Official Protocol Title:	A Phase 3 Randomized, Open-Label, Clinical Trial to Study the Immunogenicity and Safety of Concomitant and Non-Concomitant Administration of V260 and Inactivated Poliomyelitis Vaccine (IPV) in Chinese Healthy Infants
NCT number:	NCT04481191
Document Date:	01-Jun-2022

Title Page

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Protocol Title: A Phase 3 Randomized, Open-Label, Clinical Trial to Study the Immunogenicity and Safety of Concomitant and Non-Concomitant Administration of V260 and Inactivated Poliomyelitis Vaccine (IPV) in Chinese Healthy Infants

Protocol Number: 074-03

Compound Number: V260

Sponsor Name:

Merck Sharp & Dohme LLC
(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

EudraCT	2020-003329-49

Approval Date: 01 June 2022

Sponsor Signatory

Typed Name: Title:	Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
V260-074-03	01-JUN-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
V260-074-02	11-AUG-2020	The purpose of this amendment is to add the EudraCT number to the protocol and to clarify baseline characteristics to be collected at enrollment and collection of non-study vaccination on the VRC.
V260-074-01	30-JAN-2020	The China Regulatory Agency released a new guideline on the grading scales for adverse events in vaccine clinical studies. The main purpose of this amendment is to update the protocol with the new guideline.
V260-074-00	18-NOV-2019	Original protocol

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: [03]

Overall Rationale for the Amendments:

Sponsor underwent an entity name change and update to the address.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Title Page Section 10.1.1 Code of Conduct for Clinical Trials	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3 Randomized, Open-Label, Clinical Trial to Study the Immunogenicity and Safety of Concomitant and Non-Concomitant Administration of V260 and Inactivated Poliomyelitis Vaccine (IPV) in Chinese Healthy Infants

Short Title: Immunogenicity and safety assessment of concomitant administration of V260 and IPV in Chinese healthy infants

Acronym: V260-074

Hypotheses, Objectives, and Endpoints:

In healthy Chinese infants 48-63 days of age:

Note: Participants randomized to non-concomitant administration of V260 and IPV (staggered-use group) will receive the two study vaccines in a staggered-use schedule.

Objectives	Endpoints
Primary	
• Objective: To demonstrate that the immunogenicity of IPV in the concomitant-use group is non-inferior to that in the staggered-use group. Hypothesis (H1): The seroconversion percentage at 1 month post dose 3 for each of poliovirus types 1, 2, and 3 in the concomitant-use group is non-inferior to those in the staggered-use group. The statistical criterion for non-inferiority requires that the lower bound of two-sided 95.0% confidence interval for the difference (concomitant-use group minus staggered-use group) in seroconversion percentages be greater than -10% for each poliovirus type.	• Neutralizing antibody seroconversion to each of poliovirus types 1, 2, and 3

Objectives	Endpoints
Secondary	
• Objective: To evaluate immune responses to IPV at 1 month post dose 3 in the concomitant-use and staggered-use groups as measured by geometric mean titers (GMTs) of neutralizing antibodies to poliovirus types 1, 2, and 3.	• Neutralizing antibody titer to each of poliovirus types 1, 2, and 3
• Objective: To evaluate immune responses to IPV at 1 month post dose 3 in the concomitant-use and staggered-use groups as measured by the proportions of participants with neutralizing antibody titer ≥1:8 and ≥1:64 for each of poliovirus types 1, 2, and 3.	• Neutralizing antibody responses to each of poliovirus types 1, 2, and 3
• Objective: To evaluate the safety of concomitant administration of V260 and IPV based on the proportions of participants experiencing solicited injection-site adverse events (AEs), solicited systemic AEs, and serious AEs (SAEs).	• Solicited injection-site AEs (following vaccination of IPV) • Solicited systemic AEs • SAEs

Overall Design:

Study Phase	Phase 3
Primary Purpose	Prevention
Indication	Prevention of rotavirus gastroenteritis in infants and children caused by the serotypes G1, G2, G3, G4, and G9
Population	Chinese healthy infants
Study Type	Interventional
Intervention Model	Parallel This is a single-site study.

Type of Control	Active control (Staggered-use group)
Study Blinding	Unblinded Open-label
Blinding Roles	No Blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 7 months from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit. For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory result or at the time of final contact with the last participant, whichever comes last.

Number of Participants:

Approximately 400 participants will be enrolled in the study as described in Section 9.9.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Vaccine	Dose Strength	Dose Frequency	Route of Administration	Use
Concomitant-Use/Staggered-Use Group	V260 (ROTATEQ®)	2 mL/dose	3 doses	Oral	Experimental
	IPV (Sabin strain based)	0.5 mL/dose	3 doses	IM	Experimental
Abbreviations: IM=Intramuscular; IPV=Inactivated poliomyelitis vaccine.					

Total Number	Two treatment groups
Duration of Participation	Each participant will participate in the study for approximately 3.5 months from the time the participant's legally acceptable representative signs the Informed Consent Form through the final contact. After enrollment, each participant will be receiving 3 doses of V260 and IPV in a concomitant-use or staggered-use schedule. After each vaccination of V260 and/or IPV, each participant will be followed for 30 days in the concomitant-use group and for 15 days in the staggered-use group.

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
Insert Other Oversight Committee	No

Study Accepts Healthy Volunteers: Yes

A list of abbreviations used in this document can be found in Appendix 8.

1.2 Schema

The study design is depicted in Figure 1.

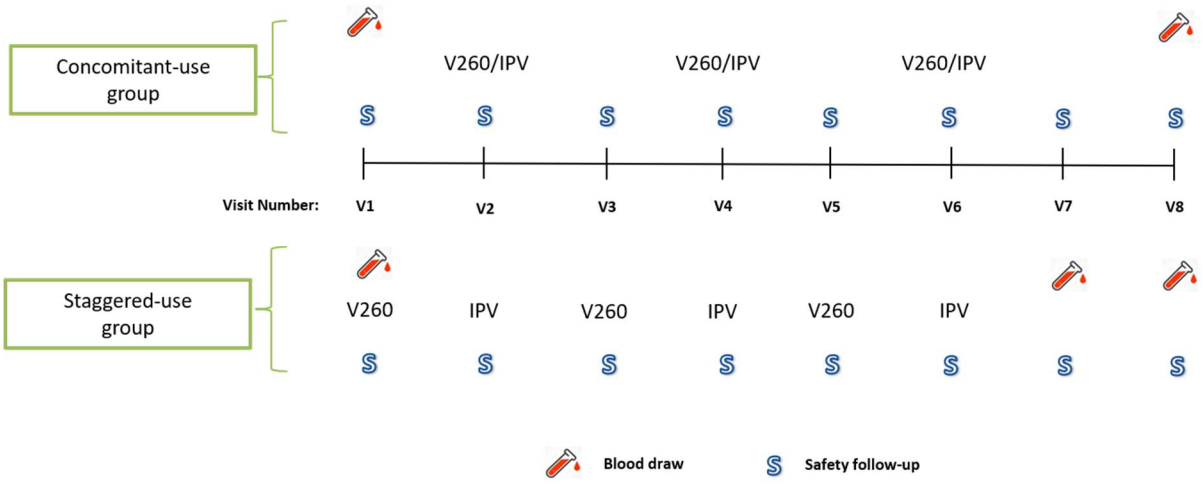

Figure 1 Study Diagram

1.3 Schedule of Activities

Visit Number		1	2	3	4	5	6	7	8	Notes
Study Month		Day 1	Month 0.5	Month 1	Month 1.5	Month 2	Month 2.5	Month 3	Month 3.5	
Recommended Age (Months)		~1.5	~2	~2.5	~3	~3.5	~4	~4.5	~5	
Concomitant-Use Group	Scheduled Day	Day 1	15 days after V1	15 days after V2	30 days afterV2	15 days after V4	30 days after V4	15 days after V6	30 days after V6	
	Visit Window	48-63 days of age	15-21d after V1 (≤84 days of age)	15-21d after V2	30-42d after V2	15-21d after V4	30-42d after V4	15-21d after V6	30-42d after V6	
Staggered-Use Group	Scheduled Day	Day 1	15 days after V1	30 days after V1	30 days after V2	30 days after V3	30 days after V4	30 days after V5	30 days after V6	
	Visit Window	48-63 days of age	15-21d after V1	30-42d after V1 & ≥V2+15d	30-42d after V2 & ≥V3+15d	30-42d after V3 & ≥V4 +15d	30-42d after V4 & ≥V5+15d	30-42d after V5	30-42d after V6	
Administrative Procedures										
Informed Consent		X								Screening procedures may not be performed on the same day of ICF, but screening or rescreening visit should be on the same day as randomization. Screening procedures may be repeated after consultation with the Sponsor.
Assignment of Screening Number		X								
Participant Identification Card		X								
Inclusion/Exclusion Criteria		X								
Medical History		X								
Prior/Concomitant Medications Review		X	X	X	X	X	X	X	X	

Visit Number		1	2	3	4	5	6	7	8	Notes
Study Month		Day 1	Month 0.5	Month 1	Month 1.5	Month 2	Month 2.5	Month 3	Month 3.5	
Recommended Age (Months)		~1.5	~2	~2.5	~3	~3.5	~4	~4.5	~5	
Concomitant-Use Group	Scheduled Day	Day 1	15 days after V1	15 days after V2	30 days afterV2	15 days after V4	30 days after V4	15 days after V6	30 days after V6	
	Visit Window	48-63 days of age	15-21d after V1 (≤84 days of age)	15-21d after V2	30-42d after V2	15-21d after V4	30-42d after V4	15-21d after V6	30-42d after V6	
Staggered-Use Group	Scheduled Day	Day 1	15 days after V1	30 days after V1	30 days after V2	30 days after V3	30 days after V4	30 days after V5	30 days after V6	
	Visit Window	48-63 days of age	15-21d after V1	30-42d after V1 & ≥V2+15d	30-42d after V2 & ≥V3+15d	30-42d after V3 & ≥V4 +15d	30-42d after V4 & ≥V5+15d	30-42d after V5	30-42d after V6	
Assignment of Treatment/Randomization Number		X								The treatment/randomization number will be randomly assigned by an interactive response technology (IRT) system.
V260 Administration	Concomitant-Use Group		X		X		X			1st dose of V260 should be given by 84 days of age (inclusive). 3rd dose of V260 should be given by 224 days of age (inclusive). The minimum and maximum interval between each dose of V260 should be 4 weeks (28 days) and 10 weeks (70 days), respectively.
	Staggered-Use Group	X		X		X				
IPV Administration	Concomitant-Use Group		X		X		X			The minimum age for the 1st dose of IPV should be is 2 months of age. The minimum interval between each dose of IPV should be 1 month (30 days). In the staggered-use group, the minimum interval between V260 and subsequent IPV is should be 15 days.
	Staggered-Use Group		X		X		X			

Visit Number		1	2	3	4	5	6	7	8	Notes
Study Month		Day 1	Month 0.5	Month 1	Month 1.5	Month 2	Month 2.5	Month 3	Month 3.5	
Recommended Age (Months)		~1.5	~2	~2.5	~3	~3.5	~4	~4.5	~5	
Concomitant-Use Group	Scheduled Day	Day 1	15 days after V1	15 days after V2	30 days afterV2	15 days after V4	30 days after V4	15 days after V6	30 days after V6	
	Visit Window	48-63 days of age	15-21d after V1 (≤84 days of age)	15-21d after V2	30-42d after V2	15-21d after V4	30-42d after V4	15-21d after V6	30-42d after V6	
Staggered-Use Group	Scheduled Day	Day 1	15 days after V1	30 days after V1	30 days after V2	30 days after V3	30 days after V4	30 days after V5	30 days after V6	
	Visit Window	48-63 days of age	15-21d after V1	30-42d after V1 & ≥V2+15d	30-42d after V2 & ≥V3+15d	30-42d after V3 & ≥V4 +15d	30-42d after V4 & ≥V5+15d	30-42d after V5	30-42d after V6	
Immunogenicity Procedures										
Blood Sample Collection	Concomitant-Use Group	X							X	In the concomitant-use group, at least 2.5 mL blood sample will be collected from each participant at Visit 1 prior to vaccination and Visit 8, respectively.
	Staggered-Use Group	X						X	X	In the staggered-use group, at least 2.5 mL blood sample will be collected prior to vaccination at Visit 1; at least 1.5mL blood sample will be collected at Visit 7 and Visit 8, respectively.
Safety Procedures										
Full Physical Examination		X								A full physical examination will be performed on all participants at Visit 1. Height and weight will also be measured at Visit 1.
Symptom/Sign-Directed Physical Examination			X	X	X	X	X	X	X	A symptom/sign-directed physical examination will be performed at subsequent visits as needed.

