Clinical Study Protocol M5 – ABMG

Amendment 2

4 March 2019 (Version 3.0)

A Phase 2 study to evaluate the safety and immunogenicity of two novel oral polio type 2 vaccine candidates in healthy children aged 1 to 5 years and in healthy bOPV-IPV vaccinated infants.

Product	- nOPV2 candidate 1 (S2/cre5/S15domV/rec1/hifi3) 2018 - nOPV2 candidate 2 (S2/S15domV/CpG40) 2016 - nOPV2 candidate 2 (S2/S15domV/CpG40) 2018
Protocol Number	M5 – ABMG
ClinicalTrials.gov Number	NCT03554798
Clinical Phase	II
Clinical Indication	Oral polio vaccine immunization
Issue Date	Initial Protocol Version 1.0 (21 June 2018)
Issue Date (this version)	Amendment 2 Version 3.0 (4-March-2019)

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
Sponsor Representative	Dr. Ricardo Rüttimann Tel + 1 305 854 0075, Fax + 1 305 856 7847

SIGNATURES

Signature of Sponsor Representative

Title: A Phase 2 study to evaluate the safety and immunogenicity of two novel oral polio type 2 vaccine candidates in healthy children aged 1 to 5 years and in healthy bOPV-IPV vaccinated infants.

Name: Dr. Ricardo Rüttimann
Tel + 1 305 854 0075, Fax + 1 305 856 7847

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

Signature:

Date:

Signature of Statistician

Title: A Phase 2 study to evaluate the safety and immunogenicity of two novel oral polio type 2 vaccine candidates in healthy children aged 1 to 5 years and in healthy bOPV-IPV vaccinated infants.

Name: Christopher Gast, Ph.D.

Affiliation: PATH

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Seattle, WA 98109 USA

This Clinical Study Protocol has been reviewed and approved by the study statistician in order to ensure that the protocol and any amendments cover all relevant statistical matters clearly and accurately, using technical terminology as appropriate.

Signature:

Date:

Signature(s) of Investigator(s)

Title: A Phase 2 study to evaluate the safety and immunogenicity of two novel oral polio type 2 vaccine candidates in healthy children aged 1 to 5 years and in healthy bOPV-IPV vaccinated 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:

Date:

Signature:

Date:

PROTOCOL HISTORY

Protocol History FIDEC – M5 – ABMG			
Document	**Issue Date**	**Amendment Type**	**Comments**
Initial Clinical Study Protocol	21 June 2018 (v 1.0)	-	This document
Protocol amendment 1	5 October 2018 (v 2.0)	Study design	Extensive changes to study design to allow sequential testing of two nOPV2 candidates, 1 and 2.
Protocol amendment 2	4 March 2019 (v 3.0)	Study design	Extensive changes to study design to allow concomitant, randomized testing of nOPV2 candidates 1 and 2 produced in 2018 using final working virus seed.

This section describes the changes in reference to Protocol Amendment 2 (Protocol Version 3.0)

Rationale:

The primary purpose of this amendment is to perform a concurrent, randomized assessment and comparison with the historical control subjects in study M2 of both nOPV2 candidates 1 and 2 using 2018 bulk lots manufactured from working virus seeds intended for future vaccine production. This follows Amendment 1 made when the simultaneous availability of both 2018 lots of the two vaccine candidates was in doubt. Under this new amendment, the initial evaluation of the 2016 preparation of nOPV2 candidate 2 already underway in Stage I becomes an interim analysis to address programmatic considerations within Stage II.

The use of lots from the final working seed in this study in which a lot from a previous working seed is used is intended to accelerate the qualification of the final working seed in order to rapidly allow production of sufficient quantities of nOPV2 vaccines in the context of the worsening epidemiology of OPV2-associated paralytic poliomyelitis. As in the ongoing part of the study candidate 1 has not yet been administered to infants, this candidate 1 (2016) will be replaced by candidate 1 (2018). The addition of candidate 2 (2018) will increase the sample size by an additional 50 children 1 to 5 years of age and 324 infants enrolled at 6 weeks of age. Under this amendment, data from subjects receiving the nOPV2 candidate produced from the 2016 working seed will no longer be compared with those from the historical M2 data but instead will be described independently in an interim analysis, to address the urgent programmatic considerations to the WHO, with M2 data to be compared with those from subjects receiving the 2018 working seed vaccine candidates in the final report.

Major changes:

1. The three nOPV2 candidate vaccine lots are identified by their year of preparation: nOPV2 candidate 1 (2018), nOPV2 candidate 2 (2016) and nOPV2 candidate 2 (2018).
2. In the Objectives it is clariified that statistical assessments and comparisons with historical data for the mOPV2 comparator obtained in study M2 will only be made for data obtained for the two 2018 vaccine candidate lots in Stage II.
3. The overview of the study design has been expanded to include the updated description and explanation for conducting Stages I and II in sequence.
4. The study diagram for Stage II has been replaced with a new version showing that both 2018 vaccine candidate lots will be assessed concurrently, initially in 1 to 5 year-olds and then in infants, but otherwise following the same design as Stage I.
5. The term "toddlers" has been replaced throughout with "1 to 5 year-olds".
6. Total number of 1 to 5 year-olds increased from 100 to 150, to include the group in Stage II to be vaccinated with nOPV2 candidate 2 (2018).
7. Total number of infants increased by 324 to 972, to include the two additional groups in Stage II to be vaccinated with nOPV2 candidate 2 (2018).
8. New summary of data from neurovirulence testing and deep sequencing of the candidate nOPV2 lots showing that this tests did not raise any safety concerns now included in Section 6.2.

Amendment to Protocol Version 2.0 dated 5 October 2018	
Rationale for the Amendment: Substantial amendment due to requirement to increase study size to allow concurrent, randomized assessment and comparison with the historical control subjects in study M2 of both nOPV2 candidates 1 and 2 prepared using 2018 bulk lots manufactured from working virus seeds intended for future vaccine production.	
Section	**Description of change**
All	Changed date and version number
Title page	Added new lot of candidate 2 to Product list and definitions of 2016 and 2018 lots
Synopsis	Updated study design
Synopsis; text	Generally distinguished how objectives apply to the different candidates in Stages I and II and to the 2018 candidate lot, rather than the 2016 candidate lot in Stage I.
Synopsis; text	Inclusion of immunungenicity assessments in Stage I subjects as secondary objectives.
Synopsis; text	Clarification of approaches to genetic stability and neurovirulence analyses in Exploratory objectives.
Synopsis; text	Inclusion in Overview of Study Design of the preparation and use of an interim analysis of Stage I for programmatic considerations to enhance the use of Stage II to advance nOPV2 development.
Synopisis; text	Clarification of "starting conditions" for Stage II.
Synopisis; text	Addition of Group A2H2 - 1 to 5 year-olds receiving candidate 2 (2018).
Synopisis; text	Addition of Groups B2L1, B2L2, B2H1 and B2H2 - infants receiving candidate 2

