs.78.2% (P=0.3517) against serotype II. The post-vaccination GMTs of neutralizing antibodies in experimental group and control group were 5761.2 vs 3196.8 (P<0.0001) against serotype I, 2074.8 vs 2097.1 (P=0.9333) against serotype III, and 27.7 vs 21.9 (P=0.1466) against serotype II. The GMT of neutralizing antibodies against serotype I in the experimental group was statistically higher than that in control group.

In the clinical trial with "2IPV+bOPV" sequential schedule, the maternal–antibody adjusted seroconversion rates of experimental and control group were 99.2% vs 100% (P=0.3332) against serotype I, 100% vs 100% (P=1.00) against serotype III, 94.9% vs 98.2% (P=0.2828) against serotype II. The post-vaccination GMTs of neutralizing antibodies in experimental and control group were 10119.2 vs 5801.7 (P<0.0001) against serotype I, 7255.1 vs 6124.2 (P=0.2236) against serotype III, 133.9 vs 84.2 (P=0.0016) against serotype II. The GMT of neutralizing antibodies against serotype I & II in the experimental group was statistically higher than those in the control group. Therefore, the immunogenicity of the investigational sIPV was non-inferiority to the control wIPV in different sequential schedules with bOPV.

2.2.3 Summary of Existing Safety Data

In the pre-clinical development stage, single dose acute toxicity test, active systemic anaphylaxis and local irritation test were performed according to GLP regulations. The results showed that no significant toxicity was observed in mice after intramuscular injection of sIPV, no systemic active allergic reaction was induced in guinea pigs after intramuscular injection of sIPV, and no irritating effect was observed in rabbits after intramuscular injection of sIPV on their injected local muscle tissues. sIPV has good safety in experimental animals. No studies related to renal, hepatic or haematological toxicity were performed during the pre-clinical development.

In the clinical development stage, three doses of investigational sIPV of market dose were inoculated for primary immunization among totally 739 infants aged 2 months old in four licensed clinical trial conducted in China. Up to 30 days after the last vaccination, all the reported reactions were general and transient adverse reactions, as listed in the Table 7 of latest IB (version 2.0). Up to 14 months after the three-doses primary immunization, the most serious adverse events (SAEs) were upper respiratory tract infection pneumonia, which are common diseases in infants. No vaccine-related SAEs were reported throughout the licensed clinical trials of sIPV. No renal, hepatic or haematological toxicity reactions were noticed during the clinical development.

Since July 2021 (marketing time of sIPV), a total of 35 episodes of AEFIs have been reported from 18 vaccinees, including 30 non-serious episodes and 5 serious episodes. The non-serious AEFIs are mainly fever, injection-site erythema, injection-site swelling and injection-site induration. The serious AEFIs are fever, injection-site erythema, injection-site swelling, injection-site induration and thrombocytopenic purpura. Among them, there are no sufficient evidence to support the judgement of causal relationship between the vaccination of sIPV and the two serious AEFI, i.e., thrombocytopenic purpura and fever.

2.3 Benefit-risk assessment

2.3.1 Risks related to study participation

Based on the existing safety data of the studied sIPV, recipients of sIPV in the present study may experience pain and/or redness at injection site, fever, diarrhea, vomiting, decreased appetite etc. Overall, the studies sIPV was well tolerated, without significant safety issues identified. As with any vaccination, there is potential for an anaphylactic reaction. Additionally, there is a theoretical possibility of risks that the sponsor is currently unaware of. To facilitate the management of these potential risks, experienced medical staff in the management of anaphylactic reaction will observe patient for at least 30 minutes following vaccination to ensure that any anaphylactic reaction occurred can be managed in a timely manner.

The vaccination schedule specified in this present study for the staggered administration groups is slightly different with the exact EPI schedule, with a two-week delay for routine infant vaccines (PCV10 & DTP-HepB-Hib vaccine) or sIPV compared to the EPI schedule. However, the vaccination schedule in any group of this study met the recommendations of the package insert of study vaccines. Immune protection in early life could be accomplished by maternal antibodies transferred from mother to offspring. Maternal antibodies are very effective in protecting neonates and infants against most infectious disease, and maternal antibodies wane over a period of 6-12 months [8-11]. The staggered administration groups will be vaccinated with sIPV or routine infant vaccines at 2 months old of the infants, thus is not considered to pose additional risk of infectious disease among the study participants.

2.3.2 Benefit/risk assessment

According to the existing clinical data, three doses sIPV could induce a high immunogenicity against all the three serotypes of polioviruses. Participants in this study will be provided with three doses of sIPV to effectively prevent polio. Thus, it's considered the risks and benefits in this study are balanced.

3. OBJECTIVES AND ENDPOINTS

The objectives and endpoints of this clinical trial are as follows:

	Objectives	Endpoints
Primary	To evaluate the non-inferiority of immune response to polio vaccination, when administered concomitantly with routine vaccines	• Seroconversion rates of neutralizing antibody against polioviruses of three serotypes, at 28 days after three doses of vaccination
	To evaluate the safety in terms of ARs (Vaccine-related AEs)	• Incidence of adverse reactions within 7 days after each dose of vaccination
Secondary	To evaluate non-inferiority of immune response to diphtheria and tetanus antigens, when routine vaccines are administered concomitantly with sIPV	• Sero-protection rate of IgG antibodies against diphtheria (DT) and tetanus (TT), at 28 days after vaccination
	To evaluate non-inferiority of immune response to acellular pertussis antigens, when routine vaccines are administered concomitantly with sIPV	• Seropositivity rate of IgG antibodies against pertussis toxin (PT), Filamentous hemagglutinin (FHA), Pertactin (PRN), at 28 days after vaccination
	To evaluate other immunogenicity against diphtheria, tetanus, acellular pertussis antigens	• GMC/GMFR of IgG antibodies against DT, TT, PT, FHA, PRN, at 28 days after vaccination
	To evaluate other immunogenicity of sIPV, when administered concomitantly with routine vaccines	• Sero-protection rate of neutralizing antibody against polioviruses of three serotypes, at 28 days after three doses of vaccination • GMT/GMFR of neutralizing antibodies against polioviruses of three serotypes, at 28 days after three doses of vaccination
	To evaluate the immunogenicity against hepatitis B and Hib, when routine vaccines are administered concomitantly with sIPV	• Sero-protection rate of IgG antibodies against hepatitis B and Hib, at 28 days after vaccination • GMC/GMFR of IgG antibodies against hepatitis B and Hib, at 28 days after vaccination
	To evaluate the immunogenicity against pneumococcal, when routine vaccines are administered concomitantly with sIPV	• Sero-protection rate of IgG antibodies against pneumococcal, at 28 days after vaccination • GMC/GMFR of IgG antibodies against pneumococcal, at 28 days after vaccination
	To evaluate other safety in terms of ARs (Vaccine-related AEs)	• Incidence of adverse reactions since first dose until 28 days after the last dose

	Objectives	Endpoints
	To evaluate the safety in terms of SAEs	• Incidence of SAEs throughout the study

DT= Diphtheria, TT= Tetanus, PT=Pertussis toxin, FHA=Filamentous hemagglutinin, PRN=Pertactin, Hib= Haemophilus influenzae type b, GMC=Geometric Mean Concentration, GMT=Geometric Mean Titer, GMFR=Geometric Mean Fold Rise, SAE=Serious Adverse Events.

4. STUDY DESIGN

4.1 Overall Design

This is a multi-country multi-center study, and the enrollment plan will be specified in each country. The study protocol will be adjusted based on local conditions and requests from local IRB/IEC.

This is a multi-country, multi-center, open-labelled, randomized, controlled, extended phase III clinical trial. Totally 1440 healthy infants of 6 weeks old (42-47 days) for Bangladesh and of 6-8 weeks old (42-56 days) for Pakistan are planned to be enrolled, and then randomized in a 1:1:1:1 ratio into four groups, i.e., co-administration group 1 (group C1), co-administration group 2 (group C2), staggered administration group 1 (group S1) and staggered administration group 2 (group S2). Participants in group C1 and C2 will receive sIPV at 6,10, 14 weeks old (at 4-week intervals), administered concomitantly with routine infant vaccine (may include DTP-HepB-Hib vaccine, PCV or rotavirus vaccine in accordance with the local routine vaccination schedule). Participants in group S1 will receive sIPV at 6,10,14 weeks old, and receive routine infant vaccines at 8,12,16 weeks old (at 4-week intervals, respectively). Participant s in group S2 will receive routine infant vaccines at 6,10,14 weeks old, and receive sIPV at 8,12, 16 weeks old (at 4-week intervals, respectively).