Visit Number		1	2	3	4	5	6	7	8	Notes
Study Month		Day 1	Month 0.5	Month 1	Month 1.5	Month 2	Month 2.5	Month 3	Month 3.5	
Recommended Age (Months)		~1.5	~2	~2.5	~3	~3.5	~4	~4.5	~5	
Concomitant-Use Group	Scheduled Day	Day 1	15 days after V1	15 days after V2	30 days afterV2	15 days after V4	30 days after V4	15 days after V6	30 days after V6	
	Visit Window	48-63 days of age	15-21d after V1 (≤84 days of age)	15-21d after V2	30-42d after V2	15-21d after V4	30-42d after V4	15-21d after V6	30-42d after V6	
Staggered-Use Group	Scheduled Day	Day 1	15 days after V1	30 days after V1	30 days after V2	30 days after V3	30 days after V4	30 days after V5	30 days after V6	
	Visit Window	48-63 days of age	15-21d after V1	30-42d after V1 & ≥V2+15d	30-42d after V2 & ≥V3+15d	30-42d after V3 & ≥V4 +15d	30-42d after V4 & ≥V5+15d	30-42d after V5	30-42d after V6	
Axillary Temperature Measurement	Concomitant-Use Group	X	X		X		X			Pre-vaccination axillary temperature will be collected for all participants at Visit 1 and at each subsequent vaccination visits. Axillary is the only acceptable method of obtaining participant's temperature. If participant has a fever (defined as axillary temperature ≥37.5˚C or equivalent) within 24 hours prior to each vaccination, the vaccination should be rescheduled after fever is resolved.
	Staggered-Use Group	X	X	X	X	X	X			
30-Minute Post-Vaccination Observation	Concomitant-Use Group		X		X		X			
	Staggered-Use Group	X	X	X	X	X	X			

Visit Number		1	2	3	4	5	6	7	8	Notes
Study Month		Day 1	Month 0.5	Month 1	Month 1.5	Month 2	Month 2.5	Month 3	Month 3.5	
Recommended Age (Months)		~1.5	~2	~2.5	~3	~3.5	~4	~4.5	~5	
Concomitant-Use Group	Scheduled Day	Day 1	15 days after V1	15 days after V2	30 days afterV2	15 days after V4	30 days after V4	15 days after V6	30 days after V6	
	Visit Window	48-63 days of age	15-21d after V1 (≤84 days of age)	15-21d after V2	30-42d after V2	15-21d after V4	30-42d after V4	15-21d after V6	30-42d after V6	
Staggered-Use Group	Scheduled Day	Day 1	15 days after V1	30 days after V1	30 days after V2	30 days after V3	30 days after V4	30 days after V5	30 days after V6	
	Visit Window	48-63 days of age	15-21d after V1	30-42d after V1 & ≥V2+15d	30-42d after V2 & ≥V3+15d	30-42d after V3 & ≥V4 +15d	30-42d after V4 & ≥V5+15d	30-42d after V5	30-42d after V6	
Vaccination Report Card (VRC) Distribution	Concomitant-Use Group	X	X		X		X			Although study vaccination is not scheduled at Visit 1 in the concomitant-use group, VRC will be provided to participant to record any reportable safety events from randomization until the 1st dose of study vaccination (see Section 8.4.1 for safety reporting requirement).
	Staggered-Use Group	X	X	X	X	X	X			
Review and Collection of VRC Data			X	X	X	X	X	X	X	At least one telephone contact will be made within 7 days after each visit of VRC distribution. The main purpose of phone call contact is to remind the participant's legally acceptable representative to record the VRC and answer any questions related to VRC.
Clinical Follow-up for Safety		X	X	X	X	X	X	X	X	Review and follow AEs, SAEs and other reportable safety events.

2 INTRODUCTION

2.1 Study Rationale

Since initial approval in the US in 2006, V260 (RotaTeq®) has been licensed in more than 100 countries including Canada, Australia, and countries in the European Union, Latin America, Africa, Southeast Asia and Western Pacific. V260 was approved in China as a prophylactic live, oral, pentavalent rotavirus vaccine in April 2018.

The administration of V260 with licensed pediatric vaccines (including INFANRIX™, IPOL™, INFANRIX™ hexa, etc.) has been evaluated in the global studies (Protocol 006, 010, and 060) [Rodriguez, Z. M., et al 2007] [Ciarlet, M., et al 2009] [Okada, K., et al 2013]. Inactivated poliomyelitis vaccine (IPV) evaluated in these studies included Salk-IPV (wIPV) (Protocol 006 and 010) and Sabin-IPV (sIPV) (Protocol 060).

Concomitant administration of V260 with trivalent oral poliomyelitis vaccine (tOPV), and diphtheria, tetanus toxoids and acellular pertussis (DTaP) vaccine in Chinese infants was evaluated in the Protocol 024, an efficacy registration study conducted in China. Since 2016, at least one dose of sIPV was introduced into the routine polio immunization schedule in China. The immunization schedule in China was gradually transitioned to a 2-dose IPV schedule in 2019 and is expected to be changed to the all-IPV schedule in the future.

Although concomitant administration with sIPV was evaluated in Japanese infants (Protocol 060), the sIPV in Japan is different with the sIPV marketed in China with respect to antigen amounts. This study (Protocol 074) will evaluate the immunogenicity and safety of concomitant administration of V260 and sIPV in Chinese infants. V260 and sIPV will be provided by local sourcing in the study.

2.2 Background

Refer to the Investigator's Brochure (IB)/ approved labeling for detailed background information on V260.

2.2.1 Pharmaceutical and Therapeutic Background

Rotavirus is the leading cause of severe diarrhea in infants and young children. Rotavirus infection was responsible for an estimated 128,500 deaths and 258 million episodes of diarrhea worldwide among children younger than 5 years of age in 2016 [Troeger, C., et al 2018]. In China, rotavirus caused over 40% of hospitalization due to diarrhea and about 30% of diarrhea related outpatient visits in children under 5 years of age [Zhang, J., et al 2015].

Rotavirus gastroenteritis is characterized by the sudden onset of watery diarrhea, fever, and vomiting. Severity varies from asymptomatic infection to dehydrating gastroenteritis that may be fatal. Nearly all children are infected with rotavirus by the age of 5 years regardless of socioeconomic status or standards of health and sanitation [Vesikari, T., et al 2006]. This suggests that improvements in sanitation are unlikely to reduce the incidence rate of rotavirus gastroenteritis. Currently, there is no antiviral therapy available to treat rotavirus

gastroenteritis, and the only available therapy is treatment of associated symptoms, such as supportive oral or intravenous rehydration for dehydration.

V260 is a live, oral, pentavalent combination vaccine developed by Merck that contains five human-bovine reassortant rotavirus strains (G1, G2, G3, G4 and P1A[8]). A phase 3 study in healthy infants has been conducted in China (Protocol 024; May 2014 to June 2015) in 4,040 infants aged 6-12 weeks to investigate the efficacy, immunogenicity, and safety of V260 in Chinese healthy infants. The study showed that the vaccine efficacy against any-severity of rotavirus gastroenteritis caused by vaccine serotypes was 69.3% and the efficacy against severe rotavirus gastroenteritis caused by vaccine serotypes was 78.9% as compared to placebo [Mo, Z., et al 2017].

In 2009, the World Health Organization recommended rotavirus vaccination to be included in all national immunization programs for the first time to ensure access to rotavirus vaccines in the world's poorest countries [World Health Organization 2009].

2.3 Benefit/Risk Assessment

V260 has been licensed in over 100 countries since 2006 and was approved in China in 2018 for the protection against rotavirus gastroenteritis in infants and children caused by serotypes G1, G2, G3, G4, and G9.

Benefit/risk for concomitant administration of V260 with IPV has been established to be favorable in the global studies. This study aims to establish this in Chinese infants.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

In healthy Chinese infants 48-63 days of age:

Objectives	Endpoints
Primary	
• Objective: To demonstrate that the immunogenicity of IPV in the concomitant-use group is non-inferior to that in the staggered-use group. Hypothesis (H1): The seroconversion percentage at 1 month post dose 3 for each of poliovirus types 1, 2, and 3 in the concomitant-use group is non-inferior to those in the staggered-use group. The statistical criterion for non-inferiority requires that the lower bound of two-sided 95.0% confidence interval for the difference (concomitant-use group minus staggered-use group) in seroconversion percentages be greater than -10% for each poliovirus type.	• Neutralizing antibody seroconversion to each of poliovirus types 1, 2, and 3
Secondary	
• Objective: To evaluate immune responses to IPV at 1 month post dose 3 in the concomitant-use and staggered-use groups as measured by geometric mean titers (GMTs) of neutralizing antibodies to poliovirus types 1, 2, and 3.	• Neutralizing antibody titer to each of poliovirus types 1, 2, and 3
• Objective: To evaluate immune responses to IPV at 1 month post dose 3 in the concomitant-use and staggered-use groups as measured by the proportions of participants with neutralizing antibody titer ≥1:8 and ≥1:64 for each of poliovirus types 1, 2, and 3.	• Neutralizing antibody responses to each of poliovirus types 1, 2, and 3

Objectives	Endpoints
• Objective: To evaluate the safety of concomitant administration of V260 and IPV based on the proportions of participants experiencing solicited injection-site adverse events (AEs), solicited systemic AEs, and serious AEs (SAEs).	• Solicited injection-site AEs (following vaccination of IPV) • Solicited systemic AEs • SAEs
Exploratory	
• Objective: To evaluate immune responses to V260 at 1 month post dose 3 in the concomitant-use and staggered-use groups using anti-rotavirus type-specific IgA based on GMTs and proportions of participants with ≥3-fold increase in titer post-vaccination from baseline.	• Anti-rotavirus type-specific IgA antibody responses to rotavirus serotypes G1, G2, G3, G4, and P1A[8]

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, single-site, open-label study of concomitant administration of V260 and IPV in Chinese healthy infants to be conducted in conformance with Good Clinical Practices.

Approximately 400 participants between the ages of 48 days and 63 days will be enrolled and randomly assigned in a 1:1 ratio to receive V260 and IPV in a concomitant (concomitant-use group) or non-concomitant administration (staggered-use group) schedule. Each participant will participate in the study for approximately 3.5 months from the time the participant's legally acceptable representative signs the informed consent through the final contact, including 8 study visits for vaccination, blood sample collection, and safety follow-up.

In the concomitant-use group, an oral dose of V260 (2 mL/dose) will be concomitantly administered (same day) with an intramuscular injection of IPV (0.5 mL/dose) at Visit 2, Visit 4, and Visit 6, respectively. In the staggered-use group, an oral dose of V260 (2mL/dose) will be administered at Visit 1, Visit 3, and Visit 5, respectively, and an intramuscular injection of IPV (0.5 mL/dose) will be administered at Visit 2, Visit 4, and Visit 6, respectively.

In the concomitant-use group, serum samples will be obtained from each participant at Visit 1 prior to vaccination and Visit 8 (1 month post dose 3 of V260 and IPV), respectively. In the staggered-use group, serum samples will be obtained from each participant at Visit 1 prior to vaccination, Visit 7 (1 month post dose 3 of V260), and Visit 8 (1 month post dose 3 of IPV), respectively.

