Clinical Study Protocol nOPV2-002-ABMG

14 August 2021 (Version 1.0)

A Phase III open-label randomized controlled study to evaluate the safety and immunogenicity of nOPV2 at different intervals of administration in infants.

Product	Novel Oral Poliomyelitis Type 2 Vaccine (live, attenuated) [strain S2/cre5/S15domV/rec1/hifi3]
Protocol Number	nOPV2-002-ABMG
Clinical Phase	III
ClinicalTrials.gov Number	*To be completed*
Clinical Indication	Oral polio vaccine immunization
Issue Date	Initial Protocol Version 1.0 (14 August 2021)

Sponsor	FIDEC – Fighting Infectious Diseases in Emerging Countries (with grant support from the Bill and Melinda Gates Foundation) 1390 S Dixie Hwy Suite 1106 Coral Gables , FL 33146 USA
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SIGNATURES

Signature of Sponsor Representative

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This Clinical Study Protocol has been reviewed and approved by the Sponsor in order to ensure compliance with Good Clinical Practice.

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Title: A Phase III open-label randomized controlled study to evaluate the safety and immunogenicity of nOPV2 at different intervals of administration in infants.

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This Clinical Study Protocol has been reviewed and approved by the Sponsor in order to ensure compliance with Good Clinical Practice.

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Signatures of Investigators

Title: A Phase III open-label randomized controlled study to evaluate the safety and immunogenicity of nOPV2 at different intervals of administration in infants.

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I have read this Clinical Study Protocol and agree that it contains all information necessary for proper conduct of the study. I will carry out the study as outlined herein and will complete the study within the designated time.

Signature:

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Signatures of Investigators

Title: A Phase III open-label randomized controlled study to evaluate the safety and immunogenicity of nOPV2 at different intervals of administration in infants.

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I have read this Clinical Study Protocol and agree that it contains all information necessary for proper conduct of the study. I will carry out the study as outlined herein and will complete the study within the designated time.

Signature:

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PROTOCOL HISTORY

Protocol History FIDEC – nOPV2-002-ABMG			
Document	**Issue Date**	**Amendment Type**	**Comments**
Initial Clinical Study Protocol	14 August 2021	-	-

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PROTOCOL SYNOPSIS

Study Title	**A Phase III open-label randomized controlled study to evaluate the safety and immunogenicity of nOPV2 at different intervals of administration in infants.**		
Product	Novel Oral Poliomyelitis Type 2 Vaccine (live, attenuated) [strainS2/cre5/S15domV/rec1/ hifi3]	**Clinical Phase**	III
Protocol Number **ClinicalTrial.gov Number**	nOPV2-002-ABMG *To be completed*	**Indication**	Oral polio vaccine immunization

Sponsor	FIDEC
Sponsor Representative	Dr. Ricardo Rüttimann
Clinical Center	*To be completed*

Objectives:

The primary objective of the study is to determine if the immune response (seroconversion rate to poliovirus type 2) 28 days following administration of 2 doses of novel oral poliovirus vaccine type 2 (nOPV2) given at different intervals of 1 week or 2 weeks is non-inferior to that following the standard 4-week interval in infants.

Secondary objectives are:

- To assess and compare the immune response to poliovirus type 2 (geometric mean and median neutralizing antibody titers, fold-rise and seroprotection rate) 28 days following administration of 2 doses of nOPV2 given at shorter intervals of 1 week or 2 weeks relative to the standard 4-week interval.
- To assess the immunogenicity to poliovirus type 2 (geometric mean and median neutralizing antibody titers, fold-rise, seroconversion rate and seroprotection rate) 1, 2, or 4 weeks following 1 dose of nOPV2.
- To assess the safety expressed as incidence, severity and causality of serious adverse events (SAEs), solicited adverse events (AEs), unsolicited AEs and any important medical events (IMEs) following administration of nOPV2 given at shorter intervals of 1 week or 2 weeks or at the standard 4-week interval.

The exploratory objective is to compare the immunogenicity to poliovirus type 2 (geometric mean and median neutralizing antibody titers, fold-rise, seroconversion rate and seroprotection rate) following 2 doses administered 1 week apart relative to 2 weeks apart.

Study Endpoints:

Primary

Cumulative seroconversion rate of type 2 polio neutralizing antibodies 28 days following administration of 2 doses of nOPV2 in 1-, 2-, and 4-week intervals to infants 6 to 8 weeks of age.

Seroconversion is defined as seropositive (titer ≥1:8) in those initially seronegative, or among those initially seropositive, as a minimum 4-fold higher titer (and seropositivity) than that which is expected due to maternal antibodies, using an exponential model to estimate the maternally-derived antibody titers at post-vaccination time points from the pre-vaccination time point, assuming a half-life of 28 days.

Secondary

Immunogenicity:

- Geometric mean and median titers of type 2 polio neutralizing antibodies at Day 0 and 28 days after the second dose of nOPV2 when administered 1, 2, or 4 weeks apart.
- Cumulative fold-rise (from Day 0) in titers of type 2 polio neutralizing antibodies 28 days after the second dose of nOPV2 when administered 1, 2, or 4 weeks apart. Cumulative fold-rise will be computed relative to the expected level of maternally-derived antibody titers in accordance with the seroconversion definition.
- Fold-rise (from post-dose-1 level) in titers of type 2 polio neutralizing antibodies 28 days after the second dose of nOPV2 when administered 1, 2, or 4 weeks after dose-1. This fold-rise will be computed from the level attained following the first dose, with the pre-dose-2 serum sample.
- Seroprotection rate to poliovirus type 2, at Day 0 and 28 days after the second dose of nOPV2 when administered 1, 2, or 4 weeks apart.
  Seroprotection rate is defined as the percentage of subjects with type 2-specific antibody titers ≥ 1:8.
- Geometric mean and median titers of type 2 polio neutralizing antibodies 1, 2, and 4 weeks after 1 dose of nOPV2.
- Fold-rise in titers of type 2 polio neutralizing antibodies 1, 2, and 4 weeks after 1 dose of nOPV2. This fold-rise will be computed relative to the expected level of maternally-derived antibody titers in accordance with the seroconversion definition.
- Seroconversion rate 1, 2, and 4 weeks after 1 dose of nOPV2.
- Seroprotection rate 1, 2, and 4 weeks after 1 dose of nOPV2.

Safety:

- Incidence of SAEs and IMEs from the date of informed consent throughout the study period in all groups by severity and by causal association.
- Incidence of mild, moderate and severe solicited AEs (fever, vomiting, abnormal crying, drowsiness, loss of appetite, diarrhea and irritability) for 7 days after each dose of study vaccine in all groups.
- Incidence of mild, moderate and severe unsolicited AEs for 28 days after each dose of study vaccine by causal association in all groups.

Exploratory

- Geometric mean and median titers of type 2 polio neutralizing antibodies at Day 0 and 28 days after the second dose of nOPV2 when administered 1 or 2 weeks apart.
- Cumulative fold-rise (from Day 0) in titers of type 2 polio neutralizing antibodies 28 days after the second dose of nOPV2 when administered 1 or 2 weeks apart.
- Seroprotection rate to poliovirus type 2, at Day 0 and 28 days after the second dose of nOPV2 when administered 1 or 2 weeks apart.

- Seroconversion rate to poliovirus type 2, 28 days after the second dose of nOPV2 when administered 1 or 2 weeks apart.

Overview of the Study Design:

This will be a multicenter, randomized, controlled, open-label, parallel-group Phase III study in healthy infants aged 6 to 8 weeks who have never been vaccinated against poliomyelitis.

Approximately 900 infants will be included in the study and randomized with a 1:1:1 ratio to the following treatment groups:

- Group A: approximately 300 subjects to receive 2 doses of nOPV2 administered 1 week apart, at Day 0 and Day 7;
- Group B: approximately 300 subjects to receive 2 doses of nOPV2 administered 2 weeks apart, at Day 0 and Day 14;
- Group C (control group): approximately 300 subjects to receive 2 doses of nOPV2 administered 4 weeks apart, at Day 0 and Day 28.

A total of 4 on-site visits are planned. Approximately 7 days after each administration of study vaccine, a phone call or on-site visit will be performed to monitor subjects' safety and review with the subject's parent(s)/guardian(s) any solicited AEs reported in the electronic diary card. All subjects will have a safety follow-up phone call 6 months after the last dose of study vaccine.

All infants will receive concomitant routine vaccinations included in the National Immunization Program (NIP) in Dominican Republic, as follows:

- Group A: pentavalent vaccine (diphtheria, tetanus, whole-cell pertussis, hepatitis B, *Haemophilus influenzae* type b, [DTPw-HB-Hib]) and pneumococcal conjugate vaccine (PCV) at 6-8 weeks of age, rotavirus vaccine at 8-10 weeks of age and the first dose of inactivated poliovirus vaccine (IPV) at 11-13 weeks of age;
- Group B: pentavalent vaccine (DTPw-HB-Hib) and PCV at 6-8 weeks of age, rotavirus vaccine at 9-11 weeks of age and the first dose of IPV at 12-14 weeks of age;
- Group C: pentavalent vaccine (DTPw-HB-Hib) and PCV at 6-8 weeks of age, rotavirus vaccine at 11-13 weeks of age and the first dose of IPV at 14-16 weeks of age.

A Data and Safety Monitoring Board (DSMB) will monitor the safety aspects of this study.

Assign Data Management and Biostatistics will be responsible for the generation of randomization codes and files.

Study Duration:

The total study duration will be approximately 8 to 9 months. Each infant will participate for a duration of up to approximately 7 months, which includes a 6-month follow-up period after last vaccine administration to gather additional safety data on the nOPV2 vaccine.

Study Population:

This study will be performed with the participation of approximately 900 infants aged 6 to 8 weeks who have not received prior vaccination against poliomyelitis.

Eligibility Criteria:

Inclusion Criteria:

1. Infants aged 6 to 8 weeks with birth weight > 2,500 g.
2. Healthy infants without obvious medical conditions like immunodeficiency diseases, severe congenital malformations, severe neurological diseases or any other disease that require high doses of corticosteroids or immunotherapies that preclude the subject from participating in the study as established by the medical history and physical examination.
3. Written informed consent obtained from 1 or 2 parent(s) or legal guardian(s) as per country regulations.

Exclusion Criteria:

1. Infants who have received previous vaccination against poliomyelitis.
2. Infants with anyone under 5 years of age in their household (living in the same house or apartment unit) who does not have the complete "age appropriate" vaccination status with respect to poliovirus vaccines at the time of study vaccine administration according to the Dominican Republic NIP.
3. Infants having a member of their household (living in the same house or apartment unit) who is under 6 months of age at the moment of study vaccine administration.
4. Infants having a member of their household (living in the same house or apartment unit) who has received OPV in the previous 3 months before study vaccine administration.
5. Any confirmed or suspected immunosuppressive or known immunodeficient condition including human immunodeficiency virus infection in the potential participant or any member of the subject's household.
6. Family history of congenital or hereditary immunodeficiency.
7. Major congenital defects or serious uncontrolled chronic illness (neurologic, pulmonary, gastrointestinal, hepatic, renal, or endocrine).
8. Known allergy to any component of the study vaccine or to any antibiotics that share molecular composition with the nOPV2 vaccine.
9. Administration of immunoglobulins and/or any blood products since birth or planned administration during the study period.
10. Acute severe febrile illness on the day of vaccination deemed by the Investigator to be a contraindication for vaccination (the child can be included at a later time if within age window and all inclusion criteria are met.).
11. Subject who, in the opinion of the Investigator, is unlikely to comply with the protocol or is inappropriate to be included in the study for the safety or the benefit-risk ratio of the subject.
12. Infants from multiple births or born prematurely (< 37 weeks of gestation).