For all the participants, the immediate reactions within 30 minutes after each dose of vaccination will be observed on site. Guardians of participants will utilize the diary card to record solicited adverse events from the time of vaccination for 7 days post-vaccination of each dose. From the time of the first vaccination and 28 days post-vaccination of the last dose, unsolicited adverse events and any SAEs will be required to be recorded in the diary card.

About 3 ml venous blood will be collected before the first vaccination and 28 days (+7) after the last vaccination of sIPV or routine vaccines. Antibodies level will be determined using the collected sera for immunogenicity evaluation. The antibody testing required for reach group is shown in Table 4. Group C1 and S1 will be compared in terms of immunogenicity against polio; Group C2 and S2 will be compared in terms of immunogenicity against diphtheria, Tetanus, Pertussis, Hepatitis B, Hib and Pneumococcal.

Table 4 Study Design

Group Code	Sample size	Vaccination schedule						Antibody tests	
		6 weeks	8 weeks	10 weeks	12 weeks	14 weeks	16 weeks	Blood collection time	Testing item
C1	**360**	sIPV+ Routine vaccines		sIPV+ Routine vaccines		sIPV+ Routine vaccines		**Baseline 18 weeks**	Neutralizing antibody against polioviruses of type 1,2,3
C2	**360**	sIPV+ Routine vaccines		sIPV+ Routine vaccines		sIPV+ Routine vaccines		**Baseline 18 weeks**	Antibodies against Diphtheria, Tetanus, Pertussis (FHA, Pertactin, Pertussis toxoid), Hepatitis B, Hib; Pneumococcal antibodies*
S1	**360**	sIPV	Routine vaccines	sIPV	Routine vaccines	sIPV	Routine vaccines	**Baseline 18 weeks**	Neutralizing antibody against polioviruses of type 1,2,3
S2	**360**	Routine vaccines	sIPV	Routine vaccines	sIPV	Routine vaccines	sIPV	**Baseline 18 weeks**	Antibodies against Diphtheria, Tetanus, Pertussis (FHA, Pertactin, Pertussis toxoid),Hepatitis B, Hib; Pneumococcal antibodies*
Total	**1440**								

*Only for serotype 1, 5, 6B, 14, 19F.

4.2 Rationale for Study Design

This study is designed to study the immunogenicity and safety of sIPV co-administered with other routine infant vaccines. According to the national immunization schedule of Bangladesh and Pakistan, sIPV was administered concomitantly with PCV, DTP-HepB-Hib and other vaccines at 6, 10 and 14 weeks old. Thus, this study set up the concomitant vaccination schedule according to the real practice in study area. The primary hypothesis of this study is that the seroconversion rate of polio vaccination when administered concomitantly with routine vaccines is non-inferior to that of being administered alone. The secondary hypothesis is that the sero-protection rates of diphtheria, tetanus, and the seropositivity rate of pertussis when routine vaccines are administered concomitantly with sIPV are non-inferior to those administered without sIPV. Two staggered administration groups were designed in this study, one is administered with sIPV at 6 weeks old as the comparator for the non-inferiority evaluation of immune response to polio; another is administered with routine infant vaccines at 6 weeks old, as the comparator for the non-inferiority evaluation of immune response to diphtheria, tetanus, and pertussis. In that way, effects of age on the immune response after vaccination are avoided.

4.3 Justification for Dose

Antigen doses for sIPV in this study were determined based on the its phase II, dose-finding clinical trial, which is conducted among Chinese infants aged 2 months (60-90 days) old. According to the phase II clinical trial, after three doses of vaccination, the maternal-antibody adjusted seroconversion rates in groups of high dosage, medium dosage, low dosage of sIPV, and control wIPV (Pasteur) were 100%, 98.2%, 100% and 100% respectively, for type I; 99.1%, 100%, 98.1% and 97.1% respectively, for type II; 100%, 100%, 100% and 99.0% respectively, for type III. The GMTs in the high, medium, and low dosage group were 7714.4, 4634.6, and 3197.2 respectively against type I, 465.7, 341.6, and 162.1 respectively against type II, and 2786.7, 2217.9, and 1373.6 respectively against type III. A significant dose-response relationship was found in the immunogenicity of the three-dosage groups according to the results of GMT. Taking both immunogenic and safety results into consideration, the medium antigen dose (15,45,45DU/0.5ml for type I,II,III) has been determined as the dosage which was further demonstrated in the further phase III trial to produce robust immunogenicity non-inferior to the control wIPV. Thus, the sIPV manufactured by Sinovac, with antigen contents of 15,45,45DU/0.5ml for type I,II,III was approved for post-marking use by National Medical Products Administration (NMPA), and then applied in this study.

4.4 End-of-study Definition

A participant is considered to have completed the study if he/she has completed all visits of the study. The end of the study is defined as the date of last visit of the last participant in the study.

5. STUDY POPULATION

The inclusion and exclusion criteria for enrolling participants in this study are described below. There will be no prospective approval of protocol deviation to recruitment and enrollment criteria (also known as protocol waivers or exemptions).

5.1 Inclusion Criteria

1) Infants of 6 weeks old (42-47 days) for Bangladesh and of 6-8 weeks old (42-56 days) for Pakistan;
2) For whom a parent/legal guardian has given written informed consent after the study has been explained;
3) Be able to provide the vaccination records after birth;
4) Negative results in SARS-CoV-2 rapid antigen testing, within 24 hours before enrollment;
5) The participant's mother was tested negative for HIV, Syphilis, Hepatitis A, Hepatitis B, Hepatitis C infection during or before (during pregnancy) her child's enrollment to this study (the test result should be provided, and that obtained during pregnancy is acceptable).

5.2 Exclusion Criteria

1) History of polio vaccination (except the OPV at birth, and the second dose OPV＞14 days before for Pakistan);
2) Prior vaccination with routine infant vaccines against Diphtheria, Tetanus, Pertussis, Haemophilus influenzae type b (Hib), Pneumococcal or Rotavirus;
3) History of severe allergic reaction after previous vaccinations or hypersensitivity to any vaccine component;
4) Infants with premature labor (delivery before week 37 of gestation) and low body weight (In Bangladesh, birth body weight is <2500 g, while in Pakistan, set at <2200g);
5) Infants with difficult labor at birth, asphyxiation rescue and history of nervous system injury;
6) Congenital malformation or development disorder, genetic defect, severe malnutrition, etc.;
7) Autoimmune disease or immunodeficiency/immunosuppression;
8) Patients with serious chronic diseases (such as Down's syndrome, diabetes, sickle cell anemia, or neurological disorders);
9) Abnormal coagulation functions (such as coagulation factor deficiency, blood coagulation disease and blood platelet disorders) or obvious bruise or blood coagulation disorders diagnosed by the doctors;
10) Those who have received immunosuppressant therapy, cytotoxic drug therapy and inhaled corticosteroid therapy (excluding the corticosteroid aerosol therapy for allergic rhinitis and surface corticosteroid therapy for acute non-complicated dermatitis);
11) The volunteer has received blood products before inoculation of the trial vaccine;
12) The volunteer has received other study drugs within 30 days before inoculation of the trial vaccine;
13) The volunteer has received live attenuated vaccines within 14 days before inoculation of the trial vaccine;
14) The volunteer has received subunit or inactivated vaccines within 7 days before inoculation of the trial vaccine;
15) Various acute diseases or acute exacerbation of chronic diseases within recent 7 days;
16) Significant acute disease or chronic infection within the previous 7 days or axillary temperature ≥37.3℃ prior to vaccination in the present study;
17) The volunteer has any other factors which are unsuitable for participation in the clinical trial as judged by the investigators.

5.3 Exclusion Criteria for the Subsequent Vaccination

If any of the following 1)-3) occurs, it's forbidden to continue vaccination, but other study procedure can be continued according to the investigator's judgement; if the following 4) occurs, the it's up to the investigator to decide whether to vaccinate or not; if the following 5)-6) occurs, the vaccination could be postponed within the required time window.

1) Any newly confirmed or suspected autoimmune disease or immunodeficiency disorders;
2) Any serious adverse events related to vaccination in this study;
3) Severe allergic reactions after vaccination in this study;
4) Other reactions (e.g., severe pain, severe swelling, severe activity limitation, persistent high fever, etc.) or factors which are considered to have influence on the vaccination according to the investigator's judgement;
5) Various acute disease or acute exacerbation of chronic diseases by the time of vaccination;
6) Axillary temperature ≥37.3℃.