	(2018).
Synopisis; text	Added new details of high dose (10^6 $CCID_{50}$) 2018 lots, one dose being 1.0 ml.
Synopsis; text	In Statistical Methods noted that primary immunogenicity endpoints will be restricted to 2018 lots of both vaccine candidates.
Synopsis: Time & Events Tables	Clarifications added for acceptable time windows for receipt of informed consent forms, and for parents to supply their child's stool samples after vaccination.
Introduction, 1.2, p.34	Added description of new candidate lots prepared in 2018, and reason for their importance.
Introduction, 1.2, p.34	Added note about assessment of safety data from Stage I by DSMB to initiate Stage II.
Introduction, 1.2.1, p.35	Added note that preclinical data suggest new candidates will not increase VAPP.
Secondary objectives, 2.2, p.37	Noted that all immunogenicity parameters for infants in Stage I will be Secondary Objectives.
Secondary objectives, 2.2, p.37	Clarification of groups in which viral shedding will be assessed as a Secondary Objective.
Secondary objectives, 2.2, p.37	Clarification of groups in which potential for neurovirulence will be assessed as a Secondary Objective.
Exploratory objectives, 2.3, p.37	Clarification of groups in which viral shedding will be assessed as an Exploratory Objective.
Exploratory objectives, 2.3, p.38	Clarification of groups in which potential for neurovirulence will be assessed as an Exploratory Objective.
Study Endpoints. 3 p.38-40.	Endpoints aligned with changes in Primary, Secondary and Exploratory objectives.
Study Design, 4.1, p.41-42.	Clarification of "starting conditions" for Stage II
Study Design, 4.2, p.42-43.	Clarification of randomization in Stages I and II.
Vaccines, 6.2, p.47	Additional information on preclinical testing of the candidate vaccine lots for neurovirulence and genetic stability through deep sequencing analysis.
Vaccines, 6.5, p.48	Note added about use of opened vials within 48 hours.
Vaccines, 6.6, p.49	Details of Stage II with additional candidate added.
Vaccines, 6.7 p.49	Details of each candidate vaccine and dose added, specifically to note large volume required for high doses of 2018 lots of both candidates.
Immunogenicity, 8.2, p.52	Note added about seroconversion in infants from Day -84, as well as from Day 0.
Statistical Methods, 10.1, p.55	Clarification that only data from 2018 lots of candidates 1 and 2 will be compared statistically with historical controls, while data from Stage I with candidate 2 (2016) will be analysed descriptively and included in an interim report.
Statistical Methods, 10.1.2, p.56-57	Defintion of analysis sequence added.
Statistical Methods, 10.1.5, p.59	Additional details of neurovirulence testing added.

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PROTOCOL SYNOPSIS

Study Title	**A Phase 2 study to evaluate the safety and immunogenicity of two novel oral polio type 2 vaccine candidates in healthy children aged 1 to 5 years and in bOPV-IPV vaccinated healthy infants.**		
Product	- nOPV2 candidate 1 (S2/cre5/S15domV/rec1/ hifi3) [2018] - nOPV2 candidate 2 (S2/S15domV/CpG40) [2016] - nOPV2 candidate 2 (S2/S15domV/CpG40) [2018]	**Clinical Phase**	II
Protocol Number	M5 – ABMG	**Indication**	Oral polio vaccine immunization
ClinicalTrials.gov Number NCT03554798			

Sponsor	FIDEC
Sponsor Representative	Dr. Ricardo Rüttimann
Clinical Center	CEVAXIN, Panama

Objectives:

The co-primary objectives of the study are:

- To assess the safety (incidence of serious adverse reactions [SARs] and severe adverse reactions [AEs; grade 3 according to CTCAE 4.03], important medical reactions [IMR] and any clinically-relevant clinical laboratory deviations) in infants and young children after administration of one or two doses of each dose level of nOPV2 vaccine candidates and to contrast this with a control sample of similarly aged children receiving one or two doses of Sabin mOPV2 in a prior study (M2) designed to serve as a historical control for the current study.
- To assess and compare the immunogenicity (seroprotection rate against poliovirus type 2) of a single dose (at both 10^5 and 10^6 $CCID_{50}$ dose levels) of each of the nOPV2 vaccine candidates (2018 lots) in infants at approximately 18–22 weeks of age after having been previously vaccinated with 3 doses of bOPV and 1 dose of IPV, relative to a control sample of infants receiving the same vaccination schedule followed by a single dose of Sabin mOPV2 in a prior study (M2) designed to serve as a historical control for the current study.

Secondary objectives are:

- To assess the safety expressed as incidence, severity and causality of any serious adverse event (SAE), any solicited AE, any unsolicited AEs, any important medical events (IME) and laboratory deviations with the exception of SAE, severe AEs/IME considered consistent with causal association to study vaccine and clinically-relevant clinical laboratory deviations (primary objective) following one or two doses of the nOPV2 candidates at the 10^6 $CCID_{50}$ dose level in healthy children aged 1 to 5 years, and of one or two doses of the nOPV2 candidates at both 10^5 and 10^6 $CCID_{50}$ dose levels in infants at approximately 18–22 weeks of age after having been previously vaccinated with 3 doses of bOPV and 1 dose of IPV and contrast this safety with participants who received the same vaccination schedule followed by one or two doses of Sabin mOPV2 in a prior study (M2) designed to serve as a control for the current study.
- To assess the immunogenicity (median and geometric mean neutralizing antibody titers, seroconversion rates, seroprotection rates against poliovirus type 2) of one or two 10^6 $CCID_{50}$ doses of each of the nOPV2 vaccine candidate lots in healthy children aged 1 to 5 years, and contrast this immunogenicity with a control sample of similarly aged children receiving one or two doses of Sabin mOPV2 in a prior study (M2) designed to serve as a historical control for the current study.
- To assess the immunogenicity (median and geometric mean neutralizing antibody titers and seroconversion rates against poliovirus type 2) of one or two doses, and the seroprotection rates after two doses of each of the nOPV2 candidates (2018 lots) at both 10^5 and 10^6 $CCID_{50}$ dose levels at approximately 18–22 weeks of age in infants previously vaccinated with 3 doses of bOPV and 1 dose of IPV, and contrast this immunogenicity with a control sample of participants receiving the same vaccination schedule followed by one or two doses of Sabin mOPV2 in a prior study (M2) designed to serve as a control for the current study.
- To assess the immunogenicity (median and geometric mean neutralizing antibody titers, seroconversion rates, seroprotection rates against poliovirus type 2) of one or two doses (at both 10^5 and 10^6 $CCID_{50}$ dose levels) of nOPV2 vaccine candidate 2 (2016 lot) in infants at approximately 18–22 weeks of age.
- To assess the extent of viral shedding in stool at fixed time points following administration of one dose of the nOPV2 candidates (2016 and 2018 lots) at the 10^6 $CCID_{50}$ dose level in healthy children aged 1 to 5 years, and in infants at approximately 18–22 weeks of age, and contrast this shedding with a control sample of participants receiving the same vaccination schedule followed by one dose of Sabin mOPV2 in a prior study (M2) designed to serve as a control for the current study.
- To assess the potential for neurovirulence of virus isolated from a subset of stool samples of children aged 1 to 5 years, and infants at approximately 18–22 weeks of age after having been previously

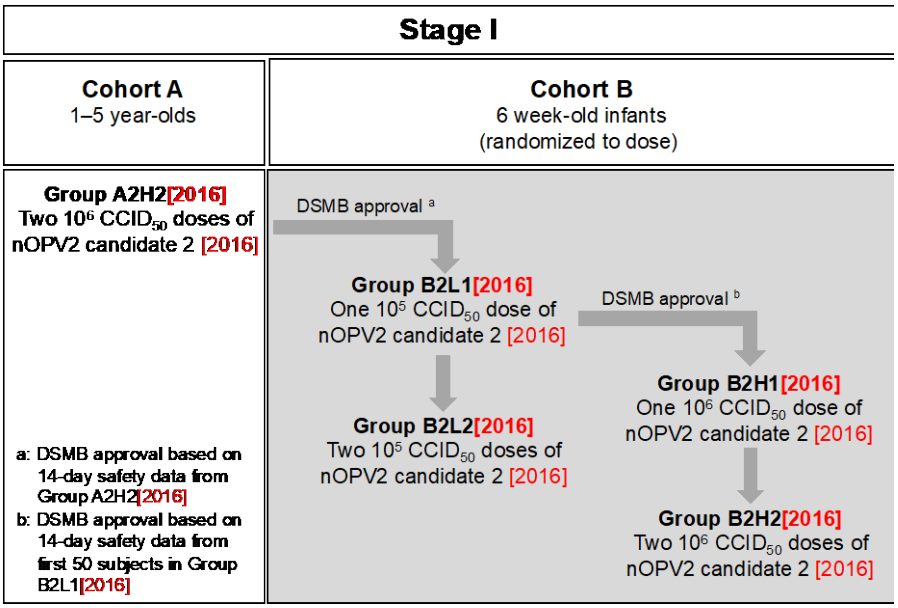
vaccinated with 3 doses of bOPV and 1 dose of IPV, following one dose of the nOPV2 candidates (2018 lots) at the 10^6 $CCID_{50}$ dose level, as measured in an animal model, and contrast this with a control sample of participants receiving the same vaccination schedule followed by one dose of Sabin mOPV2 in a prior study (M2) designed to serve as a control for the current study.