Test Product, Dose, Mode of Administration:

The nOPV2 vaccine, manufactured by Bio Farma, Indonesia, has been developed as an attenuated serotype 2 poliovirus derived from a modified Sabin 2 infectious cDNA clone to improve the strain's genetic stability and make it less prone to reversion to virulence. It is propagated in Vero cells. Each dose of the nOPV2 vaccine will contain no less than $10^{5.0}$ $CCID_{50}$ (0.1 mL, 2 drops).

The vaccine will be administered orally.

Statistical Methods:

Sample size

This study is designed to demonstrate the non-inferiority of different intervals of administration of nOPV2 (1-week and 2-week intervals) *versus* the standard 4-week interval based on the seroconversion rates of type 2 polio neutralizing antibodies 28 days following the second nOPV2 administration. Non-inferiority would be verified if the lower bound of the two-sided 95% confidence interval (CI) around each difference (shorter interval minus standard interval) is greater than -10%.

The nOPV2 vaccine has recently been demonstrated to be non-inferior to Sabin-strain monovalent oral poliovaccine type 2 (mOPV2) in a Phase 2 study. In this Phase 2 study, among infants aged 18 weeks who had previously been vaccinated with bivalent oral polio vaccine (bOPV) and IPV, and using a 4-week interval between 2 doses, the cumulative seroconversion rates were near 100%, similar to the mOPV2 historical control group. A prior study of dosing intervals of 1, 2, and 4 weeks conducted with mOPV2 in Bangladesh demonstrated seroresponse rates of 93.1%, 95.5% and 97.2% respectively, with lower confidence bounds of 88.3%, 91.3%, and 93.7%.

This study will be conducted in the Dominican Republic, and it is not anticipated that immune response rates will be lower than those observed in the previous mOPV2 study. Therefore, with a conservative assumed cumulative 2-dose seroconversion rate of 85% in each group, 270 evaluable subjects per group are required to demonstrate non-inferiority of each of the shorter intervals to the standard interval, using margin 10%, two-sided Type I error rate of 5%, and requiring 90% power. This will be further increased to 300 per group to account for loss to follow-up or other loss from the evaluable population.

Immunogenicity

At each pre-and post-vaccination time point where neutralizing antibody titers are obtained:

- Cumulative seroconversion rates (with 95% exact CIs) will be computed from Day 0 at post-vaccination time points. Seroconversion is defined as seropositive (reciprocal titer ≥8) in those initially seronegative, or among those initially seropositive, as a minimum 4-fold higher titer (and seropositivity) than that which is expected due to maternal antibodies, using an exponential model to estimate the maternally-derived antibody titers at post-vaccination time points from the pre-vaccination time point, assuming a half-life of 28 days.
- Seroprotection rates (with 95% exact CIs) will be computed
- Geometric mean and median neutralizing antibody titers (with 95% CIs) will be computed
- Plots of the reverse cumulative distribution of antibody titers will be generated for each group.
- Geometric mean fold-rise (with 95% exact CIs) will be computed

Safety

Safety parameters will be tabulated and analyzed descriptively.

Analyses described below will be performed for solicited and unsolicited AEs by severity as well as for SAEs and IMEs. Events will only be considered as solicited AEs if onset occurs within 7 days of a vaccine adminstration. All events with onset between Days 8 and 28 post-vaccination will be considered unsolicited AEs, with only SAEs and IMEs recorded after 28 days post-last-vaccination.

The original terms used in the designated sections of the electronic case report forms by Investigators to identify unsolicited AEs will be fully described and coded according to the Medical Dictionary for Regulatory Activities.

All AEs will be summarized by group, type, by post-vaccination timepoint and overall (regardless of timing of onset), by severity and occurrence in relation to vaccination, and overall, separately for solicited and unsolicited AEs. Determination of causal association of unsolicited AEs, SAEs and IMEs to the study

vaccines will be assigned using the individual causality assessment algorithm published by the World Health Organization (WHO).

Separate tables and listings will be created for subjects who died, discontinued the study vaccine due to an AE, or experienced an SAE. Summaries, listings, and narratives may be provided, as appropriate. Unsolicited AEs occurring within 28 days of any vaccine administration will be summarized, as will any data obtained on SAEs or IMEs reported during the safety follow-up.

Data Safety Monitoring Board:

A DSMB will monitor the benefit-risk and data integrity of this study. The composition and functioning of the DSMB will be documented in the DSMB charter.

TIME AND EVENTS SCHEDULE

Table 1 Group A: Administration of 2 doses of nOPV2, 1 week apart

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Time of Visit/Phone call (days) Visit Window	D 0	D 7 (+ 2 days)	D 14 (+ 2 days)	D 35 (+ 2 days)	D 187[a] (+ 7 days)
On-site/phone call	On-site	On-site	On-site	On-site	Phone-call
Informed consent[b]	X				
In-/exclusion criteria	X				
Medical history/concomitant diseases	X				
Medication/vaccination history	X				
Demographic data	X				
Physical examination	X	X			
Randomization	X				
Serum sample for polio antibody measurement[c]	X	X		X	
Administration of nOPV2[d]	X	X			
Vaccination according to the NIP[e]	X		X	X	
Solicited adverse events (diary)[f]	X	X	X		
Unsolicited adverse events[g]	X	X	X	X	
Concomitant therapies[h]	X	X	X	X	X
Adverse events[h]	X	X	X	X	X

D: day; NIP: national immunization program

a. In case of early termination the subjects' parents will be contacted by phone within 14 days after discontinuation for assessments as outlined on Day 187.
b. No study-related assessment is to be carried out before signing the informed consent form.
c. Serum sample for immunogenicity assessments is to be collected before administration of nOPV2 and IPV.
d. Subjects will be kept under medical supervision for at least 30 min after vaccination.
e. Infants participating in the study should receive vaccines as recommended by the NIP. They will receive:
   - At 6-8 weeks of age (D0): pentavalent vaccine (diphtheria, tetanus, whole-cell pertussis, hepatitis B, *Haemophilus influenzae* type b, [DTPw-HB-Hib]) and pneumococcal conjugate vaccine (PCV)
   - At 8-10 weeks of age (D14): rotavirus vaccine,
   - At 11-13 weeks of age (D35): IPV
f. Solicited AEs will be collected for 7 days following each administration of nOPV2 using electronic diaries.
g. Unsolicited AEs will be collected for a period of 28 days after each administration of nOPV2 during study visits.
h. SAEs, IMEs and intake of concomitant medication(s) will be monitored continuously from the informed consent signature date until Day 187.

Table 2 Group B: Administration of 2 doses of nOPV2, 2 weeks apart

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Time of Visit/Phone call (days) Visit Window	**D 0**	**D 7 (+ 2 days)**	**D 14 (+ 2 days)**	**D 21 (+ 2 days)**	**D 42 (+ 2 days)**	**D 194[a] (+ 7 days)**
On-site/phone call	**On-site**	**Phone call**	**On-site**	**On-site**	**On-site**	**Phone call**
Informed consent[b]	X					
In-/exclusion criteria	X					
Medical history/concomitant diseases	X					
Medication/vaccination history	X					
Demographic data	X					
Physical examination	X		X			
Randomization	X					
Serum sample for polio antibody measurement[c]	X		X		X	
Administration of nOPV2[d]	X		X			
Vaccination according to the NIP[e]	X			X	X	
Solicited adverse events (diary)[f]	X	X	X	X		
Unsolicited adverse events[g]	X	X	X	X	X	
Concomitant therapies[h]	X	X	X	X	X	X
Adverse events[h]	X	X	X	X	X	X

D: day; NIP: national immunization program

a. In case of early termination the subjects' parents will be contacted by phone within 14 days after discontinuation for assessments as outlined on Day 194.
b. No study-related assessment is to be carried out before signing the informed consent form.
c. Serum sample for immunogenicity assessments is to be collected before administration of nOPV2 and IPV.
d. Subjects will be kept under medical supervision for at least 30 min after vaccination.
e. Infants participating in the study should receive vaccines as recommended by the NIP. They will receive:
   - At 6-8 weeks of age (D0): pentavalent vaccine (DTPw-HB-Hib) and PCV
   - At 9-11 weeks of age (D21): rotavirus vaccine,
   - At 12-14 weeks of age (D42): IPV.
f. Solicited AEs will be collected for 7 days following each administration of nOPV2 using electronic diaries.
g. Unsolicited AEs will be collected for a period of 28 days after each administration of nOPV2 during phone calls or study visits.
h. SAEs, IMEs and intake of concomitant medication(s) will be monitored continuously from the informed consent signature date until Day 194.

Table 3 Group C: Administration of 2 doses of nOPV2, 4 weeks apart

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Time of Visit/Phone call (days) Visit Window	**D 0**	**D 7 (+ 2 days)**	**D 28 (+ 2 days)**	**D 35 (+ 2 days)**	**D 56 (+ 2 days)**	**D 208[a] (+ 7 days)**
On-site/phone call	**On-site**	**Phone call**	**On-site**	**On-site**	**On-site**	**Phone call**
Informed consent[b]	X					
In-/exclusion criteria	X					
Medical history/concomitant diseases	X					
Medication/vaccination history	X					
Demographic data	X					
Physical examination	X		X			
Randomization	X					
Serum sample for polio antibody measurement[c]	X		X		X	
Administration of nOPV2[d]	X		X			
Vaccination according to the NIP[e]	X			X	X	
Solicited adverse events (diary)[f]	X	X	X	X		
Unsolicited adverse events[g]	X	X	X	X	X	
Concomitant therapies[h]	X	X	X	X	X	X
Adverse events[h]	X	X	X	X	X	X

D: day; NIP: national immunization program

a. In case of early termination the subjects' parents will be contacted by phone within 14 days after discontinuation for assessments as outlined on Day 208.
b. No study-related assessment is to be carried out before signing the informed consent form.
c. Serum sample for immunogenicity assessments is to be collected before administration of nOPV2 and IPV.
d. Subjects will be kept under medical supervision for at least 30 min after vaccination.
e. Infants participating in the study should receive vaccines as recommended by the NIP. They will receive:
   - At 6-8 weeks of age (D0): pentavalent vaccine (DTPw-HB-Hib) and PCV
   - At 11-13 weeks of age (D35): rotavirus vaccine,
   - At 14-16 weeks of age (D56): IPV.
f. Solicited AEs will be collected for 7 days following each administration of nOPV2 using electronic diaries.
g. Unsolicited AEs will be collected for a period of 28 days after each administration of nOPV2 during phone calls or study visits.
h. SAEs, IMEs and intake of concomitant medication(s) will be monitored continuously from the informed consent signature date until Day 208.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

List of Abbreviations

AE	Adverse Event
AEFI	Adverse Event Following Immunization
bOPV	bivalent Oral Poliovirus Vaccine
$CCID_{50}$	50% cell culture infective dose
CI	Confidence Interval
CRO	Contract Research Organization
cVDPV	Circulating Vaccine-Derived Poliovirus
cVDPV2	Circulating Vaccine-Derived Poliovirus type 2
DNA	Deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
DTPw-HB-Hib	Diphtheria, Tetanus, Whole-cell Pertussis, Hepatitis B, *Haemophilus influenzae* type b vaccine
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EUL	Emergency Use Listing
GCP	Good Clinical Practice
GMT	Geometric Mean Titer
GPEI	Global Polio Eradication Initiative
ICF	Informed Consent Form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IME	Important Medical Event
IPV	Inactivated Poliovirus Vaccine
IRB	Institutional Review Board
LLOQ	Lower Limit of Quantification
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
mOPV2	Monovalent Oral Poliovirus Vaccine type 2
NIP	National Immunization Program
nOPV2	Novel Oral Poliovirus Vaccine type 2
OPV	Oral Poliovirus Vaccine
PCV	Pneumococcal Conjugate Vaccine
PP	Per-Protocol
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SAGE	Strategic Advisory Group of Experts
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction (SAE related to vaccination)
SUSAR	Suspected Unexpected Serious Adverse Reaction
tOPV	trivalent Oral Poliovirus Vaccine
TVP	Total Vaccinated Population
ULOQ	Upper Limit of Quantification

VAPP	Vaccine-Associated Paralytic Poliomyelitis
WHO	World Health Organization

STUDY ADMINISTRATIVE STRUCTURE

SPONSOR	**FIDEC** – Fighting Infectious Diseases in Emerging Countries (with grant support from the Bill and Melinda Gates Foundation 2050 Coral Way, Suite 407 Miami, FL 33145 USA Medical Expert : Ricardo Rüttimann MD
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MANUFACTURING	**Bio Farma** JL. Pasteur No.28, Pasteur, Sukajadi, Kota Bandung, Jawa Barat 40161, Indonesia
CLINICAL ANALYSES	**Centers for Disease Control and Prevention** Polio and Picornavirus Laboratory Branch 1600 Clifton Road, NE MS-G17, Room 6053 Atlanta, GA 30333 USA Contact: Jennifer Anstadt, PhD Team Lead, Population Immunity Laboratory
PHARMACOVIGILANCE	**Assign Data Management and Biostatistics GmbH** Stadlweg 23, 6020 Innsbruck, Austria

1. INTRODUCTION

1.1 BACKGROUND INFORMATION

In 2013 the Global Polio Eradication Initiative (GPEI) launched the Polio Eradication and Endgame Strategic Plan with the objective to end all polio disease globally[1]. The 4 main objectives of the Polio Eradication and Endgame Strategic Plan were: to detect and interrupt all poliovirus transmission, strengthen immunization systems and withdraw the historic oral polio vaccine (OPV), contain poliovirus and certify interruption of transmission and legacy planning.