5.4 Lifestyle Considerations

A. Restrictions relating to prohibited and restricted therapy during the study are described in Section 6.7.

B. Participants must agree to follow all requirements that must be met during the study as noted in the inclusion and exclusion criteria.

5.5 Screening Failures

Screen failures are defined as participants who consent to participate in the clinical study but not subsequently randomly received study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria.

6. STUDY VACCINATION AND CONCOMITANT THERAPY

6.1 Investigational Vaccines Administered

Arm Name	**Arm 1/Arm2/Arm 3**
Intervention name	Poliomyelitis Vaccine (Vero cells), Inactivated, Sabin Strains (hereinafter as "sIPV")
Type	Vaccine
Dose Formulation	Pre-filled syringe or vial with an extractable volume of 0.5 ml
Unit Dose Strengths	15DU/45DU/45DU for serotype Ⅰ, Ⅱ, Ⅲ per 0.5ml
Route of Administration	Intramuscular injection (preferably in anterolateral thigh muscles)
Use	Experimental
Investigational Medical product (IMP)	Yes
Sourcing	Provided by Sinovac
Packaging and Labeling	The study vaccines will be packed in individual participant kits, one kit will be used only by one participant. Each kit will contain single-use syringe or a vial.

6.2 Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

- The study vaccines should be stored and transported protected from light at approximately 2°C to 8°C. If there is a break in the cold chain, a report should be sent to the sponsor to determine whether the affected supplies can be used or will be replaced. All the affected study vaccine must be quarantined until further instruction from the sponsor is received.
- Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention.
- Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (e.g., physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

Accountability

The investigator or designee is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). All study interventions will be accounted for using a study intervention accountability form/record.

Unused study interventions must be available for verification by the sponsor's site monitor during on-site monitoring visits. Unused study interventions will be destroyed on-site and documented on the Investigational Product (IP) accountability form.

6.3 Measures to Minimize Bias: Randomization and Blinding

Randomization

The enrolled participants will be randomly separated into four groups (i.e., the co-administration group 1, co-administration group 2, staggered administration group 1 and staggered administration group 2) at a 1:1:1:1 ratio. Stratified Blocked Randomization will be carried out, taking the study site as a stratification factor. The independent randomization statistician will use SAS 9.4 software or later versions to generate a randomization code list. In order to minimize the probability of relevant persons being informed of the group, the paper randomization card with numbers will be used. For each eligible participant, after enrollment, the grouping information will be revealed, including the name of the vaccine and the site of vaccination.

Blinding

This study adopted an open-labelled design, it would not be possible to blind the participant group. However, during blood collection, it should be guaranteed the Phlebotomist/Study Nurse/Medical Technologist are not aware of the participant group to reduce bias. In addition, lab personnel will be completely blind during the laboratory assessment as each sample will be labelled with unique ID code without grouping information.

6.4 Study Treatment Compliance

Study interventions will be administered by the investigator or designee, and the date and time of vaccine administration and the injection location will be recorded in the eCRF.

The study site is responsible for ensuring that participants comply with the study windows allowed. If a participant missed a visit, every effort should be made to contact the participant and complete a visit within the defined visit window. If a participant does not complete a visit within the time window, that visit will be classified as a missed visit and the participant will continue with subsequent scheduled study visit. All safety requirements of the missed visit will be captured and included in the subsequent visit.

6.5 Dose Modification

Not applicable.

6.6 Treatment of Overdose

For this study, any dose of the study vaccines greater than the assigned dose will be considered as overdose. The sponsor does not recommend specific treatment for an overdose.

In the event of a known overdose, the investigator should:

- Contact the medical monitor immediately.
- Closely monitor the participant for AE/SAE.
- Document the quantity of the excess dose in the source document.
- Any overdose will be tracked as protocol deviations and reported to the IRB/IEC and Sponsor.

6.7 Concomitant Medications and Therapies

➢ Permitted During the Study

- If an AE occurs during the study period, necessary drug therapy and medical treatment are allowed;
- If severe allergic reaction or life-threatening reaction occur, first aid measures should be taken immediately;
- The investigator should record detailed information on any concomitant medicine during the study, including name, doses, duration, etc.
- Participants will not be prohibited from receiving vaccine for an emergency medical indication, such as rabies;
- Administration of any vaccines other than the study vaccine during the study should be recorded in detail, including name, dosage and usage, date, etc.

➢ Prohibited During the Study

- Participants are prohibited to receive vaccines other than the study vaccine throughout the study, except for an emergency medical indication as abovementioned;
- Refer to Section 5.2 for further details of prohibited therapy.

7. DELAY/DISCONTINUATION OF STUDY VACCINATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Participants Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request. A participant will be withdrawn from the study for any of the following reasons:

- Guardian's decision;
- An intolerant AE, whether related to the investigational product or not;
- The physical condition of the participant is not suitable for the study;
- Any abnormal clinical symptoms, the causality to the investigational product will be decided by the investigator, who will decide the participant's withdrawal;
- The investigator decision for any other reasons.

The investigator or designee will attempt to contact those guardians of participants who do not return for scheduled visits or follow-up. The reason for withdrawal will be recorded in the eCRF. If withdrawal is due to an AE after vaccination, appropriate follow-up visits or medical care will be arranged, with the agreement of the participant, until the AE has resolved. In any circumstance, every effort should be made to document participant outcome, if possible. If a participant withdraws from the study, data and blood samples collected before their withdrawal will still be used in the analysis. Storage of blood will continue unless the participant specifically requests otherwise.

7.2 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant's guardians and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts (e.g., dates of telephone calls and registered letters) should be documented in the participant's medical record. A participant should not be considered lost to follow-up until these efforts have been made.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

7.3 Study Vaccination Pausing Rules

A committee consisting of the representatives of the sponsor and collaboration partners, along with the principal investigator will monitor safety profiles during the study, including the study vaccination pausing rules.

The occurrence of any of the following events will lead to a pause in further study vaccination:

- More than 15% of the participants have grade 3 or severe adverse reactions, including local reactions, systemic reactions, and vital signs.

Based on the pausing criteria, the sponsor's medical monitor or designee then decides whether a study pause is warranted.

7.4 Study Early Termination Rules

The occurrence of any of the following situation will lead to early termination of the study:

- After the pausing of the clinical trial, the investigator and sponsor will jointly discuss and decide whether to terminate the trial;
- The sponsor requests complete termination of the trial and explains the reason;
- The ethics committee requests complete termination of the trial and explained the reason;
- The regulatory agency requests complete termination of the trial and explained the reason.

8. STUDY ASSESSMENTS AND PROCEDURES

Guardians of potential participants should sign an informed consent form (ICF) before performing any study specific procedures. Participants will undergo study procedures at the time points specified in the Schedule of Activities (SoA). Protocol waivers or exemptions are not allowed.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigators will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure the protocol-required tests and procedures are completed as described. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that processed as possible. In addition, the study team must be informed of these incidents in a timely manner.

All needed materials for collection, handling, storage, and shipment of samples will be provided to the investigator site prior to initiation of the study.

8.1 Immunogenicity Assessments

8.1.1 Blood Collection and Laboratory Testing

Blood samples from all participants will be obtained for humoral immunogenicity testing at the visits specified in the SoA. All the serum samples for the immunogenicity assay will be sent to the assigned laboratory for analysis. In terms of antibody testing, the laboratory method and definition of immune response are summarized in the following table:

Table 5 Laboratory Testing Method and Definition of Immune Response

Antigens	Method	Category of antibody	Cutoff	Definition of immune response
Poliovirus type 1-3	Micro-neutralization	Neutralizing antibody	≥1:8**	Seroconversion: pre-vaccination titer <1:8 and post vaccination titer ≥1:8, or 4-fold titer increase in case that pre-vaccination titer ≥1:8
				Sero-protection:≥1:8
DT	ELISA	IgG	≥0.1 IU/ml**	Sero-protection:≥0.1 IU/ml
TT	ELISA	IgG	≥0.1 IU/ml**	Sero-protection:≥0.1 IU/ml
PT	ELISA	IgG	≥20EU/ml	Seropositivity:≥20EU/ml
FHA	ELISA	IgG	≥20EU/ml	Seropositivity:≥20EU/ml
PRN	ELISA	IgG	≥20EU/ml	Seropositivity:≥20EU/ml
HepB	ELISA	IgG	10 mIU/ml**	Sero-protection:≥10 mIU/ml
Hib	ELISA	IgG	0.15μg/mL**	Sero-protection:≥0.15μg/mL
Pneumococcal*	ELISA	IgG	0.35μg/mL**	Sero-protection:≥0.35μg/mL

*The following serotypes will be detected in this study: 1, 5, 6B, 14, 19F

**Cut-off accepted as indicative of protection.

8.1.2 Sample Management

Serum Separator tube (SST) should be used to collected the blood samples.