Paper Vaccination Report Card (VRC) will be used by each participant's legally acceptable representative to record participant's daily axillary temperature from Day 1 through Day 7 post each study vaccination; solicited injection-site AEs (erythema, swelling, induration, and pain at the injection-site of IPV) from Day 1 through Day 7 post each vaccination of IPV, and solicited systemic AEs (diarrhea and/or vomiting) from Day 1 through Day 7 post each study vaccination; and any other AEs from Day 1 through Day 15 post each study vaccination in both the concomitant-use and staggered-use groups. In addition, any other AEs from Day 16 through Day 30 post each study vaccination in the concomitant-use group will also be collected on the VRC.

Any SAEs regardless of causality, cancer, overdose, and intussusception (Event of Clinical Interest [ECI]) will be collected during the entire period of study.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the SoA in Section 1.3. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

This is a post-marketing commitment study. This study is designed to assess immunogenicity of IPV when concomitantly administered with V260 in Chinese infants with the staggered-use group as a comparative control. The immunogenicity of V260 will be evaluated as exploratory objective. The safety of study vaccines will also be evaluated in the study.

4.2.1 Rationale for Endpoints

4.2.1.1 Immunogenicity Endpoints

The immunogenicity of IPV will be measured using poliovirus serum neutralizing antibody assay of National Institutes for Food and Drug Control (NIFDC, Beijing, China).

The primary endpoints are neutralizing antibody seroconversion percentages to each of poliovirus types 1, 2, and 3 at 1 month post dose 3 of IPV. The seroconversion is defined as antibody titer ≥1:8 post-vaccination in baseline seronegative participants or ≥4-fold increase in titer post-vaccination in baseline seropositive participants, which is consistent with WHO's recommendation on the immunogenicity evaluation of IPV vaccines [World Health Organization Expert Committee on Biological Standar 2014]. The cut-off value for seropositivity is 1:8 for all 3 poliovirus types [Nathanson, N. 2005].

The neutralizing antibody GMTs to each of poliovirus types 1, 2, and 3 at Day 1 prior to vaccination and 1 month post dose 3 of IPV will be summarized as secondary endpoints. In addition, the proportions of participants with neutralizing antibody titer ≥1:8 and ≥1:64 at 1 month post dose 3 of IPV will be summarized for each of poliovirus types 1, 2, and 3, as requested by local regulatory agency.

The immunogenicity of V260 will be measured using anti-rotavirus type-specific IgA assay of NIFDC as exploratory objectives. An immunological correlate of protection has not been

identified for rotavirus disease. The antibody responses to V260 at 1 month post dose 3 will be summarized using the same methods adopted in the prior efficacy study in China, i.e. based on GMTs and proportions of participants with ≥3-fold increase in titer post-vaccination from baseline.

4.2.1.2 Safety Endpoints

In the concomitant-use group, V260 and IPV will be administered on the same day with an interval of at least 30 days between each vaccination visit, and the safety of the two study vaccines will be collected for 30 days following each vaccination. In the staggered-use group, V260 and IPV will be administered separately with an interval of at least 15 days, therefore the safety of each study vaccine will be collected for 15 days following each vaccination.

Paper VRC will be provided to each participant's legally acceptable representative at each vaccination visit to record participant's daily axillary temperature from Day 1 through Day 7 post each study vaccination; solicited injection-site AEs (erythema, swelling, induration, and pain at the injection-site of IPV) from Day 1 through Day 7 post each vaccination of IPV, and solicited systemic AEs (diarrhea and/or vomiting) from Day 1 through Day 7 post each study vaccination; and any other AEs from Day 1 through Day 15 post study each vaccination in both the concomitant-use and staggered-use groups. In addition, any other AEs from Day 16 through Day 30 post each study vaccination in the concomitant-use group will also be collected on the VRC.

The solicited injection-site AEs will be collected for the safety evaluation of IPV, which is a vaccine to be intramuscularly administered.

Although participants in the concomitant-use group will not receive any study vaccines at Visit 1, VRC will be provided to each participant at Visit 1 to record any reportable safety events from randomization through the first study vaccination (See Section 8.4.1 for safety reporting requirement).

In addition, any SAEs regardless of causality, cancer, overdose, and intussusception (ECI) will be collected during the entire period of study.

4.2.2 Rationale for the Use of Comparator/Placebo

To assess the immunogenicity of IPV concomitantly administered with V260, the staggered-use group will be used as a comparative control in the study.

4.3 Justification for Dose

The dose regimens and schedules for study vaccines are based on the approved China Package Circulars (CPCs). Refer to Section 6.1 – Study Intervention(s) for details regarding the trial vaccination.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant signs the ICF. The overall study ends when the last participant completes the last study-related telephone-call or visit, withdraws from the study, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory result or at the time of final contact with the last participant, whichever comes last.

4.4.1 Clinical Criteria for Early Study Termination

There are no prespecified criteria for terminating the study early.

5 STUDY POPULATION

Healthy Chinese infants 48-63 days of age will be enrolled in this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant:

Type of Participant and Disease Characteristics

1. Is healthy Chinese infant.

Demographics

2. Is male or female from 48 days to 63 days of age (inclusive) at Visit 1. (Date of birth is 1 day of age).

Informed Consent

3. The participant's legally acceptable representative provides written informed consent for the study.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

Medical Conditions

1. Has history of rotavirus disease, congenital gastrointestinal disorders, chronic diarrhea, failure to thrive, or abdominal surgery.

2. Has history of intussusception.

3. Has history of poliomyelitis.

4. Has clinical evidence of active gastrointestinal illness. Note: Infants with gastroesophageal reflux disease [GERD] may participate in the study if the GERD is well controlled with or without medication.

5. Has known or suspected impairment of immunological function, including severe combined immunodeficiency disease (SCID).

6. Has a fever, with an axillary temperature ≥37.5°C (or equivalent) at the time of vaccination or within 24 hours prior to vaccination. Note: The Visit 1 may be rescheduled after complete resolution of febrile illness.

7. Participant who clearly has acute disease.

8. Participant who has underlying diseases such as cardiovascular, renal, liver, or blood disease.

9. Has history of known hypersensitivity to any components of rotavirus vaccine and/or IPV.

10. Participant with uncontrolled epilepsy, encephalopathy, seizure, or other progressive neurological diseases.

11. Participant with known thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injections.

12. Is residing in a household with an immunocompromised person, including individuals with congenital immunodeficiency (including SCID), human immunodeficiency virus (HIV) infection, leukemia, lymphoma, multiple myeloma, generalized malignance, chronic renal failure, organ or bone marrow transplantation, or with those receiving immunosuppressive chemotherapy including long-term systemic corticosteroids.

13. Has any condition, which in the opinion of the investigator, may interfere with the evaluation of the study objectives.

Prior/Concomitant Therapy

14. Has prior administration of any rotavirus vaccines or poliovirus vaccines.

15. Received inactivated or recombinant vaccines within 14 days prior to Visit 1 or live vaccines within 28 days prior to Visit 1.

16. Has prior receipt of investigational or non-registered product other than study vaccines or is planning to use such product during the study.

17. Has prior receipt of immunosuppressive therapies including systemic (intramuscular, oral, or intravenous) corticosteroids. Note: Participants using non-systemic corticosteroids (e.g., topical, ophthalmic, and inhaled) are considered eligible for the study.

18. Has prior receipt of a blood transfusion or blood products, including immunoglobulins or is planning to receive such product during the study.

Prior/Concurrent Clinical Study Experience

19. Participated in another interventional study prior to Visit 1 or expected anytime during the study.

Diagnostic Assessments

Not applicable.

Other Exclusions

20. Participant's legally acceptable representative is unlikely to adhere to the study procedures, keep appointments or is planning to permanently relocate from the area prior to the completion of the study or to leave for an extended period when study visits would need to be scheduled.

21. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

5.3 Lifestyle Considerations

No lifestyle restrictions are required.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

A participant who discontinues from study vaccination OR withdraws from the study will not be replaced.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 1.

Table 1 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP/ NIMP	Sourcing
Concomitant-Use Group	Experimental	V260	Biological /Vaccine	Sterile Solution	2 mL per dose	3 doses	Oral	Visit 2, 4, 6	Experimental	IMP	Local Sourcing
Concomitant-Use Group	Experimental	IPV (Sabin strain based)	Biological /Vaccine	Vial	0.5 mL per dose	3 doses	Intramuscular	Visit 2, 4, 6	Experimental	IMP	Local Sourcing
Staggered-use Group	Active Comparator	V260	Biological /Vaccine	Sterile Solution	2 mL per dose	3 doses	Oral	Visit 1, 3, 5	Experimental	IMP	Local Sourcing
Staggered-use Group	Active Comparator	IPV (Sabin strain based)	Biological /Vaccine	Vial	0.5 mL per dose	3 doses	Intramuscular	Visit 2, 4, 6	Experimental	IMP	Local Sourcing
Definition Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.											

All supplies indicated in Table 1 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (e.g., not applicable in the case where multiple lots or batches may be required due to the length of the study, etc.).

Refer to Section 8.1.8 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is provided in Section 4.3.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

The treatment/randomization number will be randomly assigned by an interactive response technology (IRT) system. The enrolled participants will be randomly assigned in a 1:1 ratio to either concomitant-use or staggered-use group.

6.3.2 Stratification

No stratification based on age, sex or other characteristics will be used in this study.

6.3.3 Blinding

This is an open-label study; therefore, the Sponsor, investigator, and participant will know the vaccines administered.

6.4 Study Intervention Compliance

Interruptions from the protocol-specified vaccination schedule (i.e. administration of 3 doses at scheduled time points) for reasons not defined in the protocol require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

Blood products (including immunoglobulin), immunosuppressive therapies, systemic corticosteroids, and other investigational medications/vaccines that have not been licensed should not be administered prior to or during the study.

If blood products, immunosuppressive therapies or systemic corticosteroids are given after entry into the study because of medical circumstances, this should be entered on the appropriate CRFs.

Any rotavirus vaccine and poliovirus vaccine other than study vaccines should not be administered prior to or during the study.

There is generally no need for any restriction to the administration of other routine pediatric vaccines (including China Expanded Program of Immunization (EPI) or non-EPI vaccines) during the study. See Section 8.1.8 for the recommendation on administration of other routine vaccines during the study.

The investigator or qualified designee will review prior and concomitant medication/vaccination use and record the information on the appropriate eCRFs as follows:

- Prior/Concomitant vaccinations will be collected from birth through the final visit of the study.

- Prior/Concomitant medications will be collected for 15 days before and after each dose of study vaccines.

6.5.1 Rescue Medications and Supportive Care

Adequate treatment provision, including epinephrine and equipment for maintaining an airway should be available for immediate use should an anaphylactic or anaphylactoid reaction occur [Centers for Disease Control and Prevention 2015].

6.6 Dose Modification

Not applicable.

6.7 Intervention After the End of the Study

There is no study-specified intervention following the end of the study.

6.8 Clinical Supplies Disclosure

This study is open-label; therefore, the participant, the study site personnel, the Sponsor, and/or designee are not blinded. Study intervention (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of vaccination regimen will continue to participate in the study as specified in Section 1.3 and Section 8.11.3.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.9.

A participant must be discontinued from study intervention but continue to be monitored in the study for any of the following reasons:

- The participant's legally acceptable representative requests to discontinue study intervention.

- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.

Participants may be allowed to begin study intervention again if deemed medically appropriate with consultation from the Clinical Director of Sponsor.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study

site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical study. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate consent is in place.

8.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the study.