The global effort to eradicate polio has made significant progress with only 2 countries where wild-type poliovirus transmission has never been interrupted —Afghanistan and Pakistan. Although wild poliovirus type 1 incidence declined annually during 2015–2017, cases in Afghanistan and Pakistan have increased since 2018. Indeed, from January to March 2020, 12 cases of wild poliovirus type 1 were reported in Afghanistan, compared with 6 cases during the same period in 2019; in Pakistan, 42 cases were detected between January and March 2020, corresponding to a 6-fold increase compared with the same period (6 cases) in 2019[2].

For a long time, trivalent oral polio vaccine (tOPV) containing poliovirus types 1, 2, and 3 was the preferred vaccine for polio control and eradication. Global use of this vaccine has enabled the elimination of wild-type poliovirus type 2. However, in many developing countries, a lower immune response to polioviruses type 1 and 3 has been observed with tOPV. The bivalent oral polio vaccine (bOPV), which does not contain type 2, is more effective against the 2 remaining wild poliovirus types. It has been documented that immune-mediated responses tend to increase in proportion to the relative valency of the vaccine with bivalent vaccines offering protection equivalent or non-inferior to monovalent preparations[3]. Moreover, in populations without sufficient immunization coverage, a history of tOPV use can result in the emergence of circulating vaccine-derived poliovirus (cVDPVs): the attenuated strains of poliovirus from the vaccine infect non-immunized individuals, replicate, circulate in the population, and may eventually mutate enough to become virulent and cause circulating vaccine-derived paralytic poliomyelitis.

As stated above, most cVDPVs are type 2 viruses (cVDPV2s). Most outbreaks have been controlled by means of focused immunization campaigns using Sabin monovalent oral poliovirus vaccine type 2 (mOPV2), and more recently, also inactivated polio vaccine (IPV). While mOPV2 is more effective than IPV in halting transmission, as long as mOPV2 was in use, the risk for cVDPV remained and polio could not be entirely eradicated from susceptible populations.

Presently, cVDPV2s continue to circulate. Most cVDPVs are type 2 viruses, derived from historical global use of tOPV as well as outbreak response immunization campaigns using Sabin strain mOPV2. The number and geographic spread of cVDPV2 outbreaks is increasing; in 2020, 959 human cases of cVDPV2 and 411 cVDPV2-positive environmental samples were reported globally from 27 countries[4].

As part of the Polio Eradication and Endgame Strategic Plan, the Strategic Advisory Group of Experts on immunization (SAGE) called for a globally synchronized switch from tOPV to bOPV in routine immunization programs (i.e., withdrawal of OPV2) as the first step towards complete withdrawal of all oral polio vaccines[5]. To mitigate the risks associated with this switch, the SAGE recommended addition of at least one dose of IPV to routine immunization programs to complement bOPV and so reduce the risk of paralytic poliomyelitis if exposure to a type 2 virus occurred after OPV2 withdrawal.

For the foreseeable future, stocks of monovalent OPVs will need to be maintained for use in case of outbreaks of wild-type poliovirus and/or cVDPVs, but the risk will remain that current OPVs will themselves be the source of a cVDPV. Therefore, as an additional step toward the elimination of cVDPV2, two novel oral poliovirus vaccine type 2 (nOPV2) vaccines were developed using attenuated serotype 2 polioviruses derived from a modified Sabin 2 infectious cDNA clone generated by modifying the Sabin-2 RNA sequence to improve genetic stability and make the strains less prone to reversion to virulence.

A comprehensive development program was launched to evaluate the safety and immunogenicity of the nOPV2 candidates, which included a broad population of adults, children, and infants from 18 weeks of age. Both candidates had an acceptable safety profile and were immunogenic in Phase I and Phase II trials, and viral shedding in stool was similar or lower than among mOPV2 recipients[6-8]. Candidate 1[9] was selected as the most appropriate for use in the context of a public health emergency. Sequencing and genetic stability data confirmed the absence of reverting mutations in the main site of attenuation which are analogous to the domain V A481G reversion in Sabin OPV2. Additional trials are ongoing, including a study of vaccine-naïve neonates in Bangladesh[10], a study of concomitant usage of nOPV2 and bivalent OPV in Bangladesh[11], and a Phase 3 lot-consistency trial in The Gambia[12].

In November 2020, the World Health Organization's (WHO) prequalification program issued an emergency use listing (EUL) recommendation for nOPV2 to allow rollout of the vaccine for limited initial use in countries affected by cVDPV2 outbreaks[13]. Multiple countries have initiated outbreak response campaigns with nOPV2 under WHO EUL, with millions of doses administered[14]. The use of nOPV2 was also included in the 2022-2026 GPEI strategy as a primary focus for outbreak response, in replacement of Sabin mOPV2[15].

1.2 OVERALL RATIONALE FOR THE STUDY

The GPEI acknowledged that additional efforts are urgently needed to address cVDPV2 circulation. The 2022-2026 strategy largely relies on the scale-up of nOPV2 use, but also includes as a pivot the improvement of vaccination campaign planning and execution to increase vaccination coverage and avoid "zero-dose" children[15]. The current recommendation is to complete 2 large (>90% of children vaccinated) vaccination campaigns within 8 weeks of the first laboratory sequencing result, but their duration might be extended to reach missed children. In addition, short-interval campaigns may be put in place, for example with intervals between 2 mOPV2 doses reduced to 1 week, under certain circumstances such as the presence of multiple circulating polioviruses or short window of access to the target population, similar to the experience with mOPV2[16].

In a phase IV randomized, controlled study in Bangladesh, the immunogenicity of 2 doses of mOPV2 when administered at varying intervals of 1 week and 2 weeks was assessed and compared to the standard 4-week interval. Between December 7th, 2015, and January 5th, 2016, 760 infants were randomized to receive 2 mOPV2 doses at intervals of 1 week (n=191), 2 weeks (n=191), 4 weeks (n=188), or 4 weeks plus IPV (n=190). Immune responses after 2 mOPV2 doses were observed in 161 (93%) of 173 infants with testable serum samples in the 1-week group, 169 (96%) of 177 in the 2-week group, and 176 (97%) of 181 in the 4-week group. One-week and 2-week intervals between 2 mOPV2 doses were non-inferior to 4-week intervals; the difference in seroconversion rate between the 1-week interval group and the 4-week interval group was -4.2 (90% confidence interval [CI]: -7.9; -0.4), and it was -1.8% (90% CI: -5.0; 1.5) in the 2-week interval group compared to the 4-week interval group[17].

To date, no data exist on the immunogenicity of nOPV2 when administered at shorter intervals. It is important to investigate shorter intervals of administration, as reducing the interval between 2 administrations could contribute to the effectiveness of the vaccination campaigns.

1.3 RISK BENEFIT ANALYSIS

1.3.1 *Potential Risks*

The nOPV2 vaccine being used in the proposed study was designed to be more genetically stable and less likely to revert to a neurovirulent phenotype than the Sabin mOPV2, and this has been confirmed in preclinical and clinical assessments. The attenuations do not appear to affect the immunogenicity of the vaccine.

In the M5 study[8], solicited adverse events (AEs) in children and infants included abnormal crying, drowsiness, fever, irritability, loss of appetite, and vomiting. No SAEs or important medical events (IMEs) considered related to vaccination were reported for nOPV2. Severe AEs considered related to vaccination were reported, the most frequent of which was abnormal crying. All were transient, usually resolving within 3 days. No clinically relevant differences were observed in SAEs, AEs or IMEs related to vaccination between nOPV2 and mOPV2 groups. SAEs that entailed hospitalization (mild bronchitis and moderate pneumonia) were not considered related to study vaccine. There were no AEs that led to death, to withdrawal, or to permanent study discontinuation.

The attenuated strains of poliovirus multiply in the gut. The fecal excretion of the vaccine virus may persist for several weeks, especially in unprotected populations, and may also be transmissible to the contacts of the vaccinees contributing to the herd immunity against polio. In populations with low immunity, a close contact with a recently vaccinated subject may very rarely be at risk of developing paralytic poliomyelitis caused by the vaccine (VAPP). Clinical data from the Phase I and Phase II adult studies (M4a and M4) and the Phase II pediatric study (M5) support the improvements in genetic and phenotypic stability of the nOPV2 vaccine, with no meaningful increase in neurovirulence observed[6-8]. Genetic stability analyses do not suggest any anticipated increase in the likelihood of VAPP with the vaccine which will be used in this study.

1.3.2 *Potential Benefits*

Infants who will be vaccinated with nOPV2 in this study will potentially develop high levels of immunity against poliovirus type 2. Indeed, a key benefit of nOPV2 is the intestinal immunity (in addition to humoral immunity) against type-2 poliovirus disease which is conferred through vaccination by the oral route.

Given the global public health need of a safer alternative to mOPV2, this study is important in establishing immunological responses to nOPV2 when administered at shorter intervals. Iif the data are supportive, it will assist in the design of a new polio vaccination strategy that will enhance the effectiveness of the vaccination campaigns to prevent emergence and further spread of cVDPV2 and generation of type 2-related VAPP cases.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of the study is to determine if the immune response (seroconversion rate to poliovirus type 2) 28 days following administration of 2 doses of nOPV2 given at different intervals of 1 week or 2 weeks is non-inferior to that following the standard 4-week interval in infants.

2.2 SECONDARY OBJECTIVES

The secondary objectives of the study are:

- To assess and compare the immune response to poliovirus type 2 (geometric mean and median neutralizing antibody titers, fold-rise and seroprotection rate) 28 days following administration of 2 doses of nOPV2 given at shorter intervals of 1 week or 2 weeks relative to the standard 4-week interval.
- To assess the immunogenicity to poliovirus type 2 (geometric mean and median neutralizing antibody titers, fold-rise, seroconversion rate and seroprotection rate) 1, 2, or 4 weeks following 1 dose of nOPV2.
- To assess the safety expressed as incidence, severity and causality of SAEs, solicited AEs, unsolicited AEs and any IMEs following administration of nOPV2 given at shorter intervals of 1 week or 2 weeks or at the standard 4-week interval.