The blood samples collected on site for the purpose of antibody testing shall be sent to the local laboratory in time to handover with lab personnel. In this local lab, the serum will be separated from blood samples based on standard laboratory procedure and placed into two cyro tubes (no less than 1ml for serum tube A for testing, and tube B for backup). After separation, serum should be stored at -20℃ or below until delivery to testing lab. The tube A serum will be shipped to testing lab of **Sinovac Biotech Co., Ltd.** to determine the antibody levels. Records should be kept for sample shipment sample handover, serum separation and sample storage. The shipment cost will be borne by the sponsor. The tube B serum shall be kept by the local lab until the official antibody testing report is issued, and then be destroyed as medical waste with the consent of the sponsor.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues. Any clinically relevant changes occurring during the study must be recorded on the AE section of the eCRF.

8.3 Physical Examinations

Physical examination will be performed on the vaccination day by the investigator or designated medically trained clinician. Any clinically relevant abnormalities or changes in severity observed during the review of body systems should be documented in the eCRF.

8.4 Vital Signs

Vital signs including height, weight, body temperature, heart rate and breathing rate will be measured during the physical examination.

For all participants, the immediate reactions for 30 minutes on site after the last injection in each vaccination visit will be observed on site. Upon the time of completion of the 30-minutes observation, body temperature will be measured for each participant. Guardians of participants will utilize the diary card to record solicited adverse events from the time of vaccination for 7 days post-vaccination of each dose. In this solicited period, guardians of participants are required to measure the participants' body temperature every day and recorded the daily temperature in the diary card.

From the time of the first vaccination and 28 days post-vaccination of the last dose, unsolicited adverse events and any SAEs will be required to recorded in the diary card. In the non-solicited period, for

participants with fevers, body temperature should be measured daily from the fever's onset untilled recovered, and the fever severity determined based on the highest temperature should be recorded in the diary card.

Body temperature is preferably measured via axillary temperature.

8.5 AEs, SAEs, and Other Safety Reporting

8.5.1 Definitions

The definitions of AEs follow the Good Clinical Practice (GCP) recommendations: E2A Guide on Clinical Safety Data Management of the International Conference on Harmonization (ICH) [12].

Adverse Event (AE)

In this study, an AE will be defined as any untoward medical occurrence that occurs in a participant who is vaccinated and that does not necessarily have a causal relationship with the vaccine's administration. Therefore, an AE may be any unfavorable and unintended sign, symptom, or disease (including an abnormal finding in a laboratory test), temporally associated with the vaccination product, regardless of whether or not it is considered to be related to the vaccination product.

Solicited/Unsolicited adverse events

In this study, the solicited period is from Day 0 to Day 7 after each vaccination. The unsolicited period is from Day 8 to Day 28 after vaccination for co-administration group, Day 8 to Day 14 after vaccination (Day 8 to day 28 after the last dose) for staggered administration group. Solicited AEs are used to assess the reactogenicity of the study vaccine and are predefined local (at injection site) and systemic events for which the participant is specifically questioned. Unsolicited AEs refer to the unsolicited symptoms occur within the solicited period, or all symptoms occur within the non-solicitation period. Unsolicited AEs are all AEs for which the participant is not specially questioned.

Solicited local (injection site) symptoms:

Redness, swelling, rashes, induration, and pruritus

Solicited systemic symptoms (including vital signs):

Fever (axillary temperature will be measured), acute allergic reaction, diarrhea, decreased appetite, irritability, decreased activity

Serious Adverse Events (SAEs)

A SAE is an AE that results in any of the following outcomes, whether or not it is considered to be related to the study intervention.

- Death.
- Life-threatening event (i.e., means that the subject is at risk of death at the time of the onset of the adverse event, rather than an adverse event that could result in death if the condition progresses to a more serious level over time.).
- Hospitalization or prolongation of existing hospitalization, regardless of length of stay, even if it is a precautionary measure for continued observation. Hospitalization (including inpatient or outpatient hospitalization for an elective procedure) for a pre-existing condition that has not worsened unexpectedly does not constitute a serious AE.
- Persistent or significant disability or incapacity (i.e., report if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.).
- Congenital anomaly or birth defect.

- An important medical event (that may not cause death, be life threatening, or require hospitalization) that may, based upon appropriate medical judgment, jeopardize the volunteer and/or require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic reaction requiring intensive treatment in an emergency room or clinic, blood dyscrasias, or convulsions that do not result in inpatient hospitalization.

Adverse Reactions (ARs)

Any harmful or undesired reactions to humans that may be associated with the experimental vaccine that occur in the clinical trial. There is at least a reasonable probability that a causal relationship between the experimental vaccine and the adverse event cannot be ruled out as a correlation.

Serious Adverse Reaction (SAR)

An AE that is both serious and, in the opinion of the reporting investigator or sponsor, believed to be possibly, probably, or definitely due to an investigational product or any other study treatments, based on the information provided.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is defined as a SAR, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the investigator's brochure (IB). The information about the medicinal product can be check the IB-chapter RSI.

8.5.2 Outcomes of Adverse Events

The outcome of AEs will be categorized as follows:

1) recovered/resolved;

2) recovering/resolving;

3) not recovered/not resolved;

4) recovered with sequelae;

5) fatal;

6) unknown.

8.5.3 Causality

According to the classification adapted from the “Uppsala Monitoring Centre” of the World Health Organization (WHO-UMC), the classification of casual relationship of AEs with the investigation product is described in Table 6 [13].

Table 6 Classification of Causal Relationship of Adverse Events with the Investigational Product

Reasonable causal relationship			**Causal relationship NOT reasonable**	
Adverse Event considered as Adverse Reaction			Adverse Event cannot be considered as Adverse Reaction.	
Definite	**Probable**	**Possible**	**Unlikely**	**Not related**
Event or change (abnormal value) in a laboratory test, with plausible temporal relationship with regarding the administration of the intervention;	A clinical event, including a change (abnormal value) in a laboratory test, with a reasonable temporal relationship regarding the administration of the intervention;	A clinical event, including a change (abnormal value) in a laboratory test, with a reasonable temporal relationship regarding the administration of the intervention;	A clinical event, including a change (abnormal value) in a laboratory test, which, due to the time of the administration of the intervention, gives cause to an unlikely, but not impossible, relationship;	A clinical event, including a change (abnormal value) in a laboratory test, which, due to the time of the administration of the intervention, gives cause to a non-existing relationship;

Reasonable causal relationship			Causal relationship NOT reasonable	
Adverse Event considered as Adverse Reaction			Adverse Event cannot be considered as Adverse Reaction.	
Definite	**Probable**	**Possible**	**Unlikely**	**Not related**
It cannot be explained by a concurrent disease or another intervention or medication; The event is defined pharmacologically or phenomenologically (i.e., a specific and objective disorder or a pharmacologically recognized phenomenon);	It is unlikely to be caused by a concomitant illness or by another intervention or medication;	It can also be explained by concurrent disease or other interventions or medications;	Another disease or another drug provide a plausible explanation	Another disease or another drug provide a plausible explanation
The response to discontinuation or withdrawal is plausible (pharmacologically, pathologically);	The response to discontinuation or withdrawal is clinically reasonable;	Lack of information or lack of clarity about withdrawal or treatment discontinuation		
Re-exposure is satisfactory, if required	Re-exposure is not required			

8.5.4 Grading Scale for Adverse Events

The severity of solicited symptoms will be graded through a numeric scale of 1 to 4, created based on the "Guidelines for grading scale of adverse events in vaccine clinical trials, 2019" of the NMPA, China [14].

Table 7 Grading of the Injection-site (Local) Solicited Symptoms

Adverse events	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potential Life-threatening (Grade 4)
Redness/Rash /Induration/ Swelling	Diameter＜2.5cm	Diameter ≥ 2.5 cm and area < 50% of the inoculated limb (referring to the anatomical limb where the vaccination site is located, such as the upper arm or thigh	Area≥50% of inoculated limb or ulceration or secondary infection or phlebitis or wound drainage	Abscess, exfoliative dermatitis, dermal or deep tissue necrosis
Pruritus	Pruritus at injection site, relieved without treatment or within 48 hours after treatment	Pruritus at injection site that did not relieve within 48 hours after treatment	Affecting daily life	NA

*The diameters should be directly measured for grading assessment of rash and induration, and the progress change of the measurement results should also be recorded.