Exploratory objectives may include:

- Assessment of the baseline humoral immunity to poliovirus type 2 as neutralizing antibodies in infants at approximately 6 weeks of age before any vaccination with either bOPV or IPV.
- Assessment of the priming by bOPV+IPV of immune responses to a single dose of the nOPV2 candidates (all lots) at 10^5 and 10^6 $CCID_{50}$ dose levels in infants at approximately 18–22 weeks of age relative to a control sample of infants receiving the same vaccination schedule followed by one or two doses of Sabin mOPV2 in a prior study (M2) designed to serve as a control for the current study.
- Investigation of the extent of viral shedding following the administration of 10^6 $CCID_{50}$ doses of nOPV2 candidates (all lots) in healthy children aged 1 to 5 years and of 10^5 $CCID_{50}$ doses of nOPV2 candidates (all lots) in infants at approximately 18–22 weeks of age.
- Assessment of the genetic sequence heterogeneity and stability of virus isolated from subsets of stool samples of participants following one or two doses of the nOPV2 candidates (2018 lots) at 10^6 $CCID_{50}$ dose level 1 to 5 year-olds, and at 10^5 and 10^6 $CCID_{50}$ dose levels in infants at approximately 18–22 weeks of age, and contrast this heterogeneity profile with a control sample of participants receiving the same vaccination schedule followed by one or two doses of Sabin mOPV2 in a prior study designed to serve as a control for the current study. A similar exploratory assessment of genetic stability of samples from 1 to 5 year-olds and infants in Stage I administered with nOPV2 candidate 2 [2016] may be performed.
- Assessment of the immune response to parallel routine vaccinations through assessment of antibodies to hepatitis B (HBV) and *Haemophilus influenzae* type b (Hib) vaccine components after a full infant primary series and contrast these values with those in participants in a prior study (M2) designed to serve as a control for the infants current study.

Overview of Study Design:

This will be a single center, multi-site, age de-escalation, partly-randomized study in a cohort of healthy children aged 1 to 5 years (cohort A) and a cohort of bOPV-IPV vaccinated healthy infants aged 6 weeks (cohort B), performed in two consecutive stages as illustrated and described below. An interim analysis of information gained in Stage I with administration of nOPV2 candidate 2 (2016) will be used to advance programmatic considerations for the nOPV2 concept in light of ongoing global polio eradication initiative efforts. Stage II will allow the randomized enrollment of the two nOPV2 candidates 1 and 2 (2018 lots) for formal comparison with data from the historical control, mOPV2, obtained in study M2. Safety, immunogenicity, and viral shedding data from Stage I will be analyzed descriptively in an interim report, with data from Stage II following in a combined final study report.



Stage I

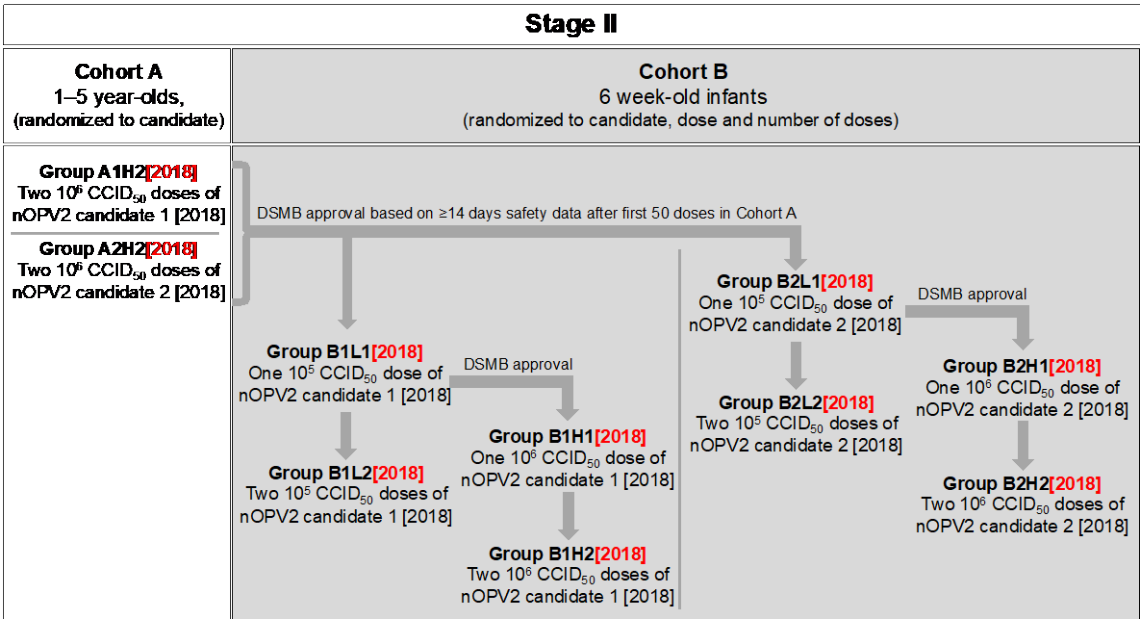
- **Group A2H2[2016]:** 50 IPV and/or OPV vaccinated participants aged 1 to 5 years administered two 10^6 $CCID_{50}$ doses of candidate 2 [2016], separated by 28 days.

Age de-escalation will be based on general safety data (solicited and unsolicited AEs and clinically significant abnormal laboratory values) through 14 days post dose 1 in 1 to 5 year-olds presented to the DSMB. After the DSMB recommendation to proceed, the younger cohort will be enrolled and randomized to the following groups:

- **Group B2L1[2016]:** 162 infants enrolled at 6 weeks of age (-7 to +14 days) vaccinated with 3 doses of bOPV at 6, 10 and 14 weeks of age and 1 dose of IPV at 14 weeks of age, followed at 18–22 weeks of age with one 10^5 $CCID_{50}$ dose of candidate 2 [2016].
    - **Group B2L2[2016]:** a sub-group of 50 infants will be randomly selected from B2L1[2016] to receive]a second 10^5 $CCID_{50}$ dose of candidate 2 [2016], 28 days later.

Following completion of post-dose 1 safety assessment from the first 50 subjects from group B2L1[2016] and after the DSMB recommends to proceed, infants will be enrolled and randomized to groups B2H1[2016] and B2H2[2016]. Dose escalation will be based on general safety data (solicited and unsolicited AEs and clinically significant abnormal laboratory values) through 14 days post dose 1-in the first 50 subjects from group B2L1[2016].

- **Group B2H1[2016]:** 162 infants enrolled at 6 weeks of age (-7 to +14 days) vaccinated with 3 doses of bOPV at 6, 10 and 14 weeks of age and 1 dose of IPV at 14 weeks of age, followed at 18–22 weeks of age with one 10^6 $CCID_{50}$ dose of candidate 2 [2016].
    - **Group B2H2[2016]:** a sub-group of 50 infants will be randomly selected from B2H1[2016] to receive a second 10^6 $CCID_{50}$ dose of candidate 2 [2016], 28 days later.



Stage II

Stage II will only be performed following completion of the enrollment in Stage I with a minimum of 14 days safety follow-up in at least 50 subjects of group B2H2[2016] after administration of 10^6 $CCID_{50}$ nOPV2 candidate 2 [2016], and with the recommendation of the DSMB. In Stage II the process will be repeated in the same fashion as in Stage I, with randomized enrollment to candidate within age group and dose level. Enrolment of subjects for Stage II may begin before the above-defined completion threshold but no administrations of nOPV2 are to be perfomed before this threshold is achieved.

New cohorts of 1–5 year old children and 6 week-old infants will be enrolled and randomly allocated to receive nOPV2 candidate 1 [2018] or nOPV2 candidate 2 [2018] in the following groups:

- **Group A1H2[2018]:** 50 IPV and/or OPV vaccinated participants aged 1 to 5 years administered two 10^6 $CCID_{50}$ doses of candidate 1 [2018] separated by 28 days.
- **Group A2H2[2018]:** 50 IPV and/or OPV vaccinated participants aged 1 to 5 years administered two 10^6 $CCID_{50}$ doses of candidate 2 [2018] separated by 28 days.