2.3 EXPLORATORY OBJECTIVE

To compare the immunogenicity to poliovirus type 2 (geometric mean and median neutralizing antibody titers, fold-rise, seroconversion rate, and seroprotection rate) following 2 doses administered 1 week apart relative to 2 weeks apart.

3. STUDY ENDPOINTS

3.1 PRIMARY ENDPOINTS

The primary endpoint is the cumulative seroconversion rate of type 2 polio neutralizing antibodies 28 days following administration of 2 doses of nOPV2 in 1-, 2-, and 4-week intervals to infants 6 to 8 weeks of age.

Seroconversion is defined as seropositive (titer ≥1:8) in those initially seronegative, or among those initially seropositive, as a minimum 4-fold higher titer (and seropositivity) than that which is expected due to maternal antibodies, using an exponential model to estimate the maternally-derived antibody titers at post-vaccination time points from the pre-vaccination time point, assuming a half-life of 28 days.

3.2 SECONDARY ENDPOINTS

Immunogenicity:

- Geometric mean and median titers of type 2 polio neutralizing antibodies Day 0 and 28 days after the second dose of nOPV2 when administered 1, 2, or 4 weeks apart.
- Cumulative fold-rise (from Day 0) in titers of type 2 polio neutralizing antibodies 28 days after the second dose of nOPV2 when administered 1, 2, or 4 weeks apart. Cumulative fold-rise will be computed relative to the expected level of maternally-derived antibody titers in accordance with the seroconversion definition.
- Fold-rise (from post-dose-1 level) in titers of type 2 polio neutralizing antibodies 28 days after the second dose of nOPV2 when administered 1, 2, or 4 weeks after dose-1. This fold-rise will be computed from the level attained following the first dose, with the pre-dose-2 serum sample.
- Seroprotection rate to poliovirus type 2, at Day 0 and 28 days after the second dose of nOPV2 when administered 1, 2, or 4 weeks apart. Seroprotection rate is defined as the percentage of subjects with type 2-specific antibody titers $\geq$ 1:8.
- Geometric mean and median titers of type 2 polio neutralizing antibodies 1, 2, and 4 weeks after 1 dose of nOPV2.
- Fold-rise in titers of type 2 polio neutralizing antibodies 1, 2, and 4 weeks after 1 dose of nOPV2. This fold-rise will be computed relative to the expected level of maternally-derived antibody titers in accordance with the seroconversion definition.
- Seroconversion rate 1, 2, and 4 weeks after 1 dose of nOPV2.
- Seroprotection rate 1, 2, and 4 weeks after 1 dose of nOPV2.

Safety:

- Incidence of SAEs and IMEs as of the informed consent signature date and throughout the study period in all groups by severity and causal association.
- Incidence of mild, moderate and severe solicited AEs (fever, vomiting, abnormal crying, drowsiness, loss of appetite, diarrhea and irritability) for 7 days after each dose of study vaccine in all groups.
- Incidence of mild, moderate and severe unsolicited AEs for 28 days after each dose of study vaccine by causal association in all groups.

3.3 EXPLORATORY ENDPOINTS

- Geometric mean and median titers of type 2 polio neutralizing antibodies at Day 0 and 28 days after the second dose of nOPV2 when administered 1 or 2 weeks apart.

- Cumulative fold-rise (from Day 0) in titers of type 2 polio neutralizing antibodies 28 days after the second dose of nOPV2 when administered 1 or 2 weeks apart.
- Seroprotection rate to poliovirus type 2, at Day 0 and 28 days after the second dose of nOPV2 when administered 1 or 2 weeks apart.
- Seroconversion rate to poliovirus type 2, 28 days after the second dose of nOPV2 when administered 1 or 2 weeks apart.

4. STUDY DESIGN

4.1 OVERVIEW OF THE STUDY DESIGN

This will be a multicenter, randomized, controlled, open-label, parallel-group Phase III study in healthy infants aged 6 to 8 weeks who have never been vaccinated against poliomyelitis.

Approximately 900 infants will be included in the study and randomized with a 1:1:1 ratio to the following treatment groups:

- Group A: approximately 300 subjects to receive 2 doses of nOPV2 administered 1 week apart, at Day 0 and Day 7;
- Group B: approximately 300 subjects to receive 2 doses of nOPV2 administered 2 weeks apart, at Day 0 and Day 14;
- Group C (control group): approximately 300 subjects to receive 2 doses of nOPV2 administered 4 weeks apart, at Day 0 and Day 28.

A total of 4 on-site visits are planned. Approximately 7 days after each administration of study vaccine, a phone call or on-site visit will be performed to monitor subjects' safety and review with the subject's parent(s)/guardian(s) any solicited AEs reported in the electronic diary card. All subjects will have a safety follow-up phone call 6 months after the last dose of study vaccine.

All infants will receive concomitant routine vaccinations included in the National Immunization Program (NIP) in the Dominican Republic, as follows:

- Group A: pentavalent vaccine (diphtheria, tetanus, whole-cell pertussis, hepatitis B, Haemophilus influenzae type b, [DTPw-HB-Hib]) and pneumococcal conjugate vaccine (PCV) at 6-8 weeks of age, rotavirus vaccine at 8-10 weeks of age and the first dose of inactivated poliovirus vaccine (IPV) at 11-13 weeks of age;
- Group B: pentavalent vaccine (DTPw-HB-Hib) and PCV at 6-8 weeks of age, rotavirus vaccine at 9-11 weeks of age and the first dose of IPV at 12-14 weeks of age;
- Group C: pentavalent vaccine (DTPw-HB-Hib) and PCV at 6-8 weeks of age, rotavirus vaccine at 11-13 weeks of age and the first dose of IPV at 14-16 weeks of age.

The total study duration will be approximately 8 to 9 months. Each infant will participate for a duration of up to approximately 7 months, which includes a 6-month follow-up period after last vaccine administration to gather additional safety data on the nOPV2 vaccine.

A Data and Safety Monitoring Board (DSMB) will monitor the safety aspects of this study.

Assign Data Management and Biostatistics will be responsible for the generation of randomization codes and files.

4.2 DISCUSSION OF STUDY DESIGN

Subjects will be randomized in a 1:1:1 ratio to increase the likelihood that known and unknown subject attributes (e.g., demographic and baseline characteristics) are evenly balanced across groups.

The study will be conducted in an open-label manner. The evaluation of the primary immunogenicity endpoint is not expected to be biased given its objective nature. Laboratory personnel will be blinded to group until such time as the neutralizing antibody assays are complete, and samples from all groups will be randomized for concurrent testing.

Subjects' safety will be closely monitored throughout the study during the on-site visits and the phone calls. Phone calls or on-site visits 7 days after each administration of nOPV2 will enable to review with the subject's parent(s)/guardian(s) any solicited AEs reported in the electronic diary. A dedicated phone visit 6 months after the last dose of study vaccine will enable the collection of long-term safety data. In addition, a DSMB will monitor the safety aspects of this study enrolling a very young population of children.

In addition to the vaccination with nOPV2, infants will receive the DTPw-HB-Hib, PCV and rotavirus vaccine as recommended by the NIP of the Dominican Republic. To avoid the interference of any additional poliovirus vaccines with nOPV2 immunogenicity assessments, it is planned to administer IPV 4 weeks after the second dose of nOPV2.

5. SELECTION OF STUDY POPULATION

For details on the sample size calculation, please refer to Section 10.2.

5.1 INCLUSION CRITERIA

1. Infants aged 6 to 8 weeks with birth weight >2,500 g.
2. Healthy infants without obvious medical conditions like immunodeficiency diseases, severe congenital malformations, severe neurological diseases or any other disease that require high doses of corticosteroids or immunotherapies that preclude the subject from participating in the study as established by the medical history and physical examination.
3. Written informed consent obtained from 1 or 2 parent(s) or legal guardian(s) as per country regulations..

5.2 EXCLUSION CRITERIA

Subjects meeting any of the following criteria are excluded from participation in this study:

1. Infants who have received previous vaccination against poliomyelitis.
2. Infants with anyone under 5 years of age in their household (living in the same house or apartment unit) who does not have the complete "age appropriate" vaccination status with respect to poliovirus vaccines at the time of study vaccine administration according to the Dominican Republic NIP.
3. Infants having a member of their household (living in the same house or apartment unit) who is under 6 months of age at the moment of study vaccine administration.
4. Infants having a member of their household (living in the same house or apartment unit) who has received OPV in the previous 3 months before study vaccine administration.
5. Any confirmed or suspected immunosuppressive or known immunodeficient condition including human immunodeficiency virus infection in the potential participant or any member of the subject's household.
6. Family history of congenital or hereditary immunodeficiency.
7. Major congenital defects or serious uncontrolled chronic illness (neurologic, pulmonary, gastrointestinal, hepatic, renal, or endocrine).
8. Known allergy to any component of the study vaccine or to any antibiotics that share molecular composition with the nOPV2 vaccine.

9. Administration of immunoglobulins and/or any blood products since birth or planned administration during the study period.

10. Acute severe febrile illness on the day of vaccination deemed by the Investigator to be a contraindication for vaccination (the child can be included at a later time if within age window and all inclusion criteria are met.).

11. Subject who, in the opinion of the Investigator, is unlikely to comply with the protocol or is inappropriate to be included in the study for the safety or the benefit-risk ratio of the subject.

12. Infants from multiple births or born prematurely (< 37 weeks of gestation).

5.3 CRITERIA FOR ELIMINATION FROM THE PER-PROTOCOL POPULATION

A review of protocol deviations, including, among others, vaccinations occurring out of window, administration of other polio vaccines, and OPV administration to household members, will be conducted prior to database lock based on predefined criteria. Subjects with major protocol deviations detected via monitoring or automated database search which are deemed likely to interfere with the assessment of immunogenicity will be removed from the per-protocol population at the time of occurrence of the first such deviation. Subjects receiving other vaccinations not per protocol (non-study polio vaccinations, or non-NIP vaccinations) will contribute safety data to the Total Vaccinated Population (TVP) prior to administration of the non-study/non-NIP vaccination, although they will still be followed for safety for the remaining study duration, with data presented in separate summaries. They will not receive further study vaccine doses.

5.4 CONTRAINDICATIONS TO FURTHER VACCINATION

The following AEs constitute absolute contraindications to further administration of the study vaccine:

- SAE, severe adverse event (grade 3) or IME after vaccination considered to be consistent with a causal association to the study vaccine.
- Known hypersensitivity to any component of the vaccine or any antibiotic or severe reaction following previous administration of the vaccine.
- Acute severe febrile illness on the day of vaccination deemed by the Investigator to be a contraindication for vaccination.
- Diagnosis between 2 visits of any of the following medical conditions:
    - Uncontrolled severe chronic disease (see above under exclusions).
    - Coagulopathy.
    - Congenital or acquired immunodeficiency syndrome.
    - Acute flaccid paralysis (to be investigated as a SAE).

If any of these AEs occur during the study, the subject should not receive the second dose of vaccine but may continue other study procedures at the discretion of the Investigator. The subject will be followed until resolution of the event and to determine the immune response.

5.5 ADDITIONAL CONSTRAINTS

Information on prohibited therapies can be found in Section 7.

6. VACCINES

Study vaccine:

The nOPV2 vaccine, live attenuated type 2 modified Sabin strain (S2/cre5/S15domV/rec1/hifi3), is produced by Bio Farma, Indonesia.

Other vaccines:

DTPw-HB-Hib, IPV, PCV and rotavirus vaccine will be provided by the NIP.

6.1 PHYSICAL DESCRIPTION OF THE STUDY VACCINES

The nOPV2 vaccine will be provided to the sites in vials presented as an aqueous yellow-red solution for oral use.

The vaccine will be administered orally.

6.2 CHARACTERIZATON OF VACCINE LOTS

Vials will be filled at concentrations so that each dose of the nOPV2 vaccine will contain no less than $10^{5.0}$ $CCID_{50}$ (0.1 mL, 2 drops).