The maximum measurement diameter or area should be used for the grading of induration, swelling, rash and redness.

The evaluation and grading should be based on the function level and actual measurement results, and the index with higher grade should be selected.

Table 8 Grading of the Non-injection Site (Systemic) Solicited Symptoms and Vital Signs

Adverse events	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potential Life-threatening (Grade 4)
Acute allergic Reaction*	Localized urticaria (blisters) not	Local urticaria requiring treatment or mild angioedema not requiring treatment	Extensive urticaria or angioedema requiring treatment or mild bronchospasm	Anaphylactic shock or life-threatening bronchospasm or laryngeal edema

Adverse events	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potential Life-threatening (Grade 4)
	requiring treatment			
Diarrhea	Mild or transient, 3 to 4 times a day, abnormal stool texture, or mild diarrhea lasting less than 1 week	Moderate or persistent, 5 to 7 times/day, abnormal stool texture, or diarrhea for > 1 week	>7 times/day, abnormal stool texture, or bloody diarrhea, orthostatic hypotension, electrolyte imbalance, requiring intravenous fluids >2L	Hypotensive shock requiring hospitalization
Decreased appetite	Decreased appetite, but not reduced food intake	Decreased appetite, decreased food intake, but no significant weight loss	Decreased appetite and significant weight loss	Requiring intervention (e.g., gastric tube feeding, parenteral nutrition)
Irritability	Mild irritability	Moderate Irritability	Unable to comfort	NA
Decreased activity	Mild inhibition	Drowsiness	Low response	NA
Fever (Axillary Temperature)	37.5～<38.0℃	38.0～<39.5℃	≥39.5℃	≥39.5℃, lasting more than 5 days

*Refers to type I hypersensitivity.

The severity of the unsolicited symptoms will be classified through a numeric scale of 1 to 5, which was created based on the "Guidelines for grading scale of adverse events in vaccine clinical trials, 2019" of the NMPA, China.

Table 9 Severity Grading Criteria for Unsolicited Symptoms

GRADE 1 (Mild)	Transient (< 48 hours) or mild discomfort; no medical intervention/therapy required
GRADE 2 (Moderate)	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3 (Severe)	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
GRADE 4 (Life-threatening)	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
GRADE 5	Death

8.5.5 Safety Follow-up

All participants will be observed for 30 minutes on site after the last injection in each vaccination visit. Diary cards will be distributed to guardians of participants to record AEs from the time of first vaccination to 28 days after last vaccination. Investigators should explain the judgment, measurement, recording, precautions and reporting method of AEs. Solicited local and systemic AE observation is carried out within 7 days after vaccination. Guardians of participants are required to closely observe participants' symptoms and temperature and fill the diary every day.

The investigator and designees verify all the AEs reported in the diary card on the 14th day after vaccination through face-to-face interviews or telephone calls; The investigator and designees verify the AEs on the 28th day after vaccination through face-to-face interview (only applicable for co-administration group and last dose of staggered administration groups).

The participants are informed to record the AEs at any time. Acute allergic reactions, AEs with severity of grade 3 and above, and SAEs should be reported to the investigator in a timely manner. SAEs will be collected from the time of first vaccination to 28 days after the last vaccination. After the investigators are informed, they should conduct investigation, verification and follow-up until the AE has resolved, and finally complete the detailed investigation and follow-up records, which should include the following contents:

- Participant's identified information
- Description of AE's start time and end time of AEs
- Seriousness of AEs

- Severity level
- Relationship to vaccination
- Laboratory testing results
- Treatment measures
- Outcome of the AEs

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize. Follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illness, must be provided.

8.5.6 Regulatory Reporting Requirements for Serious Adverse Events

a. The investigator should immediately take measures and make records after he/she is informed of SAE.

b. The investigator should report to the sponsor within 24 hours (or as the local regulation indicates), after the SAE is informed and submit the subsequent report. In case of Suspected Unexpected Serious Adverse Drug Reactions (SUSAR), the investigator should report to the local regulatory authority and IRB/IEC within 7 working days.

c. The organizations to be reported can be adjusted according to the current laws and regulations and the requirements of local regulatory authorities and IRB/IEC.

d. When the sponsor receives information on SAE from any source, an analysis and evaluation should be conducted, including the severity, relevance to the investigational vaccine, and whether it is an unexpected event. If sponsor has query basic on the analysis and evaluation about the SAE form, sponsor should send to query form to investigator as soon as possible. And investigator should send the feedback about query as soon as possible since the day he/she received the query form.

e. During clinical trial, the sponsor should expeditiously report the SUSARs which are considered definitely or suspiciously related to the investigational drug in the manner of case safety report, according to the Standards for Expedited Reporting of the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (ICH E2A).

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

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

For details, please refer to the study specific Safety Management Plan:

The sponsor representative will advise the Investigator/study site personnel how to proceed.The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the appropriate project contact for SAE receipt is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met. The investigator according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the IRB/IEC.

Contact for Reporting SAE at the Sponsor

Regular contact way:

For 24-hour Contact: The official email address of PV center:

kxpv@sinovac.com

Please Do copy the relevant stuff **YANJUN FU** as well: fuyj8305@sinovac.com. You can also communicate SAE reporting via the cell phone.

Yanjun Fu (Primary Contact Person): Tel: +86-15137100393;

For any urgent:

When investigators/sub-I/CRA etc. cannot contact Sponsor PV, please contact the backup person via their phone or e-mail.

Jing Tian (Backup)

Tel.: +86-15630590699;

Email: tianj8194@sinovac.com

8.5.7 Safety Oversight

An independent DSMB will be constituted of experts from various fields of medicine who are external to sponsor's organization. The DSMB will oversee the study in terms of safety data as per DSMB charter. DSMB will have the authority to halt or terminate the study in case of any safety signals.

The independent DSMB is applicable both for Pakistan and Bangladesh.

8.6 Study Procedures

8.6.1 Co-administration group (group C1/C2)

Screening for mothers (~Day 0)

Screening could be performed before the infant enrollment, before the infants screening or coincide with the infants screening:

Procedures:

- Preliminary notification and recruitment;
- Signed informed consent (for mothers);
- Perform HIV, syphilis, hepatitis A, hepatitis B, hepatitis C infection testing for mothers or collect the existing relevant testing results.

Screening for infants (Day -14~Day 0)

Screening could be performed within 14 days prior to the **visit 1 (Vaccination)**

Procedures:

- Participant enrollment;
- Signed informed consent (for participants);
- Obtain the participant's demography (including full date of birth, sex);
- Perform SARS-CoV-2 rapid antigen testing using nasopharyngeal swab;
- Assess all inclusion/exclusion criteria from information provided from the participants.

Visit 1-First Vaccination (Day 0)

The following procedures must be completed after the site investigator or designee obtained informed consent from participants. Baseline data will be obtained at Visit 1. Participants should be randomized and vaccinated as soon as possible after determination of eligibility. All inclusion/exclusion criteria must be assessed from data obtained within the visit. Information, including demography, medical history, physical examination, etc., will be recorded in the eCRFs.

If screening is performed on the day of **Vaccination** (recommended), Screening and Visit 1 will coincide

on Visit 1 (Day 0).

Procedures:

- Signed informed consent *(for participants, could be conducted at **Screening Visit**)*;
- Obtain the participant's demography (including full date of birth, sex) *(could be conducted at **Screening Visit**)*;
- Physical examination, vital signs including height, weight, body temperature (axillary temperature), heart rate and breathing rate will be measured and record any findings in the source documents and eCRF;
- Information on concomitant medication will be gathered;
- Check inclusion and exclusion criteria;
- Obtain the participant's randomization number;
- Baseline blood samples will be collected before vaccination;
- Site staff members(s) will dispense/administer the study intervention;
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any immediate or acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the eCRF, and on an SAE form as applicable;
- Diary Card will be provided to participants, and confirm instructions on diary card completion;
- Ask the guardians of participants to contact the site staff or investigator if a medically attended event (e.g., doctor's visit, emergency room visit) or hospitalization occurs;
- Schedule an appointment for the participant to return for the next study visit;
- Complete the source documents and eCRFs.

Visit 2- Safety-V1+14 (+3) days

- Verify the AEs, and the completeness of the Diary Card; this visit will be conducted by telephone, remotely;
- Verify concomitant vaccines (non-study vaccinations) and/or concomitant medicine;
- Verify details of any of the prohibited medications received by the participant;
- Ask the participant to contact the site staff or investigator if a medically attended event (e.g., doctor's visit, emergency room visit) or hospitalization occurs;
- Schedule an appointment for the participant to return for the next study visit.