Age de-escalation will be based, separately for each candidate, on general safety data (solicited and unsolicited AEs and clinically significant abnormal laboratory values) through 14 days post dose 1 in 1 to 5 year-olds presented to the DSMB. The DSMB must give their recommendation to proceed, based on this safety data, before any infants receive any nOPV2 candidate in the following groups:

- **Group B1L1[2018]:** 162 infants enrolled at 6 weeks of age (-7 to +14 days) vaccinated with 3 doses of bOPV at 6, 10 and 14 weeks of age and 1 dose of IPV at 14 weeks of age, followed at 18–22 weeks of age with one 10^5 $CCID_{50}$ dose of candidate 1 [2018].
    - **Group B1L2[2018]:** a sub-group of 50 infants will be randomly selected to receive a

second 10^5 $CCID_{50}$ dose of candidate 1 [2018], 28 days later.

- **Group B2L1[2018]:** 162 infants enrolled at 6 weeks of age (-7 to +14 days) vaccinated with 3 doses of bOPV at 6, 10 and 14 weeks of age and 1 dose of IPV at 14 weeks of age, followed at 18–22 weeks of age with one 10^5 $CCID_{50}$ dose of candidate 2 [2018].
    - **Group B2L2[2018]:** a sub-group of 50 infants will be randomly selected to receive a second 10^5 $CCID_{50}$ dose of candidate 2 [2018], 28 days later.

Following completion of post-dose 1 safety assessment from the first 50 subjects from each group B1L1[2018] and B2L1[2018] and after the DSMB recommends to proceed, enrolled infants will be randomized to groups B1H1[2018], B1H2[2018], B2H1[2018] and B2H2[2018]. Dose escalation will be based on general safety data (solicited and unsolicited AEs and clinically significant abnormal laboratory values) through 14 days post-dose 1 in groups B1L1[2018] and B2L1[2018].

- **Group B1H1[2018]:** 162 infants enrolled at 6 weeks of age (-7 to +14 days) vaccinated with 3 doses of bOPV at 6, 10 and 14 weeks of age and 1 dose of IPV at 14 weeks of age, followed at 18–22 weeks of age with one 10^6 $CCID_{50}$ dose of candidate 1 [2018].
    - **Group B1H2[2018]:** a sub-group of 50 infants will receive a second 10^6 $CCID_{50}$ dose of candidate 1 [2018], 28 days later.
- **Group B2H1[2018]:** 162 infants enrolled at 6 weeks of age (-7 to +14 days) vaccinated with 3 doses of bOPV at 6, 10 and 14 weeks of age and 1 dose of IPV at 14 weeks of age, followed at 18–22 weeks of age with one 10^6 $CCID_{50}$ dose of candidate 2 [2018].
    - **Group B2H2[2018]:** a sub-group of 50 infants will receive a second 10^6 $CCID_{50}$ dose of candidate 2 [2018], 28 days later.

In view of the delay between building a cohort of infants at 6 weeks of age, and administration of their first dose of nOPV2 at 18 weeks of age, enrollment of the infant cohort may begin before the 1 to 5 year-old groups. Within both stages, the randomization and allocation of 18–22 week-old infants to the different groups will be performed after the DSMB recommendation to proceed based on DSMB review of 14 days follow-up for general safety data (solicited and unsolicited AEs and clinically significant abnormal laboratory values) of the respective 1 to 5 year-old children cohort. Subjects will be randomized to candidate, within age group and dose level.

In infants who receive nOPV2 at 18–22 weeks, no other vaccines can be administered 3 weeks before and 72 days after nOPV2 with the exception of influenza vaccine according to the National Immunization Program.

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

Prior to any nOPV2 administration the DSMB will establish in the DSMB charter, and continuously assess stopping rules for safety.

Study Population:

This trial will be performed with the participation of 150 healthy children aged 1–5 years (Cohorts A) who have been fully vaccinated with IPV and/or OPV in their first year of life according to MoH recommendations and of 972 healthy 6 week-old infants (Cohorts B) who will be pre-vaccinated with 3 doses of bOPV and 1 dose of IPV before being administered the study vaccines. Cohorts will be enrolled before DSMB approval, which is only required to begin administration of nOPV2 candidates.

Eligibility Criteria:

Inclusion Criteria:

1. For Cohort A children enrolled at 1 to 5 years of age who have previously been fully vaccinated

according to MoH recommendations with OPV and/or IPV.

2. For Cohort B infants enrolled at 6 weeks of age (-1, + 2 weeks) with birth weight >2,500 gm. To be eligible to continue into the experimental phase of the study infants must be vaccinated with 3 doses of bOPV and one dose of IPV prior to administration of the study vaccine at 18–22 weeks of age to take into account the visit windows for enrollment (age 6 weeks, -1 or + 2 weeks) and subsequent OPV vaccination windows (± 1 week). The last polio vaccine must have been administered at least 4 weeks prior to the first dose of study vaccine. Subjects in Cohort B who do not complete the three routine vaccination visits will be replaced in the study, and their parents/guardians will be encouraged to complete the primary vaccinations series.
3. Healthy children 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 to be in the study as established by the medical history and physical examination.
4. Written informed consent obtained from 1 or 2 parent(s) or legal guardian(s) as per country regulations.

Exclusion Criteria:

1. For all participants the presence of anyone under 10 years of age in the subject's household (living in the same house or apartment unit) who does not have complete "age appropriate" vaccination status with respect to poliovirus vaccines at the time of study vaccine administration. For household members younger than 18 months of age appropriate vaccination is at least three (3) doses of IPV. For household members between 18 months and 10 years "age appropriate" vaccination is at least three (03) doses of IPV or tOPV plus one (1) booster dose of any antipolio vaccine.
2. For all participants having a member of the subject's household (living in the same house or apartment unit) who is under 6 months of age at the moment of study vaccine administration.
3. For all participants having a member of the subject's household (living in the same house or apartment unit) who has received OPV in the previous 3 months before study vaccine adminstration.
4. For Cohort A: receipt of polio vaccines within the 3 months prior to the administration of the study vaccine (number of previous polio vaccine doses to be documented). Any other vaccine (other than influenza vaccine) 4 weeks before study entry.
5. For Cohort A: any participating children attending day care or pre-school during their participation in the study until one month after their last nOPV2 adminstration.
6. For Cohort B: any receipt of polio vaccines prior to administration of the study vaccine other than 3 doses of bOPV and 1 dose of IPV.
7. Any confirmed or suspected immunosuppressive or known immunodeficient condition including human immunodeficiency virus (HIV) infection in the potential participant or any member of the subject's household.
8. Family history of congenital or hereditary immunodeficiency.
9. Major congenital defects or serious uncontrolled chronic illness (neurologic, pulmonary, gastrointestinal, hepatic, renal, or endocrine).
10. Known allergy to any component of the study vaccines or to any antibiotics, that share molecular composition with the nOPV2 vaccines.
11. Uncontrolled coagulopathy or blood disorder contraindicating intramuscular vaccinations.
12. Administration of immunoglobulins and/or any blood products since birth or planned

administration during the study period.

13. Acute severe febrile illness at 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.).
14. 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.

Test Product, Dose, Mode of Administration:

Two nOPV2 vaccine candidates have been developed as attenuated serotype 2 polioviruses derived from a modified Sabin 2 infectious cDNA clone to improve phenotypic stability and make the strains less prone to reversion to virulence. The nOPV2 candidates 1 and 2 are propagated in Vero cells. One lot of nOPV2 candidate 1 prepared in 2018 and two lots of nOPV2 candidate 2 prepared in 2016 and 2018, respectively, will be used.

Each dose of nOPV2 candidate 1 (S2/cre5/S15domV/rec1/hifi3) [lot 2018] and nOPV2 candidate 2 (S2/S15domV/CpG40) [lots 2016 and 2018] contains approximately 10^5 or 10^6 50% cell culture infective dose units ($CCID_{50}$).

The vaccines will be administered orally.