6.3 OTHER MEDICATION ADMINISTERED IN THE STUDY

Other vaccines are routine childhood vaccines administered according to the manufacturer's instructions.

6.4 PACKAGING AND LABELING

The nOPV2 vaccine is labelled and packed according to local law and regulatory requirements.

Detailed information on the packaging and labeling is specified in the nOPV2 Handling and Storage Instructions for the study.

6.5 STORAGE AND VACCINE ACCOUNTABILITY

The Investigator (or his/her designee) is responsible for the safe storage of all study vaccines assigned to the clinical site, in a locked, secure storage facility with access limited to those individuals authorized to dispense the study vaccine, and maintained within the appropriate ranges of temperature. All study vaccines must be stored as specified at delivery and in the original packaging.

The nOPV2 vaccine should be stored in a freezer at approximately –20°C (±5 °C). After thawing, the vaccine can be stored at +2 to +8°C for up to 2 weeks. Once opened, a vial must be used within 48 hours, when it expires.

Regular temperature logging of the study vaccine storage room at the clinical site should be performed. In case a deviation in storage conditions should occur, the clinical site must not further dispense the affected study vaccines and notify the Sponsor.

The Investigator is responsible for ensuring that all study vaccines received at the clinical site are inventoried and accounted for throughout the study.

Study vaccines should be dispensed under the supervision of the Investigator, a qualified member of the clinical staff, or by a hospital/clinic pharmacist. The Investigator must maintain accurate records demonstrating date and amount of vaccine administered to and by whom. Study vaccines will be supplied only to subjects participating in the study.

The Sponsor's designated site monitor will periodically check the supplies of study vaccines held by the Investigator or pharmacist to ensure accountability and appropriate storage conditions of all study vaccines used.

Unused study vaccine must be available for verification by the site monitor during on-site monitoring visits. After the last visit of the last subject (LSLV) in the study, any unused vaccine will be returned to the manufacturer, and any used vaccine will be destroyed at the clinical site with the Sponsor's written permission (in this case a certificate of destruction will be provided and filed in the Trial Master File [TMF]).

6.6 RANDOMIZATION AND BLINDING

This is an open-label study.

Allocation of each subject to the 3 treatment groups will be described in a computer-generated randomization schedule prepared prior to start of the study by Assign Data Management and Biostatistics GmbH, Stadlweg 23, 6020 Innsbruck using SAS® software (SAS Institute Inc., Cary, NC, USA).

The randomization will apply a 1:1:1 ratio and will be balanced using randomly permuted blocks across the groups.

Blinding of subjects and assessers will not be possible due to the different regimens employed in this study. Laboratory personnel will be blinded to group until such time as the neutralizing antibody assays are complete, and samples from all groups will be randomized for concurrent testing.

6.7 DOSE AND ADMINISTRATION

For all vaccine lots, one dose of vaccine (0.1 ml) is contained in two drops, which are delivered using the dropper supplied with the vaccine.

Other study vaccines provided under the NIP should be administered as per the manufacturer's instructions.

The vaccinees will remain under medical supervision for at least 30 min following the administration of study vaccine.

6.8 COMPLIANCE

All vaccine administrations in the study will be supervised by the Investigator or his/her designee.

7. PRIOR AND CONCOMITANT THERAPY

All therapies (prescriptions and over-the-counter medications) other than the study vaccine administered from informed consent until the last study visit must be recorded in the source documents and in the concomitant therapy section of the electronic case report form (eCRF) (name of the drug, dosage, route and dates of administration).

The Sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

There will be no restrictions in using concomitant therapies except for any medication that has a potential effect on the immune system in the opinion of the Investigator.

Infants will receive routine vaccinations according to the Dominican Republic NIP which will be provided by the NIP.

8. ASSESSMENTS

8.1 TIMING OF ASSESSMENTS

An overview of the timing of vaccine administration and assessments is given in the Time and Events Schedules.

Parent(s)/guardian(s) will be given a full explanation of the nature of the study and written informed consent (approved by the local ethics committee) will be obtained from parent(s)/guardian(s) according to local requirements before any study-related assessment will be carried out.

Adverse events and the administration of concomitant medication will be monitored continuously from informed consent until the last study-related activity at Day 187 (Group A), Day 194 (Group B) or Day 208 (Group C). Solicited AEs will be collected for 7 days following each dose, unsolicited AEs will be collected until 28 days following each study vaccination and SAEs/IMEs will be collected from the date of informed consent signature throughout the study.

After informed consent process has been completed, the assessments will proceed as outlined in the Time and Events Schedules. The subjects will be kept under medical supervision for at least 30 minutes after administration of the study vaccine. The subjects will then receive routine vaccinations outlined in the Time and Events Schedule.

An electronic diary card and a thermometer will be distributed to parent(s)/guardian(s) and their use will be explained. Paper diary cards could be used as backup.

Unscheduled visits can be planned, for instance to obtain additional information to ensure the safety of the subject. Additional blood and urine samples may be taken at the discretion of the Investigator if deemed necessary for safety observation.

Findings made during unscheduled visits should be reported in the source documents and in the designated sections of the eCRF.

8.2 IMMUNOGENICITY

8.2.1 *Immunogenicity Variables*

Blood samples for the determination of neutralizing type 2 poliovirus antibodies will be taken at the time points specified in the Time and Events Schedules. Neutralizing antibodies against poliovirus will be determined using a sero-neutralization assay.

Detailed descriptions of the collection, handling, transport and processing of the blood samples will be included in the laboratory manual.

Samples that remain after protocol-specific assessments have been performed may be used for further exploratory work on polio, including cryofreezing for future immunological studies. No human DNA or RNA analysis will be performed.

8.2.2 *Immunogenicity Criteria*

For an overview of endpoints, see Section 3.

The following endpoints will based on neutralizing type 2 poliovirus antibody titers:

- Seroconversion: defined as seropositive (titer ≥1:8) in those initially seronegative, or among those initially seropositive, a minimum 4-fold higher titer (and seropositivity) than that which is expected due to maternal antibodies, using an exponential model to estimate the maternally-derived antibody titers at post-vaccination time points from the pre-vaccination time point, assuming a half-life of 28 days. Seroconversion will be computed from Day 0 for all subjects.
- Seroprotection: defined as poliovirus serotype-specific titers ≥1:8.
- Geometric mean and median titers.
- Geometric mean fold-rise

8.3 SAFETY EVALUATIONS

The safety assessment in this study will be based on AEs.

Adverse events will be monitored continuously from the time of informed consent signature until Day 187 (Group A), Day 194 (Group B) or Day 208 (Group C) (180 + 7 days after the last administration of the study vaccine). At regular intervals during the study, at the on-site visits and over the phone, parents will be asked non-leading questions to determine the occurrence of any AEs.

For detailed definitions and reporting procedures of AEs, see Section 11.

Solicited AEs will be recorded by the subjects' parent(s)/guardian(s) for 7 days following each dose of study vaccine using a diary card. These will be reviewed by the Investigator during the phone calls or on-site visits that will be scheduled with the subject's parent(s)/guardian(s) 7 days after each dose. In addition, unsolicited AEs will be collected during regular study phone calls and on-site visits for 28 days after each vaccination. Any SAEs and IMEs will be collected from the date of the informed consent signature throughout the study.

8.4 EXPLORATORY EVALUATIONS

Not applicable.

8.5 APPROPRIATENESS OF MEASUREMENTS

The assessments which will be made in this study are either standard or are scientifically justified.

Each biological assay contains a reference material used as a control. Additional re-test of some samples may be conducted to ascertain the presence of temporal variability in assay results.

9. STUDY TERMINATION/COMPLETION

9.1 STUDY COMPLETION

9.1.1 Subject Completion

A subject will be considered to have completed the study if all study-related procedures have been completed for them 28 days after the last study vaccination (i.e, Day 35 [Group A], Day 42 [Group B] or Day 56 [Group C]) and they are not withdrawn before the final study safety follow-up 6 months after their last study vaccination (i.e, Day 187 [Group A], Day 194 [Group B] or Day 208 [Group C]).

9.1.2 *Study Completion Date*

The study completion date is considered to be the date on which the final serologic analysis is available for the purpose of assessing the primary immunogenicity objective.

9.2 REMOVAL OF SUBJECTS FROM STUDY OR INVESTIGATIONAL PRODUCT

9.2.1 *Removal from Study*

Parents(s)/guardian(s) have the right to withdraw subjects from the study at any time for any reason, including personal reasons. A subject can be withdrawn without giving a reason. The Investigator should however try to find out why a subject is withdrawn from the study and document the reason for withdrawal in the source documents and on the eCRF.

Subjects **may** be withdrawn from the study in the event of:

- A severe AE or a SAE;
- Difficulties in obtaining blood or other samples;
- Failure of the subject and/or subject's parent(s)/guardian(s) to comply with the protocol requirements or to cooperate with the Investigator.

Subjects **must** be withdrawn from the study in the event of:

- Withdrawal of consent by parent(s)/guardian(s);
- For safety reasons, if, in the Investigator's opinion, in the best interest of the subject.

In the event of a subject being withdrawn from the study, the monitor and Sponsor should be informed: in the event of withdrawal due to an SAE (for details on AE reporting see Section 11), the Sponsor should be notified within 24 hours; in the event of withdrawal for other reasons, the Sponsor should be notified within 2 days from the event.

If there is a medical reason for withdrawal, the subject will remain under the supervision of the Investigator until satisfactory health has returned.

Subjects who are withdrawn from the study prior to completion of the scheduled study procedures for any reason (e.g. AE, withdrawal of consent) should be invited to complete

the assessments as much as possible: as long as the subjects' parent(s)/guardian(s) consents, all relevant assessments of the day on which the subject withdrew from the study should be completed, at least those related to safety. In case of an AE, the appropriate follow-up will be done.

Subjects who are withdrawn from the study will not be replaced.

9.2.2 *Removal from Investigational Product*

Removal from investigational product administration concerns subjects who do not receive a complete study vaccination schedule as planned per protocol. A subject who is withdrawn from further study vaccine administration need not necessarily be withdrawn from the study as further study procedures or follow-up may be performed (safety or immunogenicity) if planned in the study protocol.

Information pertaining to premature discontinuation of the study vaccine will be documented in the eCRF. The Investigator will document whether the decision to discontinue further vaccination was made by the subjects' parent(s)/guardian(s) or the Investigator, and which of the following possible reasons was responsible for withdrawal:

- SAE/IME.
- AE.
- Other (specify).

10. STATISTICAL METHODS

10.1 STATISTICAL ANALYSIS

All statistical analyses will be performed by Assign Data Management and Biostatistics GmbH, Stadlweg 23, 6020 Innsbruck using SAS® software (SAS Institute Inc., Cary, NC, USA) under the supervision and responsibility of the Sponsor.

This document describes the basic elements of the statistical analysis to be performed. All statistical methods shall be detailed in a Statistical Analysis Plan (SAP) that will be finalized before database lock.

Unless otherwise specified, descriptive statistics include mean, standard deviation, median, maximum, minimum, and range for continuous variables and the number and percentage in each group for categorical variables.

Unless specified otherwise in the SAP, statistical tests and CIs will be computed using a two-sided 5% significance level. Exact (Clopper-Pearson) CIs will be used for univariate summaries of dichotomous variables, and Miettinen-Nurminen score-based CIs will be used for rate differences.

10.1.1 *Study Populations*

The following populations will be considered for analysis:

- The Enrolled Population is defined as all subjects for whom informed consent is provided, regardless of the subject's randomization and vaccination status.
- The TVP is defined as all subjects who received at least 1 dose of study vaccine.
- The Reactogenicity Population is defined separately for each dose (dose 1 and dose 2) as those subjects who received the respective dose and who completed the diary card.
- The Per-Protocol (PP) Population consists of all eligible study participants who are in the TVP, who provided an evaluable pre-vaccination serum sample, and who received all of the immunizations at the interval scheduled for the group to which they were allocated and excludes those subjects who received any therapy that could significantly affect the subject's immune status and those subjects who met criteria outlined in Section 5.3. The PP Population will be adapted by time point to allow subjects to contribute data to PP analyses until such time as they become disqualified. All deviations and violations occurring in the study will be reviewed prior to database lock and classified as either minor or major.