The initial ICF, any subsequent revised written ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that

captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about a study and the study population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides written informed consent. At the time of intervention allocation assigned to the participant, site personnel will add the treatment/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a healthcare provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

Medical history prior to enrollment will be obtained by the investigator or qualified designee at Visit 1. Gestational age and birth weight will be collected from each participant at Visit 1. The status of infant feeding will be collected.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication and non-study vaccination, and record any prior medications taken by the participant for 15 days before starting the study and all prior non-study vaccinations from birth to starting the study.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record concomitant medication taken by the participant during 15 days before and after each study vaccination and non-study vaccination from Visit 1 through the final visit of the study.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit. Specific details on the screening/rescreening visit requirements are provided in Section 8.11.1.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment randomization. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

8.1.8 Study Intervention Administration

Administration of study intervention will be witnessed by the investigator and/or study staff.

V260 should be administered within 30 minutes of removing it from refrigerator. The instruction of use is showed in China Package Circulars (CPCs) of V260 and IPV.

The first dose of study vaccines should be administered after collection of baseline blood samples prior to vaccination (see Section 8.2.1).

Section 8.11.2 provides additional information on the prerequisites for vaccination visits.

Study vaccines should be prepared and administered by appropriately qualified members of the study personnel (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local/state, country, and institutional guidance.

8.1.8.1 Timing of Dose Administration

In the concomitant-use group, each participant will receive 1 dose of V260 and IPV concomitantly at Visit 2, 4, and 6, respectively. In the staggered-use group, each participant will receive 1 dose of V260 at Visit 1, 3, and 5, respectively, and 1 dose of IPV at Visit 2, 4, and 6, respectively. See the SoA (Section 1.3) for the protocol pre-specified time windows of these vaccination visits. Missed study vaccination doses within the visit window should be completed as soon as possible.

The first dose of V260 should be given by 12 weeks of age (84 days of age) and the third dose of V260 should be given by 32 weeks of age (224 days of age). The minimum and maximum interval between each dose of V260 should be 4 weeks (28 days) and 10 weeks (70 days), respectively.

The minimum age for the first dose of IPV should be 2 months of age. The minimum interval between each dose of IPV should be 1 month (30 days).

In the staggered-use group, the minimum interval between V260 and subsequent IPV should be 15 days.

Administration of approved routine pediatric vaccine (excluding rotavirus vaccine and polio vaccines other than study vaccines) is allowed in the study. It is recommended other routine vaccines (including EPI and non-EPI vaccines) be administered on the same day as V260 or IPV.

If other routine vaccines are to be administered concomitantly with V260, V260 should be administered before administration of other vaccines to minimize crying and the chance of the participant spitting up V260.

If other routine vaccines are to be administered on different day of study vaccines, the interval between non-study and study vaccines should meet the prerequisites of vaccination visit (Section 8.11.2) or may be determined in accordance with the routine practice of study institution.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the vaccination regimen should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.11.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit (blood sample collection should not be done if the participant has not received all 3 doses of study vaccine) at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.10 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study.

8.1.11 Domiciling

Not applicable.

8.1.12 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Immunogenicity Assessments

8.2.1 Serum Samples for Antibody Testing

Sample collection, storage, and shipment instructions for serum samples will be provided in the Laboratory Manual. For collection of the serum samples, the study sites must follow instructions provided by the Sponsor-designated Central Laboratory. Samples should be shipped, labeled, and handled as instructed by the Sponsor/Central Laboratory.

In the concomitant-use group, at least 2.5 mL blood sample will be collected from each participant at Visit 1 (baseline sample prior to vaccination) and Visit 8 (1 month post dose 3 of V260 and IPV), respectively.

In the staggered-use group, at least 2.5 mL blood sample will be collected from each participant at Visit 1 (baseline sample prior to vaccination); at least 1.5 mL blood sample will be collected from each participant at Visit 7 (1 month post dose 3 of V260) and Visit 8 (1 month post dose 3 of IPV), respectively.

If the blood sample is not able to be obtained, it is recommended that the study visit should be rescheduled as soon as possible.

Repeat or unscheduled samples may be taken for technical issues with the samples.

8.2.2 Immunoassays for Antibody Testing

The immunogenicity of IPV will be measured using poliovirus serum neutralizing antibody assay of NIFDC, Beijing, China. The purpose of this assay is to detect and quantify serum neutralizing antibodies against each of poliovirus types 1, 2, and 3 before and after vaccination with polio vaccines. This was the primary assay used by NIFDC to evaluate the serological response to polio vaccines. Results for the assay will be reported as titer.

The immunogenicity of V260 will be measured using anti-rotavirus type-specific IgA assay developed by NIFDC. The purpose of this assay is to detect and quantify anti-rotavirus IgA antibodies against each of human rotavirus serotypes G1, G2, G3, G4, and P1A[8]. This was one of the primary assays used by NIFDC to evaluate the serological response to rotavirus vaccines. Results for the assay will be reported as Units/mL.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard at Visit 1. Height and weight will also be measured at Visit 1.

A symptom/sign-directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard at subsequent visits as needed.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Axillary Temperature Measurement

Pre-vaccination axillary temperature will be measured at Visit 1 and at subsequent study vaccination visits. Axillary is the only acceptable method of obtaining participant's temperature in the study.

If the participant has a fever within the 24-hour period prior to vaccination, the vaccination should be rescheduled as soon as possible after the fever has resolved. For the purpose of this study, a fever is defined as an axillary temperature ≥37.5°C (or equivalent), in accordance with the local routine medical practice and China Regulatory Agency's Guideline for Grading Scales of Adverse Events in Clinical Trials of Prophylactic Vaccines (see Section 10.7 - Appendix 7: China-specific Requirements).

See Section 8.11.2 for other prerequisites for vaccination visit.

8.3.3 30-Minute Post-Vaccination Observation

All participants will be observed for at least 30 minutes after each study vaccination for any immediate untoward effects with particular attention to any evidence of allergic phenomena. This observation period will be documented in the participant's study chart.

8.3.4 Vaccination Report Card

VRC will be provided to each participant's legally acceptable representative at each study vaccination visit.

Participant's legally acceptable representative will be instructed to record the following information:

- Daily axillary temperature from Day 1 through Day 7 following each study vaccination (Temperature measurement must be recorded on the VRC if a fever is suspected during Day 8 through Day 30 [concomitant-use group] or Day 8 through Day 15 [staggered-use group]);
- Solicited injection-site AEs (erythema, swelling, induration, and pain at the injection-site of IPV) from Day 1 through Day 7 following each vaccination of IPV;
- Solicited systemic AEs (diarrhea and/or vomiting) from Day 1 through Day 7 following each study vaccination;
- Any AEs from Day 1 through Day 30 (concomitant-use group) or from Day 1 through Day 15 (staggered-use group) following each study vaccination;
- Any concomitant medications from Day 1 through Day 15 following each study vaccination (both vaccination groups).
- Any non-study vaccinations from Day 1 through Day 30 (concomitant-use group) or from Day 1 through Day 15 (staggered-use group) following each study vaccination;
- Any medications due to AE during Day 16 through Day 30 following each study vaccination (concomitant-use group only).

Although Visit 1 is not a vaccination visit for participants in the concomitant-use group, VRC will be provided to each participant's legally acceptable representative to record any reportable safety events from randomization through the first study vaccination (See Section 8.4.1 for safety reporting requirement).

At least one telephone contact will be conducted by investigator within 7 days after each visit of VRC distribution to remind each participant's legally acceptable representative to record the VRC and answer their any questions related to VRC.

In the concomitant-use group, the purpose of Visit 3, 5, and 7 is only to review VRCs, so out of windows of these visits will not be reported as a protocol deviation in this vaccination group.

8.3.5 Clinical Safety Laboratory Assessments

1. There are no protocol specified laboratory assessments in this study.

- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before randomization/allocation must be reported by the investigator if they cause the participant to be excluded from the study, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo, or a procedure.

From the time of randomization/allocation through 30 days (concomitant-use group) or 15 days (staggered-use group) following the first vaccination(s) and from the time of any subsequent vaccination(s) through 30 days (concomitant-use group) or 15 days (staggered-use group) thereafter, all AEs, SAEs, and other reportable safety events must be reported by the investigator.

Additionally, SAE (regardless of causality) and intussusception (ECI) at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor. Other reportable safety events (cancer and overdose) at any time outside of the time period specified in the previous paragraph should also be reported to the Sponsor.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 2.

Table 2 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
Nonserious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report all (Follow ongoing to outcome)	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report all	Report all	Within 24 hours of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Report all	Within 5 calendar days of learning of event
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Report all	Within 5 calendar days of learning of event

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the

participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Information in this section is not applicable since participants are infants.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Not applicable to this study.

8.4.7 Events of Clinical Interest

Selected nonserious and SAEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

a. Intussusception: Any cases of intussusception during the entire study should be immediately reported to Sponsor (see Section 8.4.1 for safety reporting requirement).

8.5 Treatment of Overdose

In this study, an overdose is defined as receiving more than one dose of V260 within a 12-day period. Any overdose should be reported to Sponsor (see Section 8.4.1 for safety reporting requirement).

Sponsor does not recommend specific treatment for an overdose.

8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Future Biomedical Research Sample Collection

Future biomedical research samples will not be collected in this study.

8.10 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics are not evaluated in this study.

8.11 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.11.1 Screening

At Visit 1, if participant has a fever (axillary temperature ≥37.5°C or equivalent) within the 24-hour period prior to vaccination, screening visit may be rescheduled after the fever has resolved.

Screening procedures may not be performed on the same day of ICF, but screening or rescreening visit should be on the same day as randomization. Screening procedures may be repeated after consultation with the Sponsor.

8.11.2 Vaccination Visit

This section summarizes prerequisites for visits with study vaccinations. Deviations from these prerequisites require consultation between the investigator and the Sponsor and written documentation of the collaborative decision.

See the inclusion/exclusion criteria for specific restrictions at Visit 1 (see Section 5.1 and Section 5.2). At the subsequent vaccination visits, study personnel should verify by questioning the participant and/or by examination that:

1. The participant has not had a fever (defined as an axillary temperature of ≥37.5°C or equivalent) within the 24-hour period prior to each vaccination visit.

2. The participant has not received any systemic (oral, intravenous or intramuscular) corticosteroids within 2 weeks (14 days) prior to each vaccination visit.

3. The participant has not received a non-study inactivated or recombinant vaccine within 2 weeks (14 days) prior to each vaccination visit.

4. The participant has not received a non-study live vaccine within 4 weeks (28 days) prior to each vaccination visit.

If the participant does not meet the requirements #1 or #2 listed above during study, the vaccination visit should be rescheduled as soon as possible.

It is recommended other routine vaccines be administered on the same day as V260 or IPV. If other routine vaccines are to be administered on different day of study vaccines, the interval between non-study and study vaccines should meet the requirements #3 and #4 listed above or may be determined in accordance with institutional guidance (see Section 8.1.8.1).

8.11.3 Discontinued Participants Continuing to be Monitored in the Study

Participants who discontinue study vaccinations but continue in the study may attend study visits per the SoA (Section 1.3). However, post-vaccination serum samples will not be collected from participants who have not completed the 3-dose regimen of study vaccination.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any final database lock, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to final database lock, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2-9.12.