- For all lots (2016 and 2018) one 10^5 $CCID_{50}$ dose of vaccine (0.1 ml) is contained in two drops, which are delivered using the dropper supplied with the vaccine.
- For the 2016 lot one 10^6 $CCID_{50}$ dose of vaccine (0.3 ml) is contained in six drops, which are delivered using the dropper supplied with the vaccine.
- For both 2018 lots one 10^6 $CCID_{50}$ dose of vaccine is contained in 1.0 ml (20 drops) which may be delivered from a syringe, or using a syringe to measure the dose into a spoon.

Study Duration:

Study duration will be approximately 7 months for 1–5 year-old participants, 9 months for infants who receive one dose and 10 months for infants who receive two doses, including a 6-month follow-up period to gather additional data on the novel vaccines after last vaccine administration for all participants.

Criteria for Evaluation:

Primary

The following endpoints will be evaluated by group and overall:

- Safety: incidence of Serious Adverse Reactions (SAR), severe AR and IMR, i.e. SAEs, severe AEs (grade 3), or IMEs considered consistent with a causal association with study vaccines as of the informed consent signature date and throughout the study period in all groups.
- Immunogenicity: seroprotection rate of type 2 polio neutralizing antibodies at Day 28 following a single 10^5 or 10^6 $CCID_{50}$ dose of nOPV2 candidates (2018 lots) in infant groups. Seroprotection rate is defined as the percentage of subjects with type 2-specific antibody titers $\geq$ 1:8 per group.

Secondary

The following endpoints will be evaluated by time-point, group and overall:

Safety:

- Incidence of any SAEs, of any AEs grade 3, and of any IMEs as of the informed consent signature date and throughout the study period in all groups.
  (The following will be considered IMEs: medically significant events that do not meet any of

the SAE criteria, but may require medical or surgical consultation or intervention to prevent one of the other serious outcomes listed in the SAE definition).

- Incidence of any mild and moderate solicited AEs for 7 days after the first dose in all groups and for 7 days after the second dose in all groups receiving two doses.
- Incidence of any mild and moderate unsolicited AEs throughout the study period by causal association with study vaccines.
- Incidence and description of deviations from normal clinical laboratory assessments at Day 0 and 28 days after first dose of nOPV2 in all groups, Day 7 after the first dose of nOPV2 candidates in one dose groups, and at 28 days after the second dose in all groups receiving two doses.

Immunogenicity:

- Median and geometric mean antibody titers of type 2 polio neutralizing antibodies at Day 0 and Day 28 after the first dose of nOPV2 in all groups, and at Day 56, 28 days after the second dose of nOPV2 in in all groups receiving two doses.
- Seroconversion rate at Day 28, 28 days after the first dose of nOPV2 in all groups, and at Day 56, 28 days after the second dose of nOPV2 in in all groups receiving two doses. Seroconversion is defined as a change from seronegative to seropositive, or in seropositive subjects as an antibody titer increase of ≥ 4 fold over Day 0 titer corrected for maternal antibody titers where applicable/age-appropriate.
- Seroprotection rate of type 2 polio neutralizing antibodies at Day 0 in all groups, and at Day 28, 28 days after the first dose of nOPV2 in all 1 to 5 year-old groups and in groups receiving candidate 2 (2016), and at Day 56, 28 days after the second dose of nOPV2 in all groups receiving two doses.

Shedding of poliovirus:

- Descriptive analysis of viral shedding as determined using RT-PCR (viral identity) and 50% cell culture infective dose ($CCID_{50}$; titer) after viral extraction from a subset of stool samples taken at fixed time points following the first dose from all 1 to 5 year-old groups and all infant groups administered the 10^6 $CCID_{50}$ dose.
- Potential for neurovirulence (as measured in an animal model) of shed virus extracted from a subset of stool samples following the first dose from both 1 to 5 year-old groups and both infant groups administered the 10^6 $CCID_{50}$ dose of each of the 2018 lots of nOPV2 candidates 1 and 2, respectively.

<u>Exploratory</u>

- Median and geometric mean antibody titers of type 2 polio neutralizing antibodies in infants at 6 weeks of age (Day -84) before receiving their first bOPV vaccination to provide a measure of maternal antibodies.
- Descriptive and exploratory analysis of 1 to 5 year-olds and 18–22 week-old infants developing a polio type 2 seroconversion within 1 week of nOPV2 exposure, i.e. 7 days after their first dose of nOPV2.
- Descriptive analysis of viral shedding following a second dose in 1 to 5 year-olds, and infant groups administered two 10^6 $CCID_{50}$ doses of each nOPV2 candidate.
- Descriptive analysis of viral shedding in all infant groups administered one 10^5 $CCID_{50}$ dose of each nOPV2 candidate.
- Descriptive analysis of viral shedding in all infant groups administered two 10^5 $CCID_{50}$ doses of each nOPV2 candidate.

- Exploratory endpoints may also include assessment of the genetic stability of shed virus at one or more time points following two doses 10^6 $CCID_{50}$ of each nOPV2 candidate, following one dose of 2016 lot candidate 2, or one or two 10^5 $CCID_{50}$ doses of all nOPV2 candidates.
- Exploratory endpoints may also include assessment of the potential for neurovirulence of shed virus at one or more time points following two doses 10^6 $CCID_{50}$ of nOPV2 candidates, following one dose of 2016 lot candidate 2 (2016) or one or two10^5 $CCID_{50}$ doses of nOPV2 candidates.
- Assessment of antibody levels and proportions displaying protective levels against HBV antigen (≥ 10 mIU/mL) and PRP antigen (≥ 0.15 µg/mL) in all infant groups 4 weeks after the last dose of DTPw-HBV-Hib (coincides with Day 0 serum sample for polio antibodies).

Statistical Methods:

Sample size

As in the historical control comparator study M2, this study has safety and Day 28 post-initial vaccination seroprotection rate as primary endpoints. Each age group will be monitored for safety; the primary immunogenicity endpoint, however will be limited to the infant groups administered 2018 lots of vaccine candidates, to which both 1- and 2-dose groups will contribute. The primary comparisons will entail comparisons of post-first-dose data from the four infant groups administered 10^5 and 10^6 dose levels of candidate 1 [2018] and candidate 2 [2018], to the corresponding infant cohort from study M2. Data obtained for candidate 2 2016 material will be summarized, and not involved in direct comparisons with the historical control.

The sample size for the older children (Groups A1H2[2018], A2H2[2016], and A2H2[2018]) is chosen to provide adequate safety data prior to age de-escalation. Forty-five subjects are required to have 90% probability of observing at least one occurrence of an adverse event, when the true adverse event rate is 5%. Allowing for a 10% non-evaluability/dropout rate requires 50 subjects for the safety evaluations. Immunogenicity will be assessed as a secondary endpoint in the older cohort.

For the primary immunogenicity endpoint, it is assumed that the seroprotection rate following administration of a single dose of Sabin mOPV2 and 2018 lots of candidate nOPV2 vaccines in this population will be ≥ 95%. In the historical control comparator study, M2, a total of 91 per-protocol subjects (a 20% dropout rate from the enrolled population) were available for the immunogenicity endpoint in the younger cohort. For the current study, 129 evaluable (per-protocol) subjects per vaccine candidate and per dose level are required such that 90% power is available to declare non-inferiority to the Sabin 2 control, using the lower confidence bound of the Miettinen-Nurminen score confidence interval for inference (one-sided alpha = 0.025 for each candidate vaccine and dose level, separately, non-inferiority margin 10%). Therefore, assuming a 20% dropout rate the required enrollment is 162 subjects. Since the safety endpoint requires 50 subjects, and all subjects contribute to the immunogenicity endpoint, 50 randomly-chosen subjects will be assigned to receive two doses, and the remaining 112 subjects will receive only a single dose of each candidate vaccine.

Sample sizes for the 2016 candidate 2 groups in Stage I were selected based on the same criteria, prior to availability of the 2018 material.

Immunogenicity

Neutralizing Type 2 Poliovirus Antibody Titers

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

- Seroprotection rates with 95% confidence intervals (CIs) will be computed.
- Seroconversion rates with 95% confidence intervals (CIs) will be computed at post-vaccination time points. Seroconversion will be computed from Day 0 for all subjects, and additionally from Day -84 for infant subjects.
- Median of log2 and geometric mean antibody titers (GMT) will be computed along with 95% CIs.
- Plots of the reverse cumulative distribution of antibody titers will be generated for each group.