Unless specified otherwise, the TVP will be used for safety analysis and analysis of demographics. The Reactogenicity Population will be used to summarize incidence of solicited events. Immunogenicity analyses will be primarily conducted in the PP Population.

10.1.2 *Analysis Sequence*

A final analysis of immunogenicity outcomes will be conducted upon completion of assays and reconciliation of data, which may be in advance of the completion of safety follow-up. This will include an analysis of baseline characteristics and disposition. Safety data will be described upon completion of the study, including all safety follow-up.

10.1.3 *Initial Characteristics Data of the Subject Sample*

Descriptive statistics will be provided per group for demographic (e.g., age, weight, race, gender) and other initial subject characteristics (e.g., medical and surgical history, concomitant diseases). Demographics will be compared using Chi-squared and Fisher's exact test for categorical variables, and Kruskal-Wallis and pairwise Wilcoxon test comparisons for continuous variables.

Prior and ongoing medical history will be coded with the Medical Dictionary for Regulatory Activities (MedDRA), summarized and listed.

Prior and concomitant medications will be coded using the WHO_DRUG Dictionary, summarized, and listed.

Disposition, including receipt of doses, inclusion in study populations and reasons for dropout will be summarized and listed, and a CONSORT diagram will be prepared.

10.1.4 *Immunogenicity Data*

For an overview of primary and secondary endpoints, see Section 3.

For descriptive analyses, at each pre-and post-vaccination time point where neutralizing antibody titers are obtained:

- Cumulative seroconversion rates (with 95% exact CIs) will be computed.
- Seroprotection rates (with 95% exact CIs) will be computed.
- Geometric mean and median neutralizing antibody titers (with 95% CIs) will be computed. Mean titers will be estimated on the $\log_2$ scale using likelihood-based estimation, using a normal error assumption, to accommodate censoring at assay lower limit of quantification (LLOQ)/upper limit of quantitation (ULOQ), then reverse-transformed to obtain the geometric mean and corresponding CI. The median $\log_2$ titer will be paired with bootstrap-based CIs.
- Fold-rises will be computed as the mean of differences (subsequent time point minus prior time point) on the $\log_2$ scale, then reverse-transformed along with the corresponding 95% CI. Cumulative fold rises will be computed relative to the expected level of maternally-derived antibodies in accordance with the seroconversion definition, and secondarily for post-dose-2 samples, from the level attained following the first dose, with the pre-dose-2 serum sample.
- Plots of the reverse cumulative distribution of antibody titers will be generated for each group.
- Additional figures will include boxplots and bar charts of immune responses (seroconversion, seroprotection rates, GMTs with accompanying CIs).

Subgroup analyses, to be detailed in the SAP, will include analyses such as according to baseline immune status and according to gender.

Comparative immunogenicity analyses will be limited to baseline immunity (seroprotection rate, GMTs) and post-dose-2 time points corresponding to the study objectives, and post-dose-1 results will be descriptive only.

Comparisons for binary variables (seroconversion, seroprotection) will be based on the difference in rates (shorter interval minus standard interval), and paired with two-sided 95% Miettinen-Nurminen CIs for the difference. For the primary endpoint, non-inferiority of a shorter-interval regimen to the standard regimen will be declared if the lower bound of the CI is greater than -10%. For other comparisons, a statistically significant difference will occur if the CI excludes 0%.

Comparisons of GMTs will arise from geometric mean titer (GMT) ratios computed via a linear model of the $\log_2$ titers which incorporates left/right censoring at LLOQ/ULOQ. With the exception of the comparison of baseline immunity, a separate model will be fit for each comparison, limited to the groups involved in the comparison. For baseline immunity, a global F-test for a difference will be conducted and, if significant at level 0.10, the model will be used to produce pairwise comparisons of each group. The reverse-transformed two-sided 95% CI for the GMT ratio will be paired with the p-value corresponding to the F-test for a difference between groups. A difference between groups will be indicated if the CI excludes a GMT ratio of 1.

Median titers will be analyzed on the $\log_2$ scale, and paired with two-sided 95% bootstrap CIs. A difference between groups will be indicated if the interval excludes a difference of 0.

Fold-rises will be compared using standard normal distribution-based two-sample methodology on the $\log_2$ scale, followed by a reverse transformation. If an excess of titers reaches assay limits of quantitation, subgroup analyses will be conducted among those subjects with samples within the quantifiable range. A difference between groups will be indicated if the two-sided 95% CI for the ratio of geometric mean fold rises (reverse-transformed difference of differences) excludes a value of 1.

10.1.5 *Safety Data*

For an overview safety endpoints, see Section 3.

Safety parameters will generally be tabulated and analyzed descriptively, in the TVP, according to the actual administration interval received. Solicited events will be summarized in the Reactogenicity Population, according to the actual administration interval received. Additional analyses will aggregate across all groups following each dose and overall, including solicited events following each dose independently and overall (TVP, all groups combined), unsolicited events at any time point (TVP, all groups); the SAP will provide further detail.

Analyses described below will be performed for solicited and unsolicited AEs by severity, as well as for SAEs and IMEs. Events will only be considered as solicited if onset occurs within 7 days of a vaccination. All events with onset between Days 8 and 28 post-vaccination will be considered unsolicited. Any SAEs and IMEs will be collected from the date of the informed consent signature throughout the study and will be analyzed with unsolicited events, as well as separately.

The original terms used in the designated sections of the eCRFs by Investigators to identify AEs will be fully described and coded according to the MedDRA.

All AEs will be summarized by group, type, by post-vaccination timepoint and overall (regardless of timing of onset), by severity and occurrence in relation to vaccination, and overall, separately for solicited and unsolicited AEs. Determination of causal association to the study vaccine will be assigned using the individual causality assessment algorithm published by WHO in 2013[18]. All SAEs, IMEs and unsolicited AEs will be deemed eligible for causality assessment by the investigator or the safety monitor. After applying the Adverse Event Following Immunization (AEFI) causality algorithm, the SAE, IME or unsolicited AE will be classified as consistent or inconsistent with causal association to immunization; those which meet the definition of causality will be defined as reactions (respectively, serious adverse reactions [SARs], important medical reactions and unsolicited adverse reactions). Events with insufficient or conflicting evidence to make a determination of association will be deemed indeterminate according to the algorithm.

Separate tables and listings will be created for subjects who died, discontinued the study vaccine due to an AE, or experienced an SAE. Summaries, listings, and narratives may be provided, as appropriate. Unsolicited AEs occurring within 28 days of any vaccine administration will be summarized, as will any data obtained on SAEs or IMEs reported during the safety follow-up.

Abnormal physical exam findings and vital signs will be summarized.

10.1.6 *Exploratory*

Not applicable.

10.1.7 *Missing Data*

The reasons for any missing data will be ascertained and appropriate statistical methods will be used to accommodate these absences in the analyses of the study data that minimize potential biases and maximize efficiency conditional on the causes for data being missing. Data values that are identified by quality control procedures to be spurious will not be used in final analyses of the study data.

10.2 DETERMINATION OF SAMPLE SIZE

This study is designed to demonstrate the non-inferiority of different intervals of administration of nOPV2 (1-week and 2-week intervals) *versus* the standard 4-week interval based on the seroconversion rates of type 2 polio neutralizing antibodies 28 days following the second nOPV2 administration. Non-inferiority would be verified if the lower bound of the two-sided 95% CI around each difference (shorter interval minus standard interval) is greater than -10%.

The nOPV2 vaccine has recently been demonstrated to be non-inferior to Sabin-strain mOPV2 in a Phase 2 study[8]. In this Phase 2 study, among infants aged 18 weeks who had previously been vaccinated with bOPV and IPV, and using a 4-week interval between 2 doses, the cumulative seroconversion rates were near 100%, similar to the mOPV2 historical control group. A prior study of dosing intervals of 1, 2, and 4 weeks conducted

with mOPV2 in Bangladesh demonstrated seroresponse rates of 93.1%, 95.5% and 97.2% respectively, with lower confidence bounds of 88.3%, 91.3%, and 93.7%[17].

This study will be conducted in the Dominican Republic, and it is not anticipated that immune response rates will be lower than those observed in the previous mOPV2 study. Therefore, with a conservative assumed cumulative 2-dose seroconversion rate of 85% in each group, 270 evaluable subjects per group are required to demonstrate non-inferiority of each of the shorter intervals to the standard interval, using margin 10%, two-sided Type I error rate of 5%, and requiring 90% power. This will be further increased to 300 per group to account for loss to follow-up or other loss from the evaluable population.

11. ADVERSE EVENT REPORTING

11.1 DEFINITIONS

11.1.1 *Adverse Events*

An AEFI has been defined by the working group on vaccine pharmacovigilance of the Council for International Organizations of Medical Sciences and the WHO as "any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The AE may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease"

An AEFI 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 vaccine product.

Examples of an AE include:

- 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 vaccine administration even though they may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either vaccine or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with vaccine administration.
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).

Solicited AEs are described in Section 11.1.2. All other AEs occurring between 8 and 28 days after each vaccination will be recorded as unsolicited AEs.

Examples of an AE DO NOT include:

- Medical or surgical procedures (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an AE/SAE.
- Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination).
- 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.
- Pre-existing conditions or signs and/or symptoms present in a subject prior to the study vaccination. These events will be recorded in the medical history section of the eCRF.

11.1.2 *Solicited Adverse Events*

A solicited AE is one that is prelisted in the electronic diary card (paper diary card could be used as back up).

In this study, fever, vomiting, crying abnormal, drowsiness, loss of appetite, diarrhea and irritability will be solicited for 7 days after each study vaccine administration.

Subjects' parent(s) and/or guardian(s) will be provided with an electronic diary. A paper diary card will be provided as back up. This will include the definitions of mild, moderate and severe AEs, as described in Table 4, to facilitate the assessments of the level of functional impairment for each experienced AE. Any solicited AEs reported in the diary will be reviewed by the Investigator during the phone calls or on-site visits that will be scheduled 7 days after each dose of study vaccine.

Axillary temperature should be measured in the evening using the thermometer provided. Should additional temperature measurements be performed at other times of day, the highest temperature must be recorded in the electronic diary.

11.1.3 *Serious Adverse Events*

The Investigator will be responsible for recording and reporting within 24 hours and according to regulatory timelines all SAEs observed during the study (treatment and follow-up) period.

An SAE, experience or reaction, is any untoward medical occurrence (whether considered to be related to study drug or not) that at any dose:

- Results in death.
- Is life-threatening (the subject is at a 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: Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.
- Results in persistent or significant disability/incapacity.
- Is a congenital abnormality/birth defect detected only after study inclusion.

11.1.4 *Important Medical Event*

The Investigator will be responsible for recording and reporting within 24 hours and according to regulatory timelines all IMEs observed during the study (treatment and follow-up) period.

IMEs are medically significant events that do not meet any of the SAE criteria above, but require medical or surgical consultation or intervention to prevent this event to become one of the serious outcomes listed in the SAE definition above. Examples of IMEs include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias (e.g., neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization. Although IMEs are not SAEs, they are processed in the same way as SAEs. Every aspect described for SAEs (including study objectives and endpoints) also applies to an IME.

11.2 INTENSITY OF ADVERSE EVENTS

11.2.1 *Solicited Adverse Events*

The intensity of the solicited AEs will be assessed using the scale provided in Table 4.