Study Design Overview	A Phase 3 Randomized, Open-Label, Clinical Trial to Study the Immunogenicity and Safety of Concomitant and Non-Concomitant Administration of V260 and Inactivated Poliomyelitis Vaccine (IPV) in Chinese Healthy Infants
Treatment Assignment	Participants will be randomly assigned in a 1:1 ratio to receive V260 and IPV in a concomitant-use or staggered-use schedule
Analysis Populations	Immunogenicity: Per-Protocol Immunogenicity (PPI) population Safety: All Participants as Treated (APaT) population

Primary Endpoint(s)	**Immunogenicity:** • Neutralizing antibody seroconversion percentages to each of poliovirus types 1, 2, and 3 at 1 month post dose 3 of IPV
Secondary Endpoints	**Immunogenicity:** • Neutralizing antibody geometric mean titers (GMTs) to each of poliovirus types 1, 2, and 3 at 1 month post dose 3 of IPV • Proportions of participants with neutralizing antibody titer ≥1:8 and ≥1:64 at 1 month post dose 3 of IPV for each of poliovirus types 1, 2, and 3 **Safety**: • Proportions of participants with solicited injection-site AEs (erythema, swelling, induration, and pain at the injection-site of IPV) from Day 1 through Day 7 following any vaccination of IPV • Proportions of participants with solicited systemic AEs (diarrhea and/or vomiting) from Day 1 through Day 7 following any vaccination of V260 and/or IPV • Proportions of participants with SAEs from Day 1 through end of study
Statistical Methods for Key Immunogenicity Analyses	For the primary hypothesis, concomitant-use group will be considered non-inferior to staggered-use group if the lower bound of the two-sided 95% confidence interval (CI) for the difference in seroconversion percentage (concomitant-use group minus staggered-use group) is greater than -10% for each poliovirus type.
Statistical Methods for Key Safety Analyses	All safety data will be summarized as frequencies and percentages for the two vaccination groups.
Interim Analyses	No interim analysis is planned.
Multiplicity	Since success is required on all 3 poliovirus types for the primary hypothesis, no multiplicity adjustment will be made for the multiple tests.
Sample Size and Power	The planned sample size is 400 participants. For the seroconversion percentage to each of poliovirus types 1, 2, and 3 at 1 month post dose 3, the study has approximately an overall 90.0% power to demonstrate that the concomitant-use group is non-inferior to the staggered-use group at an overall one-sided 2.5% alpha-level, if the underlying treatment difference is 0 percentage points.

9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the SPONSOR.

This study is being conducted as a randomized, open-label study, i.e., participants, investigators, and SPONSOR personnel will be aware of participant treatment assignments after each participant is enrolled and treatment is assigned.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study intervention assignment. Randomization will be implemented using an IRT.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

9.4 Analysis Endpoints

Immunogenicity and safety endpoints that will be evaluated or summarized are listed below.

9.4.1 Immunogenicity Endpoints

A description of immunogenicity assessments is presented in Section 4.2.1.1.

The primary immunogenicity analysis endpoints are neutralizing antibody seroconversion percentages to each of poliovirus types 1, 2, and 3 at 1 month post dose 3 of IPV. The seroconversion is defined as antibody titer ≥1:8 post-vaccination in baseline seronegative participants or ≥4-fold increase in titer post-vaccination in baseline seropositive participants. The cut-off value determining baseline seropositivity is 1:8 for all 3 poliovirus types. Neutralizing antibodies to poliovirus types 1, 2, and 3 will be measured by the laboratory of NIFDC.

The secondary immunogenicity analysis endpoints include:

- Neutralizing antibody GMTs to each of poliovirus types 1, 2, and 3 at 1 month post dose 3 of IPV.
- Proportions of participants with neutralizing antibody titer ≥1:8 and ≥1:64 at 1 month post dose 3 of IPV for each of poliovirus types 1, 2, and 3.

The exploratory immunogenicity analysis endpoints include:

- Proportions of participants with ≥3-fold increase in anti-rotavirus type-specific IgA titer post-vaccination from baseline to serotypes G1, G2, G3, G4, and P1A[8] at 1 month post dose 3 of V260.
- Anti-rotavirus type-specific IgA GMTs to serotypes G1, G2, G3, G4, and P1A[8] at 1 month post dose 3 of V260.

9.4.2 Safety Endpoints

A description of safety measures is presented in Section 4.2.1.2 and Section 8.3. The analysis of safety results is described in Section 9.6.2.

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs and post-vaccination temperature measurements following V260 and/or IPV.

The safety analysis endpoints include:

- Proportions of participants with solicited injection-site AEs (erythema, swelling, induration, and pain at the injection-site of IPV) from Day 1 through Day 7 post-vaccination of IPV in the two vaccination groups

- Proportions of participants with solicited systemic AEs (diarrhea and/or vomiting) from Day 1 through Day 7 post-vaccination of V260 and IPV in the concomitant-use group, and from Day 1 through Day 7 post-vaccination of V260 plus from Day 1 through Day 7 post-vaccination of IPV in the staggered-use group

- Proportions of participants with any injection-site AEs from Day 1 through Day 15 post-vaccination of V260 and IPV in the concomitant-use group, and from Day 1 through Day 15 post-vaccination of IPV in the staggered-use group

- Proportions of participants with any systemic AEs from Day 1 through Day 30 post-vaccination of V260 and IPV in the concomitant-use group, and from Day 1 through Day 15 post-vaccination of V260 plus from Day 1 through Day 15 post-vaccination of IPV in the staggered-use group

- Proportions of participants with any vaccine-related injection-site AEs from Day 1 through Day 15 post-vaccination of V260 and IPV in the concomitant-use group, and from Day 1 through Day 15 post-vaccination of IPV in the staggered-use group

- Proportions of participants with any vaccine-related systemic AEs from Day 1 through Day 30 post-vaccination of V260 and IPV in the concomitant-use group, and from Day 1 through Day 15 post-vaccination of V260 plus from Day 1 through Day 15 post-vaccination of IPV in the staggered-use group

- Proportion of participants with any SAE, any AE which is both vaccine-related and serious, any AE resulting in discontinuation, and proportion of participants who died, proportion of participants with intussusception during the entire study period in the two vaccination groups

- Proportions of participants with maximum temperature measurements from Day 1 through Day 7 post-vaccination of V260 and IPV in the concomitant-use group, and Day 1 through Day 7 post-vaccination of V260 plus Day 1 through Day 7 post-vaccination of IPV in the staggered-use group

9.5 Analysis Populations

9.5.1 Immunogenicity Analysis Populations

The Per-Protocol Immunogenicity (PPI) population will serve as the primary population for the analysis of immunogenicity data in this study. The PP population is defined as participants who receive the 3 scheduled doses of study vaccines, adhere to guidelines for administration of study vaccines, provide baseline and post-vaccination blood samples within

acceptable day range, and do not have important deviations from the protocol that may substantially affect the results of the primary endpoint.

The final determination on important protocol deviations, and thereby the composition of the PP population, will be made prior to the final database lock.

Supportive analysis for primary immunogenicity objective will be performed on the full analysis set (FAS) of all participants who provide baseline and post dose 3 serum samples, regardless of protocol deviations.

Participants will be included in the treatment group to which they are randomized for the analysis of immunogenicity data using both the PP and FAS populations.

9.5.2 Safety Analysis Populations

Safety Analyses will be conducted in the All Participants as Treated (APaT) population, which consists of all randomized participants who receive at least one dose of study vaccination. Participants will be included in the group corresponding to the study vaccination they actually received for the analysis of safety data using the APaT population.

At least one temperature measurement obtained subsequent to study intervention is required for inclusion in the analysis of temperature.

9.6 Statistical Methods

Statistical testing and inference for immunogenicity and safety analyses are described in Section 9.6.1 and Section 9.6.2, respectively. Unless otherwise stated, all statistical tests will be conducted at the α=0.025 (1-sided) level.

9.6.1 Statistical Methods for Immunogenicity Analyses

This section describes the statistical methods that address the primary and secondary immunogenicity objectives. Methods related to exploratory objectives will be described in the supplemental SAP.

Primary Endpoint

For the primary hypothesis, seroconversion percentage at 1 month post dose 3 of IPV will be analyzed separately for each of 3 poliovirus types. The statistical criterion for non-inferiority requires that the lower bound of two-sided 95% confidence interval of the difference in seroconversion percentages (concomitant-use group minus staggered-use group) be greater than -10% for each poliovirus type. The primary hypothesis will be considered a success if the non-inferiority criteria for the difference in seroconversion percentages are met for all 3 poliovirus types in the comparisons between concomitant-use group vs. staggered-use group.

For each poliovirus type, the hypothesis to be tested at α=0.025 level (1-sided) are

$$H_0: p_1\text{-}p_2 \leq -0.1$$

$$H_a: p_1\text{-}p_2 > -0.1$$

where p_1 is the true seroconversion percentage at 1 month post dose 3 in the concomitant-use group and p_2 is the true seroconversion percentage at 1 month post dose 3 in the staggered-use group. The confidence interval will be calculated using the method proposed by Miettinen and Nurminen [Miettinen, O. and Nurminen, M. 1985].

Secondary Endpoints

For the proportion-type estimates of the secondary endpoints such as seroresponse rates of neutralizing antibodies to poliovirus types 1, 2, and 3, the 95% CIs of within each group will be provided and obtained by using exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. 1934].

The evaluation of IPV neutralizing antibody GMTs to each of poliovirus types 1, 2, and 3 will include descriptive summaries and within-group 95% CIs. Point estimates for the GMTs will be calculated by exponentiating the estimates of the mean of the natural log values. The within-group CIs will be derived by exponentiating the CIs of the mean of the natural log values based on the t-distribution.

Summary statistical analysis will be provided for exploratory endpoints. Details will be described in the supplemental SAP.

Table 3 summarizes the key immunogenicity analyses.

Table 3 Analysis Strategy for Key Immunogenicity Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach†	Statistical Method‡	Analysis Population	Missing Data Approach
Primary Objectives				
Neutralizing Antibody Seroconversion Percentages to Each of Poliovirus Types 1, 2, and 3 at 1 Month Post Dose 3 of IPV (each type will be tested separately)	P	Point and 95% CI estimation as well as statistical testing of binomial proportion based on M & N method§	PP	Observed data only
Neutralizing Antibody Seroconversion Percentages to Each of Poliovirus Types 1, 2, and 3 at 1 Month Post Dose 3 of IPV	S	Point and 95% CI estimation as well as statistical testing of binomial proportion based on M & N method§	FAS	Observed data only

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach†	Statistical Method‡	Analysis Population	Missing Data Approach
Secondary Objectives				
Neutralizing Antibody GMTs to Each of Poliovirus Types 1, 2, and 3 at 1 Month Post Dose 3 of IPV	P/S	Point and 95% CI estimation based on t-distribution of natural log values	PP/FAS	Observed data only
Proportions of Participants with Neutralizing Antibody Titer ≥ 1:8 at 1 Month Post Dose 3 of IPV for Each of Poliovirus Types 1, 2, and 3	P/S	Point and 95% CI estimation based on exact method%	PP/FAS	Observed data only
Proportions of Participants with Neutralizing Antibody Titer ≥ 1:64 at 1 Month Post Dose 3 of IPV for Each of Poliovirus Types 1, 2, and 3	P/S	Point and 95% CI estimation based on exact method%	PP/FAS	Observed data only

† P=Primary approach; S=Supportive approach.
‡ Statistical models are described in further detail below:
§ Miettinen and Nurminen method.
% Exact binomial method proposed by Clopper and Pearson (1934).

9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs and post-vaccination temperature measurements.

An overall assessment of adverse events will be summarized for each group by dose period (dose period is defined in Table 4) and across all dose periods.

Table 4 Each Group by Dose Period

Dose Period	Concomitant-Use Group (Vaccine administered)	Staggered-Use Group (Vaccine administered)
1	Visit 2 (V260 + IPV)	Visit 1 (V260)
	Visit 3	Visit 2 (IPV)
2	Visit 4 (V260 + IPV)	Visit 3 (V260)
	Visit 5	Visit 4 (IPV)
3	Visit 6 (V260 + IPV)	Visit 5 (V260)
	Visit 7	Visit 6 (IPV)

Summary statistics, counts and percentage without confidence interval, will be provided by group. Proportions of participants with solicited injection-site AEs (following vaccination of IPV), solicited systemic AEs within 7 days following study vaccination will be given. Maximum axillary temperatures recorded on the VRC from Day 1 through Day 7 post-vaccination will be summarized. Table 5 shows the safety endpoints that will be summarized.