The primary immunogenicity endpoint, seroprotection 28 days after a single dose in each 2018 candidate nOPV2 infant group, will be compared with the corresponding group receiving Sabin mOPV2 from the historical control study (M2) by computing the two-sided 95% Miettinen-Nurminen score confidence interval for the difference in seroprotection rates (nOPV2 candidate minus control), and comparing the lower bound of this interval with the non-inferiority margin, -10%, in order to establish non-inferiority. In order to control one-sided type I error at level $\alpha = 0.05$ overall, each candidate will be compared with the control at one-sided level $\alpha^* = \alpha / 2 = 0.025$. In addition, the high dose level of each 2018 candidate will be compared with the control, and only if the non-inferiority endpoint is met, the low dose level will also be tested with the same test-level type I error rate. This fixed-sequence enables control of multiplicity within each candidate-level type I error rate for the multiple dose level comparisons.

Shedding of poliovirus

Viral Shedding

Summaries of the detection of candidate vaccine via RT-PCR and viral titer ($CCID_{50}$/g of stool) among those positive for virus will be computed by group and time point, for a subset of stool samples. A viral shedding index (SIE) will be calculated as the average of log 10-transformed values of viral concentration in stool samples as determined using RT-PCR (viral identity) and $CCID_{50}$ (titer) from selected stool samples taken following each vaccine dose, and this index will be summarized by group.

Descriptive analysis and plots of the reverse cumulative distribution of the viral shedding index will be generated.

Neurovirulence

Neurovirulence data obtained from the transgenic mouse assay applied to virus isolated from select stool samples from groups given 2018 candidate vaccine lots, i.e. Groups A1H2[2018], A2H2[2018], B1H1[2018], B1H2[2018], B2H1[2018] and B2H2[2018] in this study will be combined with data from the historical control study M2, in order to directly compare the neurovirulence of samples from candidate vaccines with the control vaccine. The proportion of mice paralyzed and the odds ratio of paralysis from the single-dose assay will be the primary means of comparison of NV of shed virus between each candidate and the Sabin mOPV2 control samples. The statistical hypothesis that will be tested will be that of superiority (lower neurovirulence) of at least one 2018 vaccine candidate to Sabin 2, with respect to the frequency of mouse paralysis observed in the assay.

Safety

Safety parameters will be tabulated and analyzed descriptively.

Adverse Events

Analyses described below will be performed for solicited and unsolicited AEs by severity as well as for SAEs and IMEs.

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

(MedDRA).

All AEs will be summarized by type (solicited and unsolicited), group, severity, occurrence in causal association with vaccination, and overall.

Separate tables and listings will be created for subjects who died, discontinued the study vaccine due to an AE, or experienced a severe or serious AE or IME. Summaries, listings, and narratives may be provided, as appropriate.

Clinical Laboratory Tests

Each continuous biochemistry and hematology laboratory test will be evaluated by means of descriptive statistics (i.e., number of subjects, mean, SD, median, minimum, and maximum) on the actual values, at each assessment time point and by group. Changes from baseline outside the normal range will also be summarized by assessment time point and by group.

Relative changes in clinical laboratory test values compared with values at baseline will be evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (toxicity grades) or in accordance with the normal ranges of the clinical laboratory (below, within, or above normal range) for parameters for which no toxicity grades are defined. Investigators will assess laboratory deviations for clinical relevance, and if determined to be clinically relevant, will note any apparent causality.

A listing of subjects with any clinical laboratory test result outside the reference ranges will be provided.

Data Safety Monitoring Board:

A Data Safety Monitoring Board (DSMB) will monitor the benefit-risk and data integrity of this trial. The composition and functioning of the DSMB is documented in the DSMB charter.

TIME AND EVENTS SCHEDULE – 1 TO 5 YEAR-OLD GROUPS.

Assessments	**Groups A1H2 and A2H2**									**Follow-up phone contact**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Time of Visit (days) **Visit Window**	**D 0**	**D 7** **(± 2 days)**	**D 14** **(± 3 days)**	**D 21** **(± 2 days)**	**D 28** **(+ 2 days)**	**D 35 [a]** **(± 2 days)**	**D 42 [a]** **(± 3 days)**	**D 49 [a]** **(± 2 days)**	**D 56 [a b]** **(+ 2 days)**	**D 208** **(± 14 days)**
Informed consent[c]	X									
In-/exclusion criteria	X									
Medical history/concomitant diseases	X									
Medication/Vaccination history[d]	X									
Demographic data	X									
Physical examination	X	X			X				X	
Clinical laboratory tests[e]	X[f]	X			X[f]				X	
Administration of nOPV2[g,h]	X				X					
Serum sample for polio antibodies	X[f]	X			X[f]				X	
Stool sample for viral culture/quantitative PCR, stool sample for potential poliovirus sequencing, stool sample for potential neurovirulence[i]	X[i]----------X		X	X	X----------X		X	X	X	
Solicited systemic AEs (Diary)[j]	X----------X				X----------X					
Remote contact for safety follow-up[k]	X----------X			X	X----------X			X		X
Concomitant therapies	X	X	X	X	X	X	X	X	X	X
Adverse events[l]	X	X	X	X	X	X	X	X	X	X[m]

a. Days 35, 42, 49 and 56 are defined in relation to Day 28 (7, 14, 21 and 28 days after the second dose, respectively).
b. In case of early termination the subjects will be asked to return to the clinical site within 14 days after discontinuation for assessments as outlined on Day 56.
c. No study-related assessment is to be carried out before signing the informed consent form, which can be obtained up to 4 weeks before Visit 1.
d. Including polio vaccination history.
e. For a list of assessments, please see Appendix 1: Overview of Laboratory Assessments. If an anomaly is found at 7 days post-dose 1, further investigations will be done at the investigator's medical judgement.
f. Prior to vaccination.
g. Group A1H2[2018] receives 10^6 $CCID_{50}$ candidate 1 (2018), Group A2H2[2016] receives 10^6 $CCID_{50}$ candidate 2 (2016), Group A2H2[2018] receives 10^6 $CCID_{50}$ candidate 2 (2018).

h. The subjects will be kept under medical supervision for at least 30 min after vaccination.
i. Parents/guardians will be asked to collect if available the first stool every day in the provided receptacle and bring the samples with them at the next scheduled visit. No stool will be collected on Day 0, but after first vaccine dose, daily collection on Days 1 to 10 plus collection on Days 14, 21 and 28 (before second vaccination), and on Days 29 to 38 plus collection on Days 42, 49 and 56. It will be acceptable to collect stool samples at day 14 (-1 or +2 days) and at days, 21, 28, 42, 49 and 56 using the same time windows for the corresponding study visit.
j. Solicited AEs will be collected for Days 0-7 and Days 28-35 using electronic diaries.
k. Daily remote contact (phone call or text message) from Day 0 to Day 14 and also on Day 21 after the first vaccine dose. Thereafter, daily remote contact from Day 28 to Day 42 and also on Day 49.
l. Serious Adverse Events and intake of concomitant medication(s) will be monitored continuously from informed consent signature date until the last study-related activity. Parents/guardians can record unsolicited AEs on their child‘s diary card.
m. Parents will be asked about any Serious Adverse Events or Important Medical Events since the last visit.