Visit 3- Second vaccination-V1+28 (+7) days

- Review the AEs of participant's diary card data through a face-to-face interview;
- Collect stop dates of any AEs ongoing on the last day that the diary card was completed and record stop dates in the eCRF if required;
- Record concomitant vaccines (non-study vaccinations) and/or concomitant medicine;
- Collect the Diary Card from participants;
- *The participant's axillary temperature will be measured;*
- Check the vaccination discontinue/postpone rules;
- Site staff members(s) will dispense/administer the study intervention;
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any immediate or acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the eCRF, and on an SAE form as applicable;
- New Diary Card will be provided to participants, and confirm instructions on diary card completion;
- Ask the guardians of participants to contact the site staff or investigator if a medically attended event (e.g., doctor's visit, emergency room visit) or hospitalization occurs;
- Schedule an appointment for the participant to return for the next study visit;
- Complete the source documents and eCRFs.

Visit 4- Safety-V3+14 (+3) days

- Verify the AEs, and the completeness of the Diary Card; this visit will be conducted by telephone, remotely;
- Verify concomitant vaccines (non-study vaccinations) and/or concomitant medicine;
- Verify details of any of the prohibited medications received by the participant;
- Ask the participant to contact the site staff or investigator if a medically attended event (e.g., doctor's visit, emergency room visit) or hospitalization occurs;
- Schedule an appointment for the participant to return for the next study visit.

Visit 5- Third Vaccination-V3+28 (+7) days

- Review the AEs of participant's diary card data through a face-to-face interview;
- Collect stop dates of any AEs ongoing on the last day that the diary card was completed and record stop dates in the eCRF if required;
- Record concomitant vaccines (non-study vaccinations) and/or concomitant medicine;
- Collect the Diary Card from participants;
- *The participant's axillary temperature will be measured;*
- Check the vaccination discontinue/postpone rules;
- Site staff members(s) will dispense/administer the study intervention;
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any immediate or acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the eCRF, and on an SAE form as applicable;
- New Diary Card will be provided to participants, and confirm instructions on diary card completion;
- Ask the guardians of participants to contact the site staff or investigator if a medically attended event (e.g., doctor's visit, emergency room visit) or hospitalization occurs;
- Schedule an appointment for the participant to return for the next study visit;
- Complete the source documents and eCRFs.

Visit 6-Safety-V5+14 (+3) days

- Verify the AEs, and the completeness of the Diary Card; this visit will be conducted by telephone, remotely;
- Verify concomitant vaccines (non-study vaccinations) and/or concomitant medicine;
- Verify details of any of the prohibited medications received by the participant;
- Ask the participant to contact the site staff or investigator if a medically attended event (e.g., doctor's visit, emergency room visit) or hospitalization occurs;
- Schedule an appointment for the participant to return for the next study visit.

Visit 7-Follow Up-V5+28 (+7) days

- Review the AEs of participant's diary card data through a face-to-face interview;
- Collect stop dates of any AEs ongoing on the last day that the diary card was completed and record stop dates in the eCRF if required;
- Record concomitant vaccines (non-study vaccinations) and/or concomitant medicine (including traditional Chinese medicine);
- Collect the Diary Card from participants;
- Blood samples will be collected;
- Complete the source documents and eCRFs.

8.6.2 Staggered administration group (group S1/S2)

Screening for mothers (~Day 0)

Screening could be performed before the infant enrollment, before the infants screening or coincide with the infants screening:

Procedures:

- Preliminary notification and recruitment;
- Signed informed consent (for mothers);
- Perform HIV, syphilis, hepatitis A, hepatitis B, hepatitis C infection testing for mothers or collect the existing relevant testing results.

Screening (Day -14~Day 0)

Screening could be performed within 14 days prior to the **visit 1 (Vaccination)**

Procedures:

- Preliminary notification, participant enrollment;
- Signed informed consent;
- Obtain the participant's demography (including full date of birth, sex);
- Perform SARS-CoV-2 rapid antigen testing using nasopharyngeal swab;
- Assess all inclusion/exclusion criteria from information provided from the participants.

Visit 1-1st Vaccination (Day 0)

The following procedures must be completed after the site investigator or designee obtained informed consent from participants. Baseline data will be obtained at Visit 1. Participants should be randomized and vaccinated as soon as possible after determination of eligibility. All inclusion/exclusion criteria must be assessed from data obtained within the visit. Information, including demography, medical history, physical examination, etc., will be recorded in the eCRFs.

If screening is performed on the day of **Vaccination** (recommended), Screening and Visit 1 will coincide on Visit 1 (Day 0).

Procedures:

- Signed informed consent *(could be conducted at **Screening Visit**)*;
- Obtain the participant's demography (including full date of birth, sex) *(could be conducted at **Screening Visit**)*;
- Physical examination, including height, weight, body temperature (axillary temperature), heart rate, and breathing rate etc. will be measured and record any findings in the source documents and eCRF;
- Information on concomitant medication will be gathered;
- Check inclusion and exclusion criteria;
- Obtain the participant's randomization number;
- Baseline blood samples will be collected before vaccination;
- Site staff members(s) will dispense/administer the study intervention;
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any immediate or acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the eCRF, and on an SAE form as applicable;
- Diary Card will be provided to participants, and confirm instructions on diary card completion;
- Ask the guardians of participants to contact the site staff or investigator if a medically attended event (e.g., doctor's visit, emergency room visit) or hospitalization occurs;
- Schedule an appointment for the participant to return for the next study visit;
- Complete the source documents and eCRFs.

Visit 2- 2nd vaccination-V1+14 (+3) days

- Review the AEs of participant's diary card data through a face-to-face interview;

- Collect stop dates of any AEs ongoing on the last day that the diary card was completed and record stop dates in the eCRF if required;
- Record concomitant vaccines (non-study vaccinations) and/or concomitant medicine;
- Collect the Diary Card from participants;
- *The participant's axillary temperature will be measured;*
- Check the vaccination discontinue/postpone rules;
- Site staff members(s) will dispense/administer the study intervention;
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any immediate or acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the eCRF, and on an SAE form as applicable;
- New Diary Card will be provided to participants, and confirm instructions on diary card completion;
- Ask the guardians of participants to contact the site staff or investigator if a medically attended event (e.g., doctor's visit, emergency room visit) or hospitalization occurs;
- Schedule an appointment for the participant to return for the next study visit;
- Complete the source documents and eCRFs.

Visit 3- 3rd vaccination-V2+14 (+3) days

- Review the AEs of participant's diary card data through a face-to-face interview;
- Collect stop dates of any AEs ongoing on the last day that the diary card was completed and record stop dates in the eCRF if required;
- Record concomitant vaccines (non-study vaccinations) and/or concomitant medicine;
- Collect the Diary Card from participants;
- *The participant's axillary temperature will be measured;*
- Check the vaccination discontinue/postpone rules;
- Site staff members(s) will dispense/administer the study intervention;
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any immediate or acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the eCRF, and on an SAE form as applicable;
- New Diary Card will be provided to participants, and confirm instructions on diary card completion;
- Ask the guardians of participants to contact the site staff or investigator if a medically attended event (e.g., doctor's visit, emergency room visit) or hospitalization occurs;
- Schedule an appointment for the participant to return for the next study visit;
- Complete the source documents and eCRFs.

Visit 4- 4th Vaccination-V3+14 (+3) days

- Review the AEs of participant's diary card data through a face-to-face interview;
- Collect stop dates of any AEs ongoing on the last day that the diary card was completed and record stop dates in the eCRF if required;
- Record concomitant vaccines (non-study vaccinations) and/or concomitant medicine;
- Collect the Diary Card from participants;
- *The participant's axillary temperature will be measured;*
- Check the vaccination discontinue/postpone rules;
- Site staff members(s) will dispense/administer the study intervention;
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any immediate or acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the eCRF, and on an SAE form as applicable;
- New Diary Card will be provided to participants, and confirm instructions on diary card completion;
- Ask the guardians of participants to contact the site staff or investigator if a medically attended event (e.g., doctor's visit, emergency room visit) or hospitalization occurs;

- Schedule an appointment for the participant to return for the next study visit;
- Complete the source documents and eCRFs.