Table 5 Analysis Strategy for Safety Parameters

Safety Endpoints	Time Period	Descriptive Statistics
Solicited Injection-Site AEs	Days 1-7 post-vaccination of V260 and IPV in the concomitant-use group, and Days 1-7 post-vaccination of IPV in the staggered-use group, across all dose periods and by dose period	X
Solicited Systemic AEs	Days 1-7 post-vaccination of V260 and IPV in the concomitant-use group, and Days 1-7 post-vaccination of V260 plus Days 1-7 post-vaccination of IPV in the staggered-use group, across all dose periods and by dose period	X
Maximum Axillary Temperature	Days 1-7 post-vaccination of V260 and IPV in the concomitant-use group, and Days 1-7 post-vaccination of V260 plus Days 1-7 post-vaccination of IPV in the staggered-use group, across all dose periods and by dose period	X
Any Injection-Site AEs	Days 1-15 post-vaccination of V260 and IPV in the concomitant-use group, and Days 1-15 post-vaccination of IPV in the staggered-use group, across all dose periods and by dose period	X
Any Systemic AEs	Days 1-30 post-vaccination of V260 and IPV in the concomitant-use group, and Days 1-15 post-vaccination of V260 plus Days 1-15 post-vaccination of IPV in the staggered-use group, across all dose periods and by dose period	X
Any Vaccine-related Injection-Site AEs	Days 1-15 post-vaccination of V260 and IPV in the concomitant-use group, and Days 1-15 post-vaccination of IPV in the staggered-use group, across all dose periods and by dose period	X
Any Vaccine-related Systemic AEs	Days 1-30 post-vaccination of V260 and IPV in the concomitant-use group, and Days 1-15 post-vaccination of V260 plus Days 1-15 post-vaccination of IPV in the staggered-use group, across all dose periods and by dose period	X
Discontinuation due to any AE	Entire Study Period by Vaccination Group	X
Any Serious AEs including Intussusception	Entire Study Period by Vaccination Group	X
X = results will be provided.		

To assess the severity of adverse events, both Sponsor's criteria (see "Assessment of Intensity/Toxicity" in Section 10.3 - Appendix 3) and China Regulatory Agency's criteria (see Section 10.7 - Appendix 7: Country-specific Requirements) will be applied. The incidence of greatest adverse event severity reported by a participant based on both the two criteria will be tabulated for: all injection-site AEs and all systemic AEs across all dose periods.

For the across dose-period summaries and analyses, if the same AE occurs multiple times across dose periods, the AE will be counted once. In order to evaluate any additive safety issues for the concomitant use of V260 and IPV compared to the staggered use of these vaccines, the following summaries will also be provided: Frequencies and percentages of the solicited systemic AEs during Days 1 to 7 after V260 concomitant with IPV in the concomitant-use group, during Days 1 to 7 after V260 alone in the staggered-use group, and during Days 1 to 7 after IPV alone in the staggered-use group.

Any injection-site AEs and vaccine-related injection-site AEs during Days 1 to 30 post-vaccination of V260 and IPV in the concomitant-use group will be summarized separately.

Any reportable safety events collected between Visit 1 and 2 in the concomitant-use group will be listed separately.

For serious adverse events observed during the study, including intussusception, a detailed description will be included in the CSR.

9.6.3 Demographic and Baseline Characteristics

The comparability of the groups for each relevant demographic and baseline characteristic will be assessed by the use of summary tables. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables (e.g., age, race, gender, birth weight [kg]), medical history, prior and concomitant vaccinations and therapies will be summarized by group either by descriptive statistics or categorical tables.

9.7 Interim Analyses

No interim analyses are planned for this study.

9.8 Multiplicity

There will be no multiplicity adjustment. The success of the study requires demonstrating non-inferiority for all 3 of the poliovirus types described in the primary study hypothesis.

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power for immunogenicity Analyses

This study will randomize 200 participants into the concomitant-use group and 200 into the staggered-use group and has approximately an overall 90.0% power to establish that the concomitant-use group is non-inferior to the staggered-use group in the seroconversion percentage to IPV at 1 month post dose 3 at an overall one-sided, 2.5% alpha-level, if the underlying treatment difference is 0 percentage points. The power and sample size are based on the following assumptions:

1. There is no difference in the true seroconversion percentages for each poliovirus type at 1 month post dose 3 between the concomitant-use and staggered-use groups.

2. The true seroconversion rate for poliovirus types 1, 2, and 3 at 1 month post dose 3 of IPV is 96%, 93% and 97% respectively based on China local IPV studies.

3. The statistical criterion for non-inferiority requires that the lower bound of two-sided 95.0% confidence interval for the difference (concomitant-use group minus staggered-use group) in seroconversion percentages be greater than -10% for each poliovirus type.

4. An 85% evaluability rate for primary immunogenicity analysis population.

Table 6 Sample Size and Power Calculated Based on Neutralizing Antibody Seroconversion Percentage Difference

Antigen	Seroconversion Percentages in Staggered-use Group	Enrolled Participants in Each Group	Effective Sample Size	Power
Poliovirus Type 1	96%	200	170	0.9842
Poliovirus Type 2	93%	200	170	0.9188
Poliovirus Type 3	97%	200	170	0.9953
Overall Power	0.900[†]			

[†]Overall power is calculated by multiplying the power for each poliovirus type.

The calculation is based on the method proposed by Miettinen and Nurminen [Miettinen, O. and Nurminen, M. 1985] with 170 participants in both groups expected to be included in the analysis and is carried out using PASS 2008. The minimum criterion for success is that the lower bound of two-sided 95% CI of difference >-10%. Given the assumed seroconversion percentage of 95% in the staggered-use group, this may occur when the observed difference in response rates is approximately -3% or larger.

9.9.2 Sample Size and Power for Safety Analyses

The probability of observing at least one SAE in this study depends on the number of participants vaccinated and the underlying percentage of participants with a SAE in the study population. If the underlying incidence of a SAE is 1.7% (1 of every 59 participants receiving the vaccine), there is a 96.8% chance of observing at least one SAE among 200 participants both in the concomitant-use group and in the staggered-use group. If no SAEs are observed among the 200 participants in any group, this study will provide 97.5% confidence that the underlying percentage of participants with SAE is <1.8% (one in every 67 participants) in the group.

The estimate of and the upper bound of the 95% confidence interval for the underlying percentage of participants with a SAE given various hypothetical observed number of participants with a SAE within the group are provided in Table 7. These calculations are based on the exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. 1934].

Table 7 Estimate of Incidence of SAE and 95% Upper Confidence Bound Based on Hypothetical Number of Participants with SAE Among 200 Participants in the Group

Hypothetical Number of Participants With SAE	Estimate of Incidence	95% Upper Confidence Bound[†]
1	0.5%	2.75%
5	2.5%	5.74%
10	5%	9.00%
20	10%	15.02%
40	20%	26.22%
[†] Based on the two-tailed exact confidence interval of a binomial proportion (Clopper and Pearson, 1934).		

9.10 Subgroup Analyses

No subgroup analyses will be performed.

9.11 Compliance (Medication Adherence)

Compliance is defined in this study as receipt of all scheduled study vaccinations. To summarize compliance, the numbers and proportion of randomized participants who receive each vaccination will be tabulated.

9.12 Extent of Exposure

The extent of exposure will be summarized by the number and proportion of randomized participants administered V260 and the number and proportion of randomized participants administered IPV at each vaccination schedule.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud,

scientific/research misconduct or serious GCP-non-compliance is suspected, the issues are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with

standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.5 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.6 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

10.1.7 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during

the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.9 Study and Site Closure

The Sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

There are no protocol-specified clinical laboratory assessments in the study.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

- **Results in death**
- **Is life-threatening**
- The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- **Requires inpatient hospitalization or prolongation of existing hospitalization**
- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE.) A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.
- **Results in persistent or significant disability/incapacity**
- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- **Is a congenital anomaly/birth defect**

- In offspring of participant taking the product regardless of time to diagnosis.

- **Other important medical events**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a cancer

- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant

number, will be blinded on the copies of the medical records before submission to the Sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:

  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).

  - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies, definitely acting like something is wrong).

  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

- Injection site erythema/redness or swelling from the day of vaccination through Day 7 postvaccination will be evaluated by maximum size.

- The investigator will assess toxicity for each AE based on China Regulatory Agency's criteria (see Section 10.7 - Appendix 7: Country-specific Requirements).

Assessment of causality

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialled document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE;** the greater the correlation with the components and

their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:

- **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (diary, etc.), seroconversion or identification of vaccine virus in bodily specimen?

- **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a vaccine-induced effect?

- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors?

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in the study?

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

    (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose vaccine study; or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).

    - Yes, there is a reasonable possibility of Sponsor's product relationship:

        - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is

reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

- No, there is not a reasonable possibility of Sponsor's product relationship:
    - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- New or updated information will be recorded in the CRF.

- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.5 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).

- If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
    - Reference Section 8.4.1 for reporting time requirements.

- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Not applicable.

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

Not applicable.

10.7 Appendix 7: Country-specific Requirements

China Regulatory Agency's Criteria on Assessment of Toxicity of Adverse Events

Guideline for Grading Scales of Adverse Events in Clinical Trials of Prophylactic Vaccines (Document No.: 2019#102)

(released on 26-DEC-2019, http://www.nmpa.gov.cn/WS04/CL2182/373037.html)

I. Foreword

Prophylactic vaccines (hereinafter referred to as the "vaccines") refer to prophylactic biological products used for human immunization, including immunization-program vaccines and non-immunization-program vaccines, in order to prevent and control the occurrence and prevalence of diseases.

Clinical trials of vaccines should strictly comply with the Drug Administration Law of the People's Republic of China, the Vaccine Administration Law of the People's Republic of China, the Measures for Administration of Drug Registration, the Good Clinical Practice (GCP), the Technical Guideline for Vaccine Clinical Trials, and the Guideline for Good Clinical Practice of Vaccine Clinical Trials (Trial Implementation). As vaccines are usually used for healthy population, mostly for healthy children or infants, healthy subjects will be generally selected for clinical trials at each stage. Therefore, the requirements for safety and risk control in vaccine clinical trials shall be more stringent than those for therapeutic drugs, and the strictest management system shall be implemented, with the continuous efforts paid for risk management and control through the whole period of study.

This Guideline provided grading scales for severity assessment of adverse events in vaccine clinical trials, in order for scientific monitoring and evaluation of vaccine-related adverse reactions by reasonable assessment and determination of the relationship between adverse events and vaccination, thus minimizing the risks of healthy subjects in clinical trials and use of vaccines.

The Guidelines is developed on the basis of the available regulations, the industrial standards, and the current scientific knowledge. The selected grading scales are based on the similar guidelines issued by overseas regulatory agencies and the industrial guidelines, considering China's clinical practice, and will be updated in due course with the continuous updates of relevant regulations, standards. and the increase of scientific knowledge.

II. Scope of Application

This Guideline is applicable to evaluation of the severity (i.e. intensity) of adverse events in vaccine clinical trials. Since the subjects of vaccine clinical trials may be adults, teenagers, children or infants, the severity of clinical symptoms, signs and laboratory examination abnormalities in the trials shall be evaluated according to the physiological characteristics of different age groups. The grading scales can also be used as the emergency unblinding standards stipulated in the design of vaccine clinical trials and as the reference to determine

whether to suspend/terminate the clinical trials. Additionally, the standardized grading scales of adverse events provided by the Guidelines are also conducive to the comparison of safety data within clinical trials or between different clinical trials.

III. Basic Contents

The grading scales of adverse events in vaccine clinical trials provided by the Guidelines include two parts: (1) clinical indicators (i.e. symptoms and signs, including adverse events at the vaccination site, vital signs and adverse events at the non-vaccination site); and (2) laboratory testing indicators (i.e. blood biochemistry, blood routine examination, and urine routine examination, etc.). In clinical trials, appropriate indicators can be selected from the adverse event grading table of the Guidelines for safety monitoring and evaluation according to characteristics of vaccine, study population, and disease.

This Guidelines does not cover all safety indicators required to be observed in vaccine clinical trials. For new vaccines, new indicators may be monitored based on the safety findings from preclinical toxicological studies of vaccines or the experience from similar products. The rationale for the grading scales of new indicators should be clearly described and explained in the protocol of clinical trial.