TIME AND EVENTS SCHEDULE – ONE DOSE INFANT GROUPS

Assessments	**Groups B1L1[2018], B2L1[2016], B2L1[2018], B1H1[2018], B2H1[2016] and B2H1[2018]**								**Follow-up phone contact**
	bOPV-IPV pre-vaccination phase			**Study vaccination phase**					
Visit	**-3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**
Time of Visit (days) **Visit Window**	**D –84** **(+14,-7 days)**	**D –56** **(±7 days)**	**D –28** **(±7 days)**	**D 0**	**D 7** **(± 2 days)**	**D 14** **(± 3 days)**	**D 21** **(± 2 days)**	**D 28[a]** **(+ 2 days)**	**D 180** **(± 14 days)**
Informed consent[b]	X								
In-/exclusion criteria	X			X					
Medical history/concomitant diseases	X			X					
Medication/Vaccination history[c]	X			X					
Demographic data	X			X					
Physical examination	X			X	X			X	
Clinical laboratory tests[d]				X[e]	X			X	
Randomization for one dose only				X					
Administration of bOPV[f]	X	X	X						
Administration of IPV[f]			X						
Administration of nOPV2[f]				X[g]					
Serum sample for polio antibodies	X[e]			X[e]	X			X	
Stool sample for viral culture/quantitative PCR, stool sample for potential poliovirus sequencing, stool sample for potential neurovirulence				X----------X[h]		X	X	X	
Solicited systemic AEs (Diary)[i]				X----------X					
Remote contact for safety follow-up[j]				X----------X					X
Concomitant therapies[k]				X	X	X	X	X	X
Adverse events[k]				X	X	X	X	X	X[l]

a. In case of early termination the subjects will be asked to return to the clinical site within 14 days after discontinuation for assessments as outlined on Day 28.
b. No study-related assessment is to be carried out before signing the informed consent form.

c. Including polio vaccination history.
d. For a list of assessments, please see Appendix 1: Overview of Laboratory Assessments.
e. Prior to vaccination. Samples at V1 (day 0) will also be used to assess anti-HBs and anti-Hib antibodies.
f. The subjects will be kept under medical supervision for at least 30 min after vaccination. The subjects will concomitantly receive DTPw-HB-Hib vaccine at V-3, V-2 and V-1, pneumococcal conjugate vaccine at V-3 and V-1 and rotavirus vaccine at V-3 and V-1.
g. Group B1L1[2018] receive 10^5 $CCID_{50}$ candidate 1 (2018); Group B2L1[2016] receive 10^5 $CCID_{50}$ candidate 2 (2016); Group B2L1[2018] receive 10^5 $CCID_{50}$ candidate 2 (2018); Group B1H1[2018] receive 10^6 $CCID_{50}$ candidate 1 (2018); Group B2H1[2016] receive 10^6 $CCID_{50}$ candidate 2 (2016); Group B2H1[2018] receive 10^6 $CCID_{50}$ candidate 2 (2018).
h. Parents/guardians will be asked to collect if available the first stool every day in the provided receptacle and bring the samples with them at the next scheduled visit. After each vaccine dose, daily collection on Days 0 (before vaccination) to 10 plus collection on Days 14, 21 and 28. It will be acceptable to collect stool samples at day 14 (-1 or +2 days) and at days, 21, 28, 42, 49 and 56 using the same time windows for the corresponding study visit.
i. Solicited AEs will be collected for Days 0-7 using electronic diaries.
j. Daily remote contact (phone call or text message) from Day 0 to Day 14 and also on Day 21 after the first vaccine dose.
k. Serious Adverse Events and intake of concomitant medication(s) will be monitored continuously from informed consent signature date until the last study-related activity. Parents/guardians can record unsolicited AEs on their child‘s diary card.
l. Parents will be asked about any Serious Adverse Events or Important Medical Events since the last visit.

TIME AND EVENTS SCHEDULE – TWO DOSE INFANT GROUPS

Assessments	Groups B1L2[2018], B2L2[2016], B2L2[2018], B1H2[2018], B2H2[2016], and B2H2[2018]												Follow-up phone contact
	bOPV-IPV vaccination phase			Study vaccination phase									
Visit	-3	-2	-1	1	2	3	4	5	6	7	8	9	10
Time of Visit (days) Visit Window	D –84 (-7,14 days)	D –56 (±7 days)	D –28 (±7 days)	D 0	D 7 (± 2 days)	D 14 (± 3 days)	D 21 (± 2 days)	D 28 (+ 2 days)	D 35 [a] (± 2 days)	D 42 [a] (± 3 days)	D 49 [a] (± 2 days)	D 56 [a,b] (+ 2 days)	D 208 (± 14 days)
Informed consent[c]	X												
In-/exclusion criteria	X			X									
Medical history/concomitant diseases	X			X									
Medication/vaccination history[d]	X			X									
Demographic data	X			X									
Physical examination	X			X				X				X	
Clinical laboratory tests[e]				X[f]				X[f]				X	
Randomization for two doses				X									
Administration of bOPV[g]	X	X	X										
Administration of IPV[g]			X										
Administration of nOPV2[g,h]				X				X					
Serum sample for polio antibodies	X[f]			X[f]				X[f]				X	
Stool sample for viral culture/quantitative PCR, stool sample for potential poliovirus sequencing, stool sample for potential neurovirulence				X----------X[i]		X	X	X----------X[i]		X	X	X	
Solicited systemic AEs (diary)[j]				X----------X				X----------X					
Remote contact for safety follow-up[k]				X----------X				X----------X					X
Concomitant therapies[l]				X	X	X	X	X	X	X	X	X	X
Adverse events[l]				X	X	X	X	X	X	X	X	X	X[m]

a. Days 35, 42, 49 and 56 are defined in relation to Day 28 (7, 14, 21 and 28 days after the second dose, respectively).
b. In case of early termination the subjects will be asked to return to the clinical site within 14 days after discontinuation for assessments as outlined on Day 56.
c. No study-related assessment is to be carried out before signing the informed consent form.
d. Including polio vaccination history.
e. For a list of assessments, please see Appendix 1: Overview of Laboratory Assessments.
f. Prior to vaccination. Samples at V1 (day 0) will also be used to assess anti-HBs and anti-Hib antibodies.
g. The subjects will be kept under medical supervision for at least 30 min after vaccination. The subjects will concomitantly receive DTPw-HB-Hib vaccine at V-3, V-2 and V-1, pneumococcal conjugate vaccine at V-3 and V-1 and rotavirus vaccine at V-3 and V-1.
h. Group B1L2[2018] receive 10^5 $CCID_{50}$ candidate 1 (2018); Group B2L2[2016] receive 10^5 $CCID_{50}$ candidate 2 (2016); Group B2L2[2018] receive 10^5 $CCID_{50}$ candidate 2 (2018); Group B1H2[2018] receive 10^6 $CCID_{50}$ candidate 1 (2018); Group B2H2H[2016] receive 10^6 $CCID_{50}$ candidate 2; Group B2H2H[2018] receive 10^6 $CCID_{50}$ candidate 2 (2018).
i. Parents/guardians will be asked to collect if available the first stool every day in the provided receptacle and bring the samples with them at the next scheduled visit. After each vaccine dose, daily collection on Days 0 (before vaccination) to 10 plus collection on Days 14, 21 and 28 (before second vaccination), and Days 29 to 38 plus collection on Days 42, 49 and 56. It will be acceptable to collect stool samples at day 14 (-1 or +2 days) and at days 21, 28, 42, 49 and 56 using the same time windows for the corresponding study visit.
j. Solicited AEs will be collected for Days 0-7 and Days 28-35 using electronic diaries.
k. Daily remote contact (phone call or text message) from Day 0 to Day 14 and also on Day 21 after the first vaccine dose. Thereafter, daily remote contact from Day 28 to Day 42 and also on Day 49.
l. Serious Adverse Events and intake of concomitant medication(s) will be monitored continuously from informed consent signature date until the last study-related activity. Parents/guardians can record unsolicited AEs on their child‘s diary card.
m. Parents will be asked about any Serious Adverse Events or Important Medical Events since the last visit.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

List of Abbreviations

AE	Adverse event
AEFI	Adverse event following immunization
ALT	Alanine aminotransferase
AR	Adverse reaction (AE related to vaccination)
AST	Aspartate aminotransferase
$CCID_{50}$	50% cell culture infective dose
CI	Confidence interval
CK	Creatine kinase
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IME	Important Medical Event
IMP	Investigational medicinal product
IMR	Important Medical Reaction (IME related to vaccination)
IPV	Inactivated poliovirus vaccine
IRB	Institutional Review Board
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
mOPV2	Monovalent oral poliovirus vaccine type 2
nOPV2	Novel oral poliovirus vaccine type 2
OPV	Oral poliovirus vaccine
PD50	50% paralytic dose
PP	Per-protocol
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction (SAE related to vaccination)
SD	Standard deviation
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
bOPV	Bivalent oral poliovirus vaccine
mOPV	Monovalent oral poliovirus vaccine
TgPVR	Transgenic mice expressing the cell receptor for poliovirus
TMF	Trial Master File
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
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MONITORING	**VAXTRIALS** Ciudad del Saber, Building 230, 3rd Floor Panamá City, Panamá
Project Manager:	Jose Jimeno MD
MANUFACTURING	**Bio Farma** JL. Pasteur No.28, Pasteur, Sukajadi, Kota Bandung, Jawa Barat 40161, Indonesia
VIRAL AND 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: William Weldon, Ph.D. Team Lead, Population Immunity Laboratory Ph – 404-639-5485
	Laboratorio San Miguel Arcangel and Laboratorio Delgado Especializado, Panama
PHARMACOVIGILANCE	**Assign Data Management and Biostatistics GmbH,** Stadlweg 23, 6020 Innsbruck

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 are: to detect and interrupt all poliovirus transmission, to strengthen immunization systems and withdraw the historic oral polio vaccine (OPV), to contain poliovirus and certify interruption of transmission and legacy planning.