Table 4 Intensity scales for solicited symptoms

Adverse Event	Intensity grade	Parameter
Fever	0	<37.5°C
	1 (mild)	37.5°C to 38.0°C
	2 (moderate)	38.1°C to 39.0°C
	3 (severe)	>39.0°
Vomiting	0	None
	1 (mild)	1 episode per 24 hours
	2 (moderate)	2 - 5 episodes per 24 hours
	3 (severe)	≥6 episodes per 24 hours or requiring parenteral hydration
Abnormal crying	0	None
	1 (mild)	<1 hour
	2 (moderate)	1 - 3 hours
	3 (severe)	>3 hours
Drowsiness	0	None
	1 (mild)	Sleepier than usual or less interested in surroundings
	2 (moderate)	Not interested in surroundings or did not wake up for a feed/meal
	3 (severe)	Sleeping most of the time or difficult to wake up
Loss of appetite	0	None
	1 (mild)	Eating less than normal
	2 (moderate)	Missed 1 or 2 feeds/meals completely
	3 (severe)	Refuses ≥3 feeds/meals or refuses most feeds/meals
Irritability	0	None
	1 (mild)	Easily consolable
	2 (moderate)	Requiring increased attention
	3 (severe)	Inconsolable
Diarrhea	0	None
	1 (mild)	An increase by 3 bowel movements (above normal or baseline) that are looser than normal per day, with no limitation to activities of daily living
	2 (moderate)	An increase by 4–6 bowel movements (above normal or baseline) that are looser than normal per day, or an increase of 3–6 bowel movements per day (above normal or baseline) that are looser than normal, with some interference with activities of daily living
	3 (severe)	An increase by 7 or more bowel movements per day (above normal or baseline) that are looser than normal per day, or an increase by 3 or more bowel movements per day (above normal or baseline) that are looser than normal, with incapacitating symptoms or interference with activities of daily living, or loose stools with visible red or tarry black blood in stool

11.2.2 *Unsolicited Adverse Events*

The investigator will assess the incidence and maximum intensity that occurred over the duration of the event for all unsolicited AEs recorded during the study. The assessment will be based on the investigator's clinical judgment.

The intensity should be assigned to one of the following categories:

1 (mild)	=	An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities (in adults, such an AE would, for example, prevent attendance at work and would necessitate the administration of corrective therapy.)
4 (life-threatening)	=	An AE that puts the subject at risk of death
5 (fatal)	=	An AE that results in death

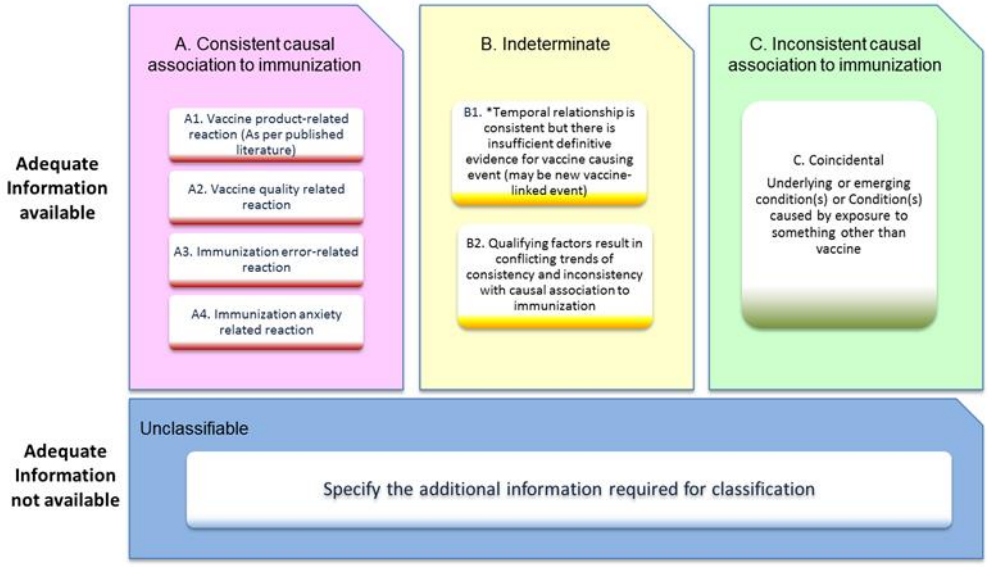
An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 11.1.3, or when it is of Grade 4 or 5.

11.3 CAUSALITY ASSESSMENT

The investigator is obligated to assess the relationship between investigational vaccine and the occurrence of each unsolicited AE/SAE/IME. The investigator will use clinical judgement to determine the relationship. Alternative plausible causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational vaccine will be considered and investigated. The investigator will also consult the Investigator's Brochure to determine his/her assessment.

Causality should be assessed by the investigator using AEFI causality algorithm developed by WHO for individual AEFI evaluation[18]. When appropriate information is available the investigator should arrive to the following possible conclusions:

Figure 1. Adverse Event Following Immunization Causality Algorithm



*B1 : Potential signal and maybe considered for investigation

SAEs considered to be causally related to the vaccination will be termed SARs.

If an event meets the criteria to be determined as 'serious' (see Section 11.1.3), additional examinations/tests will be performed by the investigator in order to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the vaccine, if applicable.
- Erroneous administration.
- Other cause (specify).

11.4 ACTION TAKEN REGARDING THE STUDY VACCINE

The action taken towards the study vaccine must be described as follows:

- Permanently discontinued.
- Stopped temporarily.
- No action taken.
- Not applicable.

11.5 OUTCOME

The outcome of each AE must be rated as follows:

- Recovered/resolved.

- Recovering/resolving.
- Not recovered/not resolved.
- Recovered with sequelae/resolved with sequelae.
- Fatal (SAEs only).

11.6 RECORDING OF ADVERSE EVENTS

All AEs occurring within 28 days of each vaccination and all SAEs occurring during the clinical investigation must be documented in the source documents and on the AE forms of the eCRF. The Investigator will inquire about the occurrence of AEs/SAEs at every visit/contact during the study.

Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record their opinion concerning the relationship of the (S)AE to the study vaccine in the source documents and on the eCRF. All measures required for (S)AE management must be recorded in the source documents and reported according to Sponsor's instructions.

All AEs occurring at any time during the study will be followed by the Investigator until satisfactory resolution (e.g., value back to baseline value) or stabilization or until final database lock. If necessary, in order to obtain additional information to ensure safety to the subject, additional blood and urine samples may be taken at the discretion of the Investigator. Certain long-term AEs related to therapy cannot be followed until resolution within the setting of this study. In these cases follow-up will be the responsibility of the treating physician.

11.7 REPORTING OF SERIOUS ADVERSE EVENTS TO THE SPONSOR

All SAEs independent of the circumstances or suspected cause must be reported on a SAE Form by the Investigator to the Sponsor, the Contract Research Organization (CRO), and to Assign Safety Desk (contractor for pharmacovigilance) within 24 h of their knowledge of the event, preferably by fax (+43 512 281 514 77).

The SAE form should include a clearly written narrative describing signs, symptoms, and treatment of the event, diagnostic procedures, as well as any relevant laboratory data and any sequelae, in order to allow a complete medical assessment of the case and independent determination of the possible causality.

Follow-up and outcomes should be reported for all subjects who experience an SAE.

It is critical that the information provided on the SAE Form matches the information recorded in the source documents and on the eCRF for the same event.

Copies of additional laboratory tests, consultation reports, postmortem reports, hospital case reports, autopsy reports, and other documents should be sent when requested and applicable. Follow-up reports relative to the subject's subsequent course must be submitted to the Sponsor and Assign (contractor for pharmacovigilance) until the event has subsided or, in the event of permanent impairment, until the condition stabilizes.

11.8 REPORTING OF SERIOUS ADVERSE EVENTS TO COMPETENT AUTHORITIES/ETHICS COMMITTEES

FIDEC assumes responsibility for appropriate reporting of AEs to the regulatory authorities. FIDEC will also report to the Investigator all SAEs that are unlisted (unexpected) and associated with the use of the vaccine. The Investigator must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol, unless otherwise required and documented by the IEC/IRB.

Adverse event reporting, including suspected unexpected serious adverse reactions (SUSARs), will be carried out in accordance with applicable local regulations.

After termination of the clinical study (determined as the LSLV), any unexpected safety issue that changes the risk-benefit analysis and is likely to have an impact on the subjects who have participated in the study, together with proposed actions, will be reported by the Sponsor to the competent authority(ies) concerned as soon as possible.

11.9 DATA MONITORING COMMITTEE

A DSMB will monitor the safety aspects of this study. The composition and functioning of the Board is documented in the DSMB charter.

12. ETHICAL ASPECTS

12.1 STUDY-SPECIFIC DESIGN CONSIDERATIONS

Potential subjects' parent(s)/guardian(s) will be fully informed of the nature of the study and of the risks and requirements of the study before any study-related assessment will be carried out. During the study, subjects' parent(s)/guardian(s) will be given any new information that may affect their child's decision to continue participation. They will be informed that their child's participation in the study is voluntary and that they may withdraw their child from the study at any time with no reason given and without penalty or loss of benefits to which they or their child would otherwise be entitled. Only subjects' whose parent(s)/guardian(s) are fully able to understand the risks, benefits, and potential AEs of the study and who provide their consent voluntarily will be enrolled in the study.

12.2 REGULATORY ETHICS COMPLIANCE

12.2.1 *Investigator Responsibilities*

The Investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the study, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae or other relevant documentation requested by the Sponsor, the IRB/IEC, or the regulatory authority(ies).

The Investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current International Council for Harmonization (ICH) guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles originating from the Declaration of Helsinki (1964 and revisions), and that the clinical study data are credible.

12.2.2 *Independent Ethics Committee or Institutional Review Board (IEC/IRB)*

An IRB/IEC should safeguard the rights, safety, and well-being of all study subjects. Special attention should be paid to studies that may include vulnerable subjects.

Before the start of the study, the Investigator (or Sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents:

- Final protocol and, if applicable, amendments.
- Sponsor-approved informed consent form (ICF) (and any updates or any other written materials to be provided to the subjects).
- Sponsor-approved subject recruiting materials.
- Prescribing information of the licensed vaccines.

- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable.
- Investigator's current curriculum vitae or other documentation evidencing qualifications (unless not required, as documented by the IEC/IRB).
- Information regarding funding, name of the Sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects.
- Any other documents that the IEC/IRB may require to fulfill its obligation.

This study will be undertaken only after the IEC/IRB has given full written approval of the final protocol and amendments (if any), the ICF(s) and updates (if any), applicable recruiting materials, and any other written information to be provided to the subjects, and the Sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study, the Investigator (or Sponsor where required) will send the following documents and updates to the IEC/IRB for its review and approval, where appropriate:

- Protocol amendments.
- Revision(s) to the ICF and any other written materials to be provided to the subjects' parents.
- New or revised subject recruiting materials approved by the Sponsor.
- Revisions to compensation for study-related injuries or payment to subjects or their parent(s)/guardian(s) for participation in the study.
- Prescribing information of the licensed vaccines.
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually).
- Reports of SUSARs.
- New information that may adversely affect the safety of the subjects or the conduct of the study.
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects.
- Report of death of any subjects under the Investigator's care.
- Notification if a new Investigator is responsible for the study at the clinical site.
- Development Safety Update Report, Short-Term Study Specific Safety Summary and Line Listings, where applicable.
- Any other requirements of the IEC/IRB.

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s), except when necessary to eliminate immediate hazard to the study subjects. If a deviation from or a change to the protocol was implemented to eliminate an immediate hazard to study subjects, then the implemented deviation or change, the reasons for it, and, if appropriate, the protocol amendment should be submitted to the IEC/IRB as soon as possible.

The Investigator (or Sponsor where required) will notify the IEC/IRB about the study completion within 90 days after the end of the study (defined as LSLV).