When the grading scales adopted in a clinical trial are inconsistent with this Guidelines due to the difference in observation or detection methods and new grading scales are to be developed, the rationale should be comprehensive and explained in the protocol of clinical trial.

The safety indicators for children and infants included in the Guidelines are limited and could be supplemented with new indicators according to the specific requirements for safety assessment of candidate vaccines.

(I) Adverse Event Grading Tables

In the monitoring of adverse events in vaccine safety trials, clinical symptoms and signs should be considered together with the corresponding laboratory testing results, and a comprehensive evaluation of causality should be carried out to obtain reliable conclusions.

During clinical trials, the detailed information of adverse events concerned should be recorded as much as possible, in addition to the recording and reporting of adverse events listed in the following tables.

1. Clinical Observations Indicators (Table 8-Table 10)

Table 8 Grading Scales for Adverse Events at Vaccination Site (Local)

Symptoms /Signs	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Pain, Tenderness (selective; tenderness is used for subjects who are unable to express pain autonomously)				
Pain	Does not affect or slightly affects limb activity	Affects limb activity	Affects daily life	Loss of basic self-care ability or hospitalization
Tenderness	Resistance or flinch of body when being touched or pressed	Cry when being touched or pressed but can be soothed	Cry continuously and unable to be soothed	Emergency treatment or hospitalization
Induration *, Swelling (selective) ** #				
>14 years old	With a diameter of 2.5 ~ 5 cm or an area of 6.25 ~<25 cm^2 and does not affect or slightly affects daily life	With a diameter of 5 ~ <10 cm or an area of 25 ~<100 cm^2 or affects daily life	With a diameter of ≥10 cm or an area of ≥100 cm^2 or causing fester or secondary infection or phlebitis or aseptic abscess or wound drainage or significantly affects daily life	Abscess, exfoliative dermatitis, dermal or deep tissue necrosis
≤14 years old	With a diameter of <2.5 cm	With a diameter of ≥2.5 cm and an area that is less than 50% of the vaccinated limb (i.e. the limb where the vaccination site is located anatomically, such as the upper arm or thigh)	With an area that is more than 50% of the vaccinated limb or causing fester or secondary infection or phlebitis or wound drainage	Abscess, exfoliative dermatitis, dermal or deep tissue necrosis
Rash*, Redness (selective) ** #				
>14 years old	With a diameter of 2.5 ~ 5 cm or an area of 6.25~<25 cm^2 and does not affect or slightly affects daily life	With a diameter of 5 ~ <10 cm or an area of 25 ~ <100 cm^2 or affects daily life	With a diameter of ≥10 cm or an area of ≥100 cm^2 or causing fester or secondary infection or phlebitis or aseptic abscess or wound drainage or significantly affects daily life	Abscess, exfoliative dermatitis, dermal or deep tissue necrosis
≤14 years old	With a diameter of <2.5 cm	With a diameter of ≥2.5 cm and an area that is less than 50% of the vaccinated limb (i.e. the limb where the vaccination site is located anatomically, such as the upper arm or thigh)	With an area that is more than 50% of the vaccinated limb or causing fester or secondary infection or phlebitis or wound drainage	Abscess, exfoliative dermatitis, dermal or deep tissue necrosis

Symptoms /Signs	Grade 1	Grade 2	Grade 3	Grade 4
Others				
Pruritus	Pruritus at the vaccination site that resolves spontaneously or resolves within 48 hours after treatment	Pruritus at the vaccination site that does not resolve within 48 hours after treatment	Affects daily life	NA
Cellulitis	NA	Non-injection therapy (e.g. treatment with oral antibacterial, antifungal and antiviral drugs) is needed	Intravenous therapy (e.g. treatment with intravenous antibacterial, antifungal and antiviral drugs) is needed	Sepsis or tissue necrosis, etc

Note: *The progressive changes of measurement results shall be recorded as well in addition to direct diameter measurement for grading evaluation.
**The maximum size of diameter or area shall be used.
#The evaluation and grading of induration and swelling or rash and redness shall be based on the functional grade and actual measurement results, and the indicators with higher grading level shall be selected.

Table 9 Grading Scales for Vital Signs

Signs	Grade 1	Grade 2	Grade 3	Grade 4
Fever* (axillary temperature [℃])				
>14 years old	37.3 ~<38.0	38.0 ~<38.5	38.5 ~<39.5	≥39.5, persists for more than 3 days
≤14 years old	37.5 ~<38.0	38.0 ~<39.5	≥39.5	≥39.5, persists for more than 5 days
Prolonged PR interval in electrocardiogram or atrioventricular conduction block (selective)				
>16 years old	With a PR interval of 0.21 ~ 0.25 seconds	With a PR interval of ⩾0.25 seconds or second degree atrioventricular block of type I	With second degree atrioventricular block of type II or ventricular interval of ≥3 seconds	Complete atrioventricular block
≤16 years old	With first degree atrioventricular block (PR interval > normal value among the population of the same age and type)	With second degree atrioventricular block of type I	With second degree atrioventricular block of type II or ventricular interval of ≥3 seconds	Complete atrioventricular block
Heart rate				
Tachycardia (beats/minute)	101 ~ 115	116 ~ 130	>130	Arrhythmia requires emergency treatment or hospitalization.
Bradycardia (beats/minute)	50 ~ 54	45 ~ 49	<45	Arrhythmia requires emergency treatment or hospitalization.

Signs	Grade 1	Grade 2	Grade 3	Grade 4
Blood pressure				
Hypertension (mmHg)				
≥18 years old	Systolic blood pressure: 140 ~< 160 or diastolic pressure: 90 ~<100	Systolic blood pressure: ≥160 ~<180 or diastolic pressure: ≥100 ~<110	Systolic blood pressure: ≥180 or diastolic pressure: ≥110	Occurrence of life-threatening complications that was not diagnosed previously (e.g. malignant hypertension) or hospitalization
<18 years old	Systolic blood pressure: >120 ~<152 or diastolic pressure: >80 ~<95	Systolic blood pressure: ≥152 ~<178 or diastolic pressure: ≥95 ~<109	Systolic blood pressure: ≥178 or diastolic pressure: ≥109	Occurrence of life-threatening complications that was not diagnosed previously (e.g. malignant hypertension) or hospitalization
Hypotension (systolic blood pressure) (mmHg)	85 ~<89	80 ~<85	<80	shock or hospitalization
Respiration frequency (times/minute)	17 ~ 20	21 ~ 25	>25	Tracheal intubation is needed

Note: *Axillary temperature is usually measured in China and can be converted into oral temperature and rectal temperature if necessary. Generally, oral temperature = axillary temperature + 0.2℃; and rectal temperature = axillary temperature + (0.3~0.5℃). In the event of sustained high fever, the cause of high fever shall be determined as soon as possible.

Table 10 Grading Scales for Adverse Events at Non-vaccination Site (Systemic)

Symptoms/ Signs by Organ System	Grade 1	Grade 2	Grade 3	Grade 4
Gastrointestinal system				
Diarrhea	Mild or transient, 3 ~ 4 times/day, abnormal fecal characteristics, or mild diarrhea lasting for less than 1 week	Moderate or persistent, 5 ~ 7 times/day, abnormal fecal characteristics, or diarrhea lasting for more than 1 week	> 7 times/day, abnormal fecal characteristics, or bloody diarrhea, orthostatic hypotension, electrolyte imbalance, requires intravenous infusion of > 2L	Hypotensive shock, hospitalization is needed

Symptoms/ Signs by Organ System	Grade 1	Grade 2	Grade 3	Grade 4
Constipation*	Requires fecal softener and dietary adjustment	Requires treatment with laxative drug	Intractable constipation that requires manual dredging or use of enema	Toxic megacolon or intestinal obstruction
Dysphagia	Mild discomfort when swallowing	Eating and drinking behavior is restricted	Eating and drinking behavior and conversation are significantly restricted; unable to eat solid food	Unable to eat liquid food; requires intravenous nutrition
Anorexia	Loss of appetite but no reduction in food intake	Loss of appetite, reduction in food intake, but no significant reduction in body weight	Loss of appetite and significant weight loss	Requires intervention (such as gastric tube feeding and parenteral nutrition)
Vomiting	1 ~ 2 times /24 hours, and does not affect daily activities	3 ~ 5 times /24 hours or affects daily activities	>6 times within 24 hours or requires intravenous fluid infusion	Hospitalization due to hypotensive shock or nutrition through other routes needed
Nausea	Transient (< 24 hours) or intermittent with normal food intake	Persistent nausea leads to reduction in food intake (24-48 hours)	Persistent nausea leads to being impossible to intake any food (> 48 hours), or requires intravenous fluid infusion	Life-threatening (e.g. hypotensive shock)
Musculoskeletal and connective tissues				
Myalgia (non-vaccination site)	Does not affect daily activities	Slightly affects daily activities	Severe muscle pain, significantly affects daily activities	Emergency treatment or hospitalization
Arthritis	Mild pain, with inflammation, erythema or joint swelling; but does not impair the function	Moderate pain, with inflammation, erythema or joint swelling; impairs function, but does not affect daily activities	Severe pain, with inflammation, erythema or joint swelling; affects daily activities	Permanent and/or disabling joint injuries
Joint pain	Mild pain, does not impair function	Moderate pain; requires treatment with analgesics and/or the pain impairs function, but does not affect daily activities	Severe pain; requires treatment with analgesics, and/or the pain affects daily activities	Disabling pain

Symptoms/ Signs by Organ System	Grade 1	Grade 2	Grade 3	Grade 4
Nervous system				
Headache	Does not affect daily activities, does not require treatment	Transient, slightly affects daily activities, may need treatment or intervention	Significantly affects daily activities, requires treatment or intervention	Refractory, requires emergency treatment or hospitalization
Syncope	Close to syncope without loss of consciousness (e.g. foreboding of syncope)	Loss of consciousness but does not require treatment	Loss of consciousness, requires treatment or hospitalization	NA
New onset of convulsion				
≥18 years old	NA	NA	1 ~ 3 times.	Long-lasting and multiple convulsions (e.g. under persistent state of convulsion) or uncontrollable (e.g. intractable epilepsy)
<18 years old	The duration of convulsion is less than 5 minutes, and the post-convulsion state lasts for less than 24 hours	The duration of convulsion is ≥5 ~<20 minutes, and the post-convulsion state lasts for less than 24 hours	The duration of convulsion is ≥20 minutes, or the post-convulsion state lasts for more than 24 hours	Long-lasting and multiple convulsions (e.g. under persistent state of convulsion) or uncontrollable (e.g. intractable epilepsy)
Respiratory system				
Cough	Transient, does not require treatment	Persistent, treatment is effective	Paroxysmal, not controlled by treatment	Requires emergency treatment or hospitalization
Acute bronchospasm	Transient, does not require treatment; FEV_1%: 70%~80%	Requires treatment; returning to normal after treatment with bronchiectasis agent; FEV_1%: 50%~70%	Unable to return to normal after treatment with bronchiectasis agent; FEV_1: 25%~50%, or continuous depression between ribs	Cyanopathy; FEV_1%<25%; or requires tracheal intubation
Dyspnea	Difficulty in breathing during exercise	Difficulty in breathing during normal activities	Difficulty in breathing during rest	Difficulty in breathing, requires oxygen-inhaling therapy, hospitalization or assisted breathing treatment