Visit 5- 5th Vaccination-V4+14 (+3) days

- Review the AEs of participant's diary card data through a face-to-face interview;
- Collect stop dates of any AEs ongoing on the last day that the diary card was completed and record stop dates in the eCRF if required;
- Record concomitant vaccines (non-study vaccinations) and/or concomitant medicine;
- Collect the Diary Card from participants;
- *The participant's axillary temperature will be measured;*
- Check the vaccination discontinue/postpone rules;
- Site staff members(s) will dispense/administer the study intervention;
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any immediate or acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the eCRF, and on an SAE form as applicable;
- New Diary Card will be provided to participants, and confirm instructions on diary card completion;
- Ask the guardians of participants to contact the site staff or investigator if a medically attended event (e.g., doctor's visit, emergency room visit) or hospitalization occurs;
- Schedule an appointment for the participant to return for the next study visit;
- Complete the source documents and eCRFs.

Visit 6- 6th Vaccination-V5+14 (+3) days

- Review the AEs of the participant's diary card data through face-to-face interview;
- Collect stop dates of any AEs ongoing on the last day that the diary card was completed and record stop dates in the eCRF if required;
- Record concomitant vaccines (non-study vaccinations) and/or concomitant medicine;
- Collect the Diary Card from participants;
- *The participant's axillary temperature will be measured;*
- Check the vaccination discontinue/postpone rules;
- Site staff members(s) will dispense/administer the study intervention;
- Site staff must observe the participant for at least 30 minutes after study intervention administration for any immediate or acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the eCRF, and on an SAE form as applicable;
- New Diary Card will be provided to participants, and confirm instructions on diary card completion;
- Ask the guardians of participants to contact the site staff or investigator if a medically attended event (e.g., doctor's visit, emergency room visit) or hospitalization occurs;
- Schedule an appointment for the participant to return for the next study visit;
- Complete the source documents and eCRFs.

Visit 7- Follow up-V5+28 (+7) days

- Review the AEs of participant's diary card data through a face-to-face interview;
- Collect stop dates of any AEs ongoing on the last day that the diary card was completed and record stop dates in the eCRF if required;
- Record concomitant vaccines (non-study vaccinations) and/or concomitant medicine (including traditional Chinese medicine);
- Blood samples will be collected;
- Complete the source documents and eCRFs.

Visit 8- Follow up-V6+28 (+7) days

- Review the AEs of participant's diary card data through a face-to-face interview;
- Collect stop dates of any AEs ongoing on the last day that the diary card was completed and record stop dates in the eCRF if required;
- Record concomitant vaccines (non-study vaccinations) and/or concomitant medicine (including traditional Chinese medicine);
- Collect the Diary Card from participants;
- Complete the source documents and eCRFs.

9. STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

The sample size in this study is calculated based on the non-inferiority hypothesis of the immune response to sIPV, taking the combination vaccination group as the test group and staggered vaccination group as the control group. The sample size calculation parameters are as follows: 1) The seroconversion rate of the control group is estimated as 90% referring to the previous clinical data of sIPV; 2) The non-inferiority criterion is: the lower limit of 95% CI of the difference between groups (test group-control group) >-10%; 3) the allocation ratio between test group and control group for immunogenicity evaluation against either polio of three serotypes is 1:1; 4) the one-sided significance level is 0.025; 5) the overall statistical power (1-β) is 80%, with a corrected statistical power of 93.3% (1-β/3) for statistical test of each serotype. The sample size calculated using PASS 2022(V22.0.2) for each group is 233. Considering a dropout rate of approximately 15%, and a blood collection failure rate of approximately 10%, sample size of 360 is determined for each group.

9.2 Analysis Sets

Analysis sets for immunogenicity evaluation

Full analysis set (FAS), following the principle of intent to treat (ITT), including all subjects who are randomized, **complete at least one vaccination against the antigen to be evaluated**, and have the valid immunogenicity results before the first vaccination. The participants who are vaccinated erroneously will be analyzed for the immunogenicity evaluation as randomized according to the ITT principle.

Per-protocol set (PPS), a subset of FAS, including all the subjects who are eligible for this study according to the inclusion and exclusion criteria, and then randomized, complete full vaccination as protocol specified, and have valid immunogenicity results before and after the vaccination. Subjects who meet the following conditions will be excluded from PPS:

1) Those who has significant protocol deviations;
2) Those who are vaccinated with the wrong vaccine;
3) Use of protocol prohibited vaccines or drugs
- Other investigational or unlicensed products (drugs or vaccines)
- Long-term use (lasting more than 14 days) of immunosuppressive or other immunomodulatory drugs (inhaled or topical steroids are allowed)
- Immunoglobulin and/or blood preparations

4) Newly diagnosed autoimmune disease, including human immunodeficiency virus (HIV) infection
5) Other situations affecting the evaluation of vaccine immunogenicity

Analysis sets for safety evaluation

Safety Set (SS): All randomized subjects who completed at least one dose vaccination will be included in the safety set. Subjects who are vaccinated with the wrong vaccine will be analyzed for safety evaluation as treated according to ASaT principle (All Subjects as Treated).

9.3 Statistical Methods

9.3.1 General Considerations

Unless otherwise stated, summary statistics including the number of participants, mean, standard deviation, median, minimum and maximum, will be presented for all continuous variables. For categorical variables, per category, the absolute counts (n) and percentages (%) of participants with data, and if appropriate, the number of patients with missing data, will be prepared.

All statistical analysis will be performed by using SAS 9.4 or later version.

9.3.2 Disposition of Participants

A summary of the analysis sets includes the number and percentage of participants for the following categories: participants screened, enrolled, numbers of subjects who complete each dose of vaccination, participants in each analysis set. The reasons for withdrawal for the participants who discontinue the study will be summarized as well. All results will be presented for each group.

A participant-level data listing of study completion information including the reason for screened failure and study discontinuation will be presented.

9.3.3 Demographic and Baseline Characteristics

Descriptive statistics of demographics (sex, age, race) and baseline characteristics (height, weight) will be presented.

9.3.4 Immunogenicity Analysis

Analysis for immunogenicity against Polio

Seroconversion rate and sero-protection rate on day 28 after the last vaccination of sIPV will be estimated, and the corresponding 95% CIs will be derived from Clopper Pearson method.

The difference of seroconversion rates between co-administration group and staggered administration group will be compared using Cochran-Mantel-Haenszel-χ^2 (CMH-χ^2) test stratified by study site . The CMH-χ^2 method will be used to calculate the rate difference between (group C1 and group S1) and 95% CIs. Non-inferiority will be concluded if the lower limit of the 95% CI of rate difference (co-administration group-staggered administration group) >-10%.

The descriptive statistics, including GMT and GMFR and corresponding 95% CIs are employed to summarize the immunogenicity data. The t-tests after log transformation will be used to compare two groups. The GMT ratio between two groups and the corresponding 95%CIs will be estimated as well.

Analysis for immunogenicity against Diphtheria, Tetanus, Pertussis

Seropositivity/sero-protection rate against Diphtheria, Tetanus and Pertussis on day 28 after the last vaccination of DTP-HepB-Hib vaccine will be estimated and the corresponding 95% CIs will be derived from Clopper Pearson method. The difference of seropositivity/sero-protection rate between co-administration group and staggered administration group will be Cochran-Mantel-Haenszel-χ^2 (CMH-χ^2) test stratified by study site . The CMH-χ^2 method will be used to calculate the rate difference between (group C2 and group S2) and 95% CIs. Non-inferiority will be concluded if the lower limit of the 95% CI of rate difference (co-administration group-staggered administration group) >-10%.

The descriptive statistics, including GMC and GMFR and corresponding 95% CIs are employed to summarize the immunogenicity data. The t-tests after log transformation will be used to compare two groups. The GMC ratio of two groups and the corresponding 95%CIs will be estimated as well.

Analysis for immunogenicity against HepB, Hib, Pneumococcal

Sero-protection rates at day 28 after the last vaccination will be estimated and the corresponding 95% CIs will be derived from Clopper Pearson method. The Chi-square tests/Fisher Exact test will be used

to compare the sero-protection rates between two groups.

The descriptive statistics including GMC and GMFR and corresponding 95%CIs are employed to summarize the immunogenicity data. The t-tests after log transformation will be used to compare two groups.

9.3.5 Safety Analysis

Treatment-emergent adverse events (TEAEs) are defined as any AEs that occurred on or after vaccination date or worsening of existing events. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 25.0 or later version.

TEAEs will be summarized by frequency and percentage, and tabulated by system organ class (SOC) and preferred term (PT). Serious adverse events (SAEs) will also be summarized.