12.2.3 *Informed Consent*

The parent(s)/guardian(s) of each subject must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form that is used must be approved by both the Sponsor and the reviewing IEC/IRB. The informed consent should be in accordance with the principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and Sponsor policy.

Before enrollment in the study, the Investigator or an authorized member of the clinical staff must explain to the parent(s)/guardian(s) of potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects' parent(s)/guardian(s) will be informed that the subject's participation is voluntary and that they may refuse to allow the subject to participate or withdraw consent for the subject to participate at any time, without penalty or loss of benefits to which the parent(s)/guardian(s) and/or subject was entitled. Finally, they will be told that the Investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that the subject's records may be accessed by health authorities and authorized Sponsor staff without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject's parent(s)/guardian(s) is authorizing such access, and agrees to allow the subject's study physician to recontact the subject's parent(s)/guardian(s) for the purpose of obtaining consent for additional safety evaluations, if needed.

The ICF will include a paragraph whereby the subject's parent(s)/guardian(s) allow or not the use of the subject's biological samples for additional polio related research, if needed.

The language about the study used in the oral and written information, including the ICF, should be non-technical and practical and should be understandable to the subjects' parent(s)/guardian(s). The subjects' parent(s)/guardian(s) will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry of the subject into the study, consent should be appropriately recorded by means of the subject's parent(s)/guardian(s) personally dated signature. After having obtained consent, a copy of the ICF must be given to the subject's parent(s)/guardian(s).

If a subject's parent(s)/guardian(s) is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject's parent(s)/guardian(s) is obtained, if permitted by local law.

12.2.4 *Privacy of Personal Data*

The collection and processing of personal data from subjects enrolled in the study will be limited to those data that are necessary to investigate the safety, quality, and immunogenicity of the nOPV2 vaccine used in the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data need to agree to keep the identity of the study subjects confidential.

The informed consent obtained from the subjects' parent(s)/guardian(s) includes explicit consent for the processing of personal data and for the Investigator to allow direct access to subjects' original medical records for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

13. ADMINISTRATIVE REQUIREMENTS

13.1 PROTOCOL AMENDMENTS/NOTIFICATIONS

Neither the Investigator nor the Sponsor will modify this protocol without a formal amendment (except modifications that do not alter the benefit/risk-see next paragraph). All protocol amendments must be issued by the Sponsor and signed and dated by the Investigator. Protocol amendments must not be implemented without prior IEC/IRB approval nor when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazard to the subjects, in which case an amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the Investigator and IEC/IRB must be provided to the Sponsor or its designee.

When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

13.2 SUBJECT IDENTIFICATION AND ENROLLMENT LOGS

The Investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the Sponsor site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the Investigator in the study file. To ensure subject confidentiality, no copies will be made. All reports and communications related to the study will identify subjects by initials and/or assigned number only.

13.3 SOURCE DOCUMENTATION

At a minimum, source documentation must be available for the following to confirm data collected in the eCRF: subject identification, eligibility, and study identification; study discussion and date of informed consent, dates of visits, results of safety and efficacy parameters as required by the protocol, record of all AEs, follow-up of AEs, concomitant medication, study vaccine receipt/dispensing/return records, study vaccine administration information, laboratory printouts, date of study completion, and reason for early discontinuation of study vaccine or withdrawal from the study, if applicable.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded on the eCRF are consistent with the original source data.

It is recommended that the author of an entry in the source documents be identifiable.

At a minimum, the type and level of detail of source data available for a study subject should be consistent with that commonly recorded at the clinical site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the Investigator before the study and will be described in the monitoring guidelines (or other equivalent document). The nature and location of all source documents will be identified in the Source Document Identification Form. Data that will

be recorded directly into the eCRF are specified in the Source Document Identification Form.

13.4 CASE REPORT FORM COMPLETION

Electronic Data Capture (EDC) will be used for this study. The study data will be transcribed by study personnel from the source documents onto an eCRF, and transmitted in a secure manner to the Sponsor. The electronic file will be considered to be the eCRF.

All eCRF entries, corrections, and alterations must be made by the Investigator or other authorized study-site personnel.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheet will become part of the subject's source documentation. Such worksheet should not resemble an eCRF. All data related to the study must be recorded on the eCRFs prepared by the Sponsor. Data must be entered into the eCRFs in English. Designated site personnel must complete the eCRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

The Investigator must verify that all data entries on the eCRFs are accurate and correct.

13.5 MONITORING

The monitoring of the study will be done under the responsibility of the Sponsor by the designated CRO.

The monitor will perform on-site monitoring visits as frequently as necessary. The monitor will record the dates of the visits in a study site visit log that will be kept at the clinical site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the Sponsor and clinical staff and are accessible for verification by the Sponsor site contact. If electronic records are maintained at the investigational site, the method of verification must be discussed with the clinical staff.

Direct access to source documentation (medical records) must be allowed at all times for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data. Findings from this review of eCRFs and source documents will be discussed with the clinical staff. During on-site monitoring visits (notified and agreed upfront with the clinical staff), the relevant clinical staff will be available, the source documentation will be accessible, and a suitable environment for review of study-related documents will be provided. The monitor will meet with the Investigator on a regular basis during the study to provide feedback on the study conduct.

13.6 DATA MANAGEMENT

Data management of the study will be performed under the responsibility of the Sponsor by Assign.

After the monitor has reviewed the data entered into the eCRFs for completeness and accuracy and the data are released by the Investigator, data will be uploaded into the

clinical database to perform cleaning activities. Computerized data cleaning checks will be used in addition to manual review, including listings review, to check for discrepancies and to ensure consistency and completeness of the data.

If necessary, queries will be generated in the EDC tool. The Investigator or an authorized member of the clinical staff must adjust the eCRF (if applicable) and complete the query. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in 3 different ways: 1- site personnel can make corrections in the EDC tool at their own initiative or as a response to an auto query (generated by the EDC tool), 2- the site manager can generate a query (field data correction form) for resolution by the clinical staff, and 3- the clinical data manager can generate a query for resolution by the clinical staff.

Laboratory data will be reconciled against records in the clinical database.

The clinical database will be locked as soon as it is considered clean. Only authorized and well-documented updates to the study data are possible after database lock. The locked database is used in the final statistical analysis for study reporting. Measures will be undertaken to protect subject data handed over by the Investigator to the data management department and during inspections against disclosure to unauthorized third parties. Subject confidentiality will be maintained at all times.

13.7 DATA QUALITY ASSURANCE

The accuracy and reliability of the study data will be assured by the selection of qualified Investigators and appropriate study sites, review of protocol procedures with the Investigator and associated personnel prior to the study, and by periodic monitoring visits by the Sponsor or designate.

The Sponsor or his designee will review the eCRF system for accuracy and completeness during (on-site) monitoring visits and after transmission to the Sponsor; any discrepancies will be resolved with the Investigator or designee, as appropriate. After upload of the data into the clinical study database, their accuracy verified using appropriate validation programs.

In accordance with ICH/GCP guidelines, the Sponsor will be entitled to audit the facilities used in the clinical and laboratory parts of the study, as well as to access all the data files pertaining to the study. Similar procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The Investigator should immediately notify the Sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

13.8 ON-SITE AUDITS

Representatives of the Sponsor's clinical quality assurance department or any other qualified auditor appointed by the Sponsor may visit the clinical site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the eCRFs. Subject privacy must, however, be respected. The Investigator and clinical staff are to be

present and available for consultation during routinely scheduled site audit visits conducted by the Sponsor or its designees.

Similar procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The Investigator should immediately notify the Sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

13.9 STUDY TERMINATION

The Sponsor has the right to terminate the study at any time. In the event of early termination of the study or temporary halt by the Sponsor, the IEC/IRB and the regulatory authorities should be notified within 15 calendar days and should be provided with a detailed written explanation of the reasons for the termination/halt.

An end-of-study declaration will be submitted to the regulatory authorities and IEC/IRB after the complete study has ended. This notification will be submitted within 90 days after the end of the study.

13.10 RECORD RETENTION

In compliance with the ICH/GCP guidelines, the Investigator/Institution will maintain all eCRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The Investigator/Institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 15 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 5 years have elapsed since the formal discontinuation of clinical development of the study vaccine. These documents will be retained for a longer period if required according to the applicable regulatory requirements or per agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

If the responsible Investigator retires, relocates, or for any other reasons withdraws from his responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the Investigator relocate or dispose of any study documents without having obtained written approval from the Sponsor.

If it becomes necessary for the Sponsor or the appropriate regulatory authority to review any documentation related to the study, the Investigator must permit access to such reports.

13.11 USE OF INFORMATION AND PUBLICATION

All information, including but not limited to, information regarding the study vaccine or the Sponsor's operations (e.g., patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the Sponsor to the Investigator and not previously published, and any data generated as a result of this study are considered confidential and remain the sole property of the Sponsor. The Investigator agrees to maintain this information in confidence, to use this information only to accomplish this study, and not to use it for other purposes without the Sponsor's prior written consent.

The Investigator understands that the information generated in this clinical study will be used by the Sponsor in connection with the continued development of the study vaccine, and thus may be disclosed as required to other clinical Investigators or regulatory agencies. To permit information derived from the clinical studies to be used, the Investigator is obliged to provide the Sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated under the responsibility of the Sponsor and will contain eCRF data from all clinical sites that participated in the study. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating Investigator.

Clinical narratives will be written for the following events (for example):

- All deaths (irrespective of vaccine relationship).
- All other SAEs and IMEs after vaccination.
- All discontinuations of the study vaccine due to AEs (irrespective of vaccine relationship).
- At the discretion of the team and after statistical analysis of the data, certain discontinuations not related to AEs or treatment failure, i.e., related to lost to follow-up or withdrawal of consent (irrespective of treatment group).
- Any events of special interest explicitly requested by the regulatory agencies.

The Principal Investigator will sign off the final version of the Clinical Study Report. A summary of this final version will be provided to the Investigators, the applicable regulatory authorities, and the IECs/IRBs, if required by the applicable regulatory requirements, within 1 year after the end of the study (LSLV).

The Sponsor shall have the right to publish study data and information without approval from the Investigator. If an Investigator wishes to publish information from the study, a copy of the manuscript must be provided to the Sponsor for review at least 30 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the Sponsor in writing, the Investigator will withhold such publication for up to an additional 30 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the Sponsor will review these issues with the Investigator. The Sponsor will not mandate modifications to scientific content and does

not have the right to suppress information. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

13.12 REGISTRATION OF CLINICAL STUDIES AND DISCLOSURE OF RESULTS

The Sponsor will register the existence and disclose the results of this clinical study as required by law, on Clinicaltrials.gov and the WHO International Clinical Trials Registry Platform.

For the public disclosure of clinical study documentation or data, e.g., the study protocol or clinical study report, appropriate measures will be taken to redact such material so as to protect the privacy and confidentiality of the data as applicable to the study subjects in agreement with the legislative authority requiring such disclosure.

13.13 INVESTIGATOR INDEMNITY

The Sponsor holds and will maintain an adequate insurance policy covering damages arising out of FIDEC-sponsored clinical research studies.

The Sponsor will indemnify the Investigator and hold him/her harmless for claims related to damages arising from the investigation, provided that the study vaccine was administered under the Investigator or deputy's supervision and in strict accordance with accepted medical practice and the study protocol.

The Investigator must notify the Sponsor immediately upon notice of any claims or lawsuits.

13.14 CONFIDENTIALITY

All study documents are provided by the Sponsor to the Investigator and appointed clinical staff in confidence. None of this material may be disclosed to any party not directly involved in the study without the Sponsor's written permission.

The Investigator must assure that subjects' anonymity will be maintained. The Investigator will keep a separate list with at least the initials, the subjects' study numbers, names, addresses, and telephone numbers. The Investigator will maintain this for the longest period of time allowed by his/her own institution and, in any case, until further communication from the Sponsor.

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