Symptoms/ Signs by Organ System	Grade 1	Grade 2	Grade 3	Grade 4
Skin and subcutaneous tissue				
Pruritus at non-vaccination sites (no skin damage)	Mild pruritus, does not affect or slightly affects daily life	Pruritus that affects daily life	Pruritus that prevents daily life	NA
Abnormal skin mucosa	Erythema/pruritus/color change	Diffuse rash/ maculopapule/ dryness/desquamation	Blister/exudation/desquamation/ulcer	Exfoliative dermatitis that involves mucosa, or erythema multiforme, or suspected Stevens-Johnsons syndrome.
Mental system				
Insomnia*	Mild difficulty in falling asleep, does not affect or slightly affects daily life	Moderate difficulty in falling asleep, affects daily life	Severe difficulty in falling asleep, significantly affects daily life, requires treatment or hospitalization	NA
Irritable or depressed	Mild irritable or depressed	Irritable or lethargic	Unable to soothe or unresponsive	NA
Mental disorders (including anxiety, depression, mania and insanity), and detailed symptoms shall be reported	Mild symptoms that does not require clinic visit, or the behavior does not affect or slightly affects daily life	With clinical symptoms, requires clinic visit, or the behavior affects daily life	Requires hospitalization, or unable to perform daily life	With the tendency to hurt him/herself or others, acute mental disorder or loss of basic self-care ability
Immune system				
Acute allergic reaction**	Local urticaria (blister), does not require treatment	Local urticaria, requires treatment, or mild angioedema, does not require treatment	Extensive urticaria or angioedema that requires treatment, or mild bronchospasm	Anaphylactic shock, life-threatening bronchospasm or laryngeal edema
Others				
Fatigue	Does not affect daily activities	Affects daily activities	Significantly affects daily activities, unable to work	Requires emergency treatment or hospitalization

Symptoms/ Signs by Organ System	Grade 1	Grade 2	Grade 3	Grade 4
Pain at non-vaccination site # (The location of pain should be specified when reporting)	Mild pain, does not affect or slightly affects daily life	Pain that affects daily life	Pain that prevents daily activities	Disabling pain, causing loss of basic self-care ability

Note: FEV_1% refers to forced expiratory volume (FEV_1)/ forced vital capacity (FVC) for one second.
* In the event of constipation and insomnia, attention shall be paid to changes before and after vaccination.
**It refers to type-I hypersensitivity.
It refers to pain in non-vaccinated sites in addition to muscle pain, arthralgia and headache.

2. Laboratory Indicators (Table 11~Table 13)

When laboratory indicators are used for safety evaluation, it is necessary to consider the update of testing technology and methods currently used in clinical practice in addition to the industrial scientific standards. Therefore, the rationale for selection of indicators and grading scales should be comprehensive and explained in the protocol of clinical trial, i.e. it should conform to the normal range of scandalized or recognized physiological and biochemical limits to prove its rationality and feasibility. The indicators listed below are provided for reference only.

Laboratory test results between the upper limit (ULN) or lower limit (LLN) of the reference range and Grade 1 will not be reported as adverse events.

Table 11 Grading Scales for Blood Biochemistry Measurements

Indicators	Grade 1	Grade 2	Grade 3	Grade 4
Liver function (elevated ALT, AST)	1.25 ~ <2.5 ×ULN	2.5~ <5.0×ULN	5.0~ <10×ULN	≥10×ULN
Elevated total bilirubin (mg/dL; μmol/L)				
>28 days of age	1.1~ <1.6×ULN	1.6~ <2.6×ULN	2.6 ~ 5.0×ULN	≥5.0×ULN
7 ~ <28 days of age (Breastfeeding)	5 ~ <10 85.5 ~ <171	10 ~ <20 171 ~ <342	20 ~ <25 342 ~ <427.5	≥25 ≥427.5
7 ~ <28 days of age (Non-Breastfeeding)	1.1 ~ <1.6×ULN	1.6 ~ <2.6×ULN	2.6 ~ 5.0×ULN	≥5.0×ULN
72 hours ~ <7 days of age	11 ~ <16 188.1 ~ <273.6	16 ~ <18 273.6 ~ <307.8	18 ~ <24 307.8 ~ <410.4	≥24 ≥410.4
48 ~ <72 hours of age	8.5 ~ <13 145.5 ~ <222.3	13 ~ <15 222.3 ~ <256.5	15 ~ <22 256.5 ~ <376.2	≥22 ≥376.2

Indicators	Grade 1	Grade 2	Grade 3	Grade 4
24 ~ <48 hours of age	5 ~ <8 85.5 ~ <136.8	8 ~ <12 136.8 ~ <205.2	12 ~ <19 205.2 ~ <324.9	≥19 ≥324.9
<24 hours of age	4 ~ <7 68.4 ~ <119.7	7 ~ <10 119.7 ~ <171	10 ~ <17 171 ~ <290.7	≥17 ≥290.7
Pancreatin (amylase, lipase)	1.1 ~ <1.5×ULN	1.5 ~ <3.0×ULN	3.0 ~ <5.0×ULN	≥5.0×ULN
Creatine phosphokinase (CPK)	1.25 ~ <1.5×ULN	1.5 ~ <3.0×ULN	3.0 ~ <10×ULN	≥10×ULN
Hypernatremia (Na, mmol/L)	146 ~ <150	150 ~ <154	154 ~ <160	≥160
Hyponatremia (Na, mmol/L)	130 ~ <135	125 ~ <130	121 ~ <125	≤120
Hyperkalemia (K, mmol/L)	5.6 ~ <6.0	6.0 ~ <6.5	6.5 ~ <7.0	≥7.0
Hypokalemia (K, mmol/L)	3.0 ~ <3.4	2.5 ~ <3.0	2.0 ~ <2.5	<2.0
Hypercalcemia (Ca, mmol/L)				
≥7 days of age	2.65 ~ <2.88	2.88 ~ <3.13	3.13 ~ <3.38	≥3.38
<7 days of age	2.88 ~ <3.10	3.10 ~ <3.23	3.23 ~ <3.38	≥3.38
Hypocalcemia (Ca, mmol/L)				
≥7 days of age	1.95 ~ <2.10	1.75 ~ <1.95	1.53 ~ <1.75	<1.53
<7 days of age	1.63 ~ <1.88	1.50 ~ <1.63	1.38 ~ <1.50	<1.38
Hyperglycemia (Glu, mmol/L)				
Fasting	6.11 ~ <6.95	6.95 ~ <13.89	13.89 ~ <27.75	≥27.75
Non-fasting	6.44 ~ <8.89	8.89 ~ <13.89	13.89 ~ <27.75	≥27.75
Hypoglycemia (Glu, mmol/L)				
≥1 month of age	3.05 ~ <3.55	2.22 ~ <3.05	1.67 ~ <2.22	<1.67
<1 month of age	2.78 ~ <3.00	2.22 ~ <2.78	1.67 ~ <2.22	<1.67

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

Table 12 Grading Scales for Blood Routine Examinations

Indicators /Grading	Grade 1	Grade 2	Grade 3	Grade 4
White blood cell count increased (WBC, 10^9/L)	11 ~ <13	13 ~ <15	15 ~ <30	≥30
White blood cell count decreased (WBC，10^9/L)				
>7 days of age	2.000 ~ 2.499	1.500 ~ 1.999	1.000 ~ 1.499	<1.000
≤7 days of age	5.500 ~ 6.999	4.000 ~ 5.499	2.500 ~ 3.999	<2.500
Lymphocyte count decreased (LY, 10^9/L)	0.75 ~ 1.00	0.5 ~ 0.749	0.25 ~ 0.49	<0.25
Neutrophil count decreased (ANC，10^9/L)				
>7 days of age	0.800 ~ 1.000	0.600 ~ 0.799	0.400 ~ 0.599	<0.400
2 ~ 7 days of age	1.250 ~ 1.500	1.000 ~ 1.249	0.750 ~ 0.999	<0.750
≤1 day of age	4.000 ~ 5.000	3.000 ~ 3.999	1.500 ~ 2.999	<1.500
Eosinophilic granulocyte (Eos, 10^9/L)	0.65 ~ 1.5	1.51 ~ 5.0	>5.0	Hypereosinophilic syndrome
Thrombocytopenia (PLT, 10^9/L)				
>12 years old	125 ~ 140	100 ~ 124	25 ~ 99	<25
>3 months ~ ≤12 years old	NA	50 ~ 75	25 ~ 49	<25
Low hemoglobin (g/dL)				
≥13 years old, male	10.0 ~ 10.9	9.0 ~ <10.0	7.0 ~ <9.0	<7.0
≥13 years old, female	9.5 ~ 10.4	8.5 ~ <9.5	6.5 ~ <8.5	<6.5
57 days~ <13 years of age (both male and female)	9.5 ~ 10.4	8.5 ~ <9.5	6.5 ~ <8.5	<6.5
36 days ~ 56 days of age (both male and female)	8.5 ~ 9.6	7.0 ~ <8.5	6.0 ~ <7.0	<6.0
22 days ~ 35 days of age (both male and female)	9.5 ~ 11.0	8.0 ~ <9.5	6.7 ~ <8.0	<6.7
8 days ~ 21 days of age (both male and female)	11.0 ~ 13.0	9.0 ~ <11.0	8.0 ~ <9.0	<8.0
≤7 days of age (both male and female)	13.0 ~ 14.0	10.0 ~ <13.0	9.0 ~ <10.0	<9.0

Table 13 Grading Scales for Urine Routine Examinations

Indicators	Grade 1	Grade 2	Grade 3	Grade 4
Urine protein (PRO) (by urine test strip)	1+	2+	3+ or higher	NA
Urine sugar (by urine test strip)	Trace ~ 1+ or ≤250 mg	2+ or >250 ~ ≤500 mg	>2+ or>500 mg	NA
Erythrocytes (microscopic examination) (red blood cell count [rbc/hpf] in each high power field [excluding results during female menstruation])	6 ~ <10	≥10	Visible hematuria with or without blood clots; cylinder shape of urine red blood cell; or treatment needed	Emergency treatment or hospitalization

(II) General principles of Grading Scales for Other Adverse Events

The intensity evaluation should be made according to the following grading scales for other adverse events that are not listed in the tables above.

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild: short-term (<48h) or mild discomfort, does not affect daily activities, does not require treatment	Moderate: mildly or moderately affects daily activities, requires clinic visit, requires no or a little medical intervention	Severe: significantly affects daily activities, requires clinic visits and treatment, may require hospitalization	Critical: possibly threatening life, extremely affects daily activities, requires intensive care	Death

Rare adverse events related to vaccination (i.e. rare adverse reactions) usually can be found in clinical trials with a large sample size or in large population after launch, therefore, it sometimes needs further evaluation in post-marketing studies. For vaccines whose primary target population is healthy population including infants, the safety requirements are stricter than those for other drugs. In pre-marketing clinical trials, the sample size shall be enlarged as much as possible in order to find signals of rare risk related to vaccination. When necessary, clinical trials with safety observation indicators as clinical evaluation endpoints can be conducted, and the minimum sample size should meet the statistical requirements of safety studies.

(III) Causality Evaluation and Safety Report

The clinical safety monitoring should focus on the evaluation of relationship between adverse events and investigated vaccines, and the special attention should be paid to serious adverse reactions related to vaccination. During clinical trials, Suspected Unexpected Serious Adverse Reactions (SUSAR) and Drug Safety Update Report (DSUR) during clinical programs should be reported in a timely manner according to ICH.

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10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
AE	adverse event
APaT	All Participants as Treated
CAC	Clinical Adjudication Committee
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CPC	China Package Circular
CRF	Case Report Form
CSR	Clinical Study Report
DMC	Data Monitoring Committee
DTaP	diphtheria, tetanus toxoids and acellular pertussis
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
EMA	European Medicines Agency
EOC	Executive Oversight Committee
FDA	The United States Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FAS	Full Analysis Set
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
GI	gastrointestinal
GMT	geometric mean titer
HBV	Hepatitis B virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IND	Investigational New Drug
IPV	Inactivated Poliomyelitis Vaccine
IRB	Institutional Review Board
IRT	interactive response technology
IV	intravenous
IVRS	interactive voice response system
IWRS	integrated web response system
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
NIFDC	National Institutes for Food and Drug Control
PPI	per-protocol immunogenicity
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCID	severe combined immunodeficiency disease
sIPV	Sabin-IPV
SoA	schedule of activities
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction

Abbreviation	Expanded Term
tOPV	trivalent oral poliomyelitis vaccine
VRC	Vaccination Report Card
VS	vital sign

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