The following summary tables and patient level listings will be presented for TEAE data:

- Overall Summary of Adverse Events
- TEAEs by SOC and PT
- TEAEs by SOC and PT, Related to Vaccination
- TEAEs by SOC and PT, Unrelated to Vaccination
- TEAEs by SOC, PT and Severity
- TEAEs by SOC, PT and Severity, Related to Vaccination
- TEAEs by SOC, PT and Severity, Unrelated to Vaccination
- TESAEs by SOC and PT
- TESAEs by SOC and PT, Related to Vaccination
- TESAEs by SOC and PT, Unrelated to Vaccination
- Listing of SAEs
- Listing of Related SAEs
- Listing of AEs

9.4 Subgroup Analysis

No subgroup analysis will be conducted in this study.

9.5 Multiplicity

The primary hypothesis will be achieved only when the non-inferiority of seroconversion rates against all poliovirus type 1, 2 and 3 are all concluded. Thus, the family-wise type Ⅰ error will not be inflated.

9.6 Method of Missing Data Handling

In immunogenicity analysis, the missing values in post-vaccination antibody data will be imputed by using the Last Observation Carried Forward (LOCF) method. The details in missing data handling will be descried in the statistical analysis plan (SAP).

10. DATA COLLECTION AND MANAGEMENT

10.1 Data Collection

eCRFs will be used for recording data for each participant enrolled in the study. The site investigators are responsible to ensure the accuracy, completeness, legibility, and timeliness of the data captured in eCRF. Data captured in the eCRF derived from source documents and should remain consistent with those source documents. In case of discrepancies, data will be clarified and corrected.

Study staff will extract all data collected in source documents and workbooks for entry into the eCRF. An Electronic Data Capture (EDC) system is a software that will be used to store the participant's data collected in this study. The EDC is a web-based application to capture data for clinical research and

create databases and projects. It is highly secure and intuitive to use. A unique username issued by clinical data management provider and an associated password will be required to log into the EDC system to access study data. This server is 24hrs online, fault tolerant and automatic back-up system. There is a logging system for collecting every event/action with logs recorded in the system. At the user end, we have daily, weekly, and monthly back-up system to back-up all the data in a local computer. The data will be stored in a main server found in China. Data can be downloaded from the server in SAS/CSV/PDF format as per project need. The entire data collection and handling will be monitored to ensure database integrity. Edit checks will be programmed in the EDC to identify data entry errors during transcription, including range and consistency checks wherever applicable.

Final data cleaning, data freezing, and data analysis will be performed by sponsor/vendor. All data will be stored in a secure database.

10.2 Safety Follow-up Method

AEs/SAEs will also be followed up at site visits and subject diaries will be given to all participants before each dose of vaccination. Diary cards will be distributed to guardians of participants to record AEs from the time of first vaccination to 28 days after last vaccination. Diary cards will be delivered by the study staff after the vaccination on V1 (day 0). The diary card will be filled in every day from the next day after each vaccination until the 7th day after the booster vaccination. From the 8th day until the 14th day after each dose (until 28th day for co-administration group and last dose of staggered administration group), AEs (if occurred) will be recorded by the guardians of participants on the diary card.

For the concomitant vaccination group: on the 14th day after each vaccination, study staff will call guardians of participants to verify the completeness of the diary card; on the 28th day after each vaccination, study staff will make a face-to-face interview to the guardians of participants with the diary card brought back, to check the completeness of the diary card.

For the staggered vaccination groups: on the 14th day after each vaccination and 28th day after last vaccination, study staff will make a face-to-face interview to the guardians of participants with the diary card brought back, to check the completeness of the diary card.

10.3 Study Records Retention

The site investigators (SI) will retain all study records that support eCRFs for this study (i.e., ICFs, source documents, investigational product dispensing records) required by sponsor and by the applicable regulations in a secure and safe facility. The SI will consult sponsor/representative before disposal of any study records and will notify the sponsor of any change in the location, disposition, or custody of the study files. These documents should be retained for at least 5 years after the study completion.

10.4 Publication and Data Sharing

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

11. QUALITY ASSURANCE

11.1 General Consideration

Quality Assurance (QA) oversight will be implemented at all stages of the trial process per ICH E6 (R2) section 5.0 and/or local government GCP requirements.

Quality Control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

The site will also develop routine operational checks to verify that critical protocol requirements and procedures are executed correctly and completely at the time the work is being performed.

The investigational site will provide direct access to all study related documents, source data/documents,

and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

11.2 Study Monitoring

The contract research organization (CRO), on half of the Sponsor of this study, is responsible for ensuring that the study is conducted in accordance with ICH GCP and regulatory requirements. For this purpose, monitors will provide remote monitoring for this study. A site initiation visit will be conducted prior to beginning the study, and monitoring will be conducted an initiation, during and at closeout of the study. During the course of the study monitors will visit (virtual visit permissible) the clinical site at intervals to verify compliance to the protocol; completeness, accuracy, and consistency of the data and study product accountability; and adherence to ICH GCP and applicable regulations. As needed and when appropriate, the monitors will also provide clarification and additional training to help the site resolve issues identified during the monitoring visit.

Investigators and/or their study staff will be trained on the study protocol and all applicable study procedures prior to study initiation.

Study progress will be monitored by sponsor study team or representative (e.g., a CRO) as frequently as necessary to ensure the rights and well-being of study participants are protected; to verify adequate, accurate and complete data collection; protocol compliance and to determine that the study is being conducted in conformance with applicable regulatory requirements. Arrangements for monitoring visits will be made in advance in accordance with the monitoring plan.

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13. ANNEX

ANNEX TO THE MASTER PROTOCOL

COUNTRY: BANGLADESH

Sample size and vaccination schedule

Approximately **720** participants aged 6 weeks old (42-47 days) will be enrolled in Bangladesh for this multi-country, multi-center, randomized, controlled, extended phase III study. The routine vaccine co-administered with the investigational vaccine include Adsorbed Diphtheria-Tetanus-whole cell Pertussis-Hepatitis B and Haemophilus influenza type b conjugate vaccine (DTP-HepB-Hib) and Pneumococcal Conjugate Vaccine, 10 valent (PCV10) in accordance with the local routine vaccination schedule. The vaccination schedule in Bangladesh is shown as followings:

Groups	Vaccination schedule					
	6 weeks	8 weeks	10 weeks	12 weeks	14 weeks	16 weeks
Group C1 & C2	sIPV DTP-HepB-Hib PCV10		sIPV DTP-HepB-Hib PCV10		sIPV DTP-HepB-Hib PCV10	
Group S1	sIPV	DTP-HepB-Hib PCV10	sIPV	DTP-HepB-Hib PCV10	sIPV	DTP-HepB-Hib PCV10
Group S2	DTP-HepB-Hib PCV10	sIPV	DTP-HepB-Hib PCV10	sIPV	DTP-HepB-Hib PCV10	sIPV

Enrollment requirements in terms of safety

Additionally, in one of the study countries, i.e., Bangladesh, after the initial 50 participants' enrollment, the further enrollment will be hold on, until the DSMB's approval based on their review conclusion on the safety data of the initial 50 participants within one month after their first vaccination.

ANNEX TO THE MASTER PROTOCOL

COUNTRY: PAKISTAN

Sample size and co-administration routine vaccines

Approximately **720** participants aged 6-8 weeks old (42-56 days) will be enrolled in Pakistan for this multi-country, multi-center, randomized, controlled, extended phase III study. The routine vaccine co-administered with the investigational vaccine include Adsorbed Diphtheria-Tetanus-whole cell Pertussis-Hepatitis B and Haemophilus influenza type b conjugate vaccine (DTP-HepB-Hib) and Pneumococcal Conjugate Vaccine, 13 valent (PCV13) in accordance with the local routine vaccination schedule, and rotavirus vaccine. The vaccination schedule in Pakistan is shown as followings:

Groups	**Vaccination schedule**					
	6 weeks	**8 weeks**	**10 weeks**	**12 weeks**	**14 weeks**	**16 weeks**
Group C1 & C2	sIPV DTP-HepB-Hib PCV13 Rotavirus vaccine		sIPV DTP-HepB-Hib PCV13 Rotavirus vaccine		sIPV DTP-HepB-Hib PCV13	
Group S1	sIPV	DTP-HepB-Hib PCV13 Rotavirus vaccine	sIPV	DTP-HepB-Hib PCV13 Rotavirus vaccine	sIPV	DTP-HepB-Hib PCV13
Group S2	DTP-HepB-Hib PCV13 Rotavirus vaccine	sIPV	DTP-HepB-Hib PCV13 Rotavirus vaccine	sIPV	DTP-HepB-Hib PCV13	sIPV