The global effort to eradicate polio has made significant progress with only 3 countries remaining where wild-type poliovirus transmission has never been interrupted — Afghanistan, Pakistan, and Nigeria.[2] In 2017, 118 cases of paralytic poliomyelitis were reported globally, 22 of which were due to wild poliovirus type 1 and 96 were associated with circulating vaccine-derived polioviruses (cVDPVs).[3] Of the cases caused by wild poliovirus type 1 14 (64%) occurred in Afghanistan, and 8 (36%) cases were reported in Pakistan. In Nigeria, four cases of wild-type poliovirus were reported in 2016, but no further cases have been reported up to September 2018.[3] Most cVDPV cases (74, 77%) were associated with the Syrian Arab Republic suffering major social unrest, the remaining 22 cases being in the Democratic Republic of the Congo.

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 two 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.[4] Moreover, in populations without sufficient immunization coverage, a history of tOPV use can result in the emergence of 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. Most cVDPVs are type 2 viruses. Several cVDPV2 outbreaks have been documented since 2000 and most were controlled by means of focused immunization campaigns using tOPV, and more recently, also inactivated polio vaccine (IPV). While OPV is more effective than IPV in halting transmission, as long as tOPV was in use, the risk for cVDPV remained and polio could not be entirely eradicated from susceptible populations.

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.

Prevaccination with IPV also improves the response to any future use of a monovalent type 2 polio vaccine in the case of an outbreak, and reduces transmission of a reintroduced type 2 virus, as well as boosting immunity to the remaining wild poliovirus serotypes 1 and 3.[6]

An important prerequisite for the global switch from tOPV to bOPV and IPV was the interruption of ongoing cVDPV2 outbreaks, and following confirmation of progress in this regard SAGE recommended that all countries should withdraw OPV2 in April 2016, and subsequent monitoring has confirmed the switch was efficient and effective.[7]

For the foreseeable future, stocks of monovalent OPV vaccines will need to be maintained for use in case of outbreaks of wild-type or cVDPV polioviruses, but the risk will remain that current OPV will themselves be the source of cVDPV. Therefore, as a further insurance for the elimination of cVDPV two novel monovalent OPV type 2 vaccine candidates (nOPV2) have been 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 phenotypic stability and make the strains less prone to reversion to virulence. Availability of such stockpiles of such vaccines which are less likely to undergo reversion to wild-type will be the ultimate means of limiting any future outbreaks.

1.2 OVERALL RATIONALE FOR THE STUDY

Sabin type 2 poliovirus was withdrawn from routine use globally from April 2016 as per the SAGE recommendations. Following this cessation of OPV2, stockpiles of mOPV2 are to be maintained for potential use if necessary in response to a future outbreak, but there will still be a risk of cVDPV2 from Sabin 2 in settings of low population immunity. Two nOPV2 vaccine candidates have been developed as attenuated serotype 2 polioviruses derived from a modified Sabin 2 infectious cDNA clone. nOPV2 Candidate 1 (*S2/cre5/S15domV/rec1/hifi3*) and nOPV2 Candidate 2 (*S2/S15domV/CpG40*) were generated by modifying the Sabin-2 RNA sequence to improve phenotypic stability and make the strains less prone to reversion to virulence. The two nOPV2 candidate vaccine strains have been used as an investigational medicinal product (IMP) in a first-in-human (FIH) Phase 1 containment trial (M4a) in two groups of 15 healthy IPV-only vaccinated adults in Belgium, to evaluate the general safety and immunogenicity of both of the nOPV2 candidate vaccine strains (EudraCT number 2017-000908-21, ClinicalTrials.gov: NCT03430349). In general, the two vaccine candidates were well tolerated with no serious adverse events reported, and no severe illnesses thought to be due to the vaccine candidates. Most health events reported during the study were generally mild, and all resolved.

Two participants (one with each nOPV2 vaccine candidate) exhibited transient, asymptomatic, severe elevations of aspartate aminotransferase (AST) associated with mild or moderate elevation of alanine aminotransferase (ALT) and severe elevation of creatine kinase (CK), but with no elevation of either gamma-glutamyltransferase (GGT) or bilirubin and with complete resolution to normal values. Other AEs on the basis of AST elevations were asymptomatic and generally mild and self-resolving, and also associated with elevated CK levels but normal GGT and bilirubin levels. All AEs on the basis of ALT elevations were transient and asymptomatic, with only one moderate AE

and the balance mild. Half of the participants exhibited asymptomatic severe elevations of CK, most often at the day 7 assessment, with resolution of values elevated in the first couple of weeks post-vaccination to normal or close to normal. A feasible explanation for these transient enzyme elevations could be intermittent, intense exercise by the participants, who were confined in the contained unit for 28 days but with exercise facilities provided.

Both candidates were immunogenic and elicited the desired protective responses against poliovirus. Shedding of virus in stools was more limited for vaccine candidate 2 compared with candidate 1, with some volunteers having more prolonged shedding than others, but none of the volunteers had any illness associated with this shedding. Data was also collected on the potential neurovirulence of virus shed in stools, which to date has not detected any meaningful increase in neurovirulence of either nOPV2 candidate relative to the vaccine itself. Sequencing has confirmed that there were no reverting mutations in the main site of attenuation which are analogous to the domain V A481G reversion in Sabin OPV2.

Further investigation is underway in adults (study M4) from whom additional safety and immunogenicity data will be obtained. Although the long-term collection of safety data will still be ongoing at the time of enrolment for the present study in young children and infants, this study was only initiated when adequate safety follow-up of the M4 study in adults had been obtained according to the sponsor and DSMB. The present study is being performed to generate data in a similar fashion on the safety, immunogenicity (humoral and intestinal) and genetic stability endpoints of these novel nOPV2 candidates in children aged 1 to 5 years and in infants approximately 18 weeks of age vaccinated with bOPV-IPV. The overall development of nOPV2 was designed before the global cessation of OPV2 use which allowed studies to be started with mOPV2 before April 2016 with similar study design to this one (specifically M2) to provide historical control data against which to compare the novel nOPV2 candidates. This will allow comparison of data from this study with data that is already being generated on the immunogenicity, safety, and genetic stability of the mOPV2 vaccine in M2 in a comparable 18–22 week-old infant population (prevaccinated with bOPV and IPV). These comparisons will support the selection of which candidate to take further in development.

The M4 study is being performed using manufacturing lots of nOPV2 candidates 1 and 2 from 2016. New lots of both candidates 1 and 2 have been manufactured in 2018, which are expected to be released in Q1 2019. These 2018 lots have been prepared from bulk lots manufactured from working virus seeds intended for future vaccine production and so more closely represent what is anticipated to be the final product versus the 2016 lots.

There is evolving concern from the GPEI about type 2 circulating vaccine-derived poliovirus (cVDPV2) outbreaks in specific geographies with poor immunization coverage. Importantly, some of the more recent cVDPV2 outbreaks have been attributed to the use of the Sabin mOPV2 stockpile, leading to a need to understand as soon as possible the potential for an nOPV2 candidate to replace Sabin mOPV2. For this reason, a cohort of infants has been prioritized in which the 2016 lot of candidate 2 has been evaluated in in Stage I of this study, together with a cohort of polio-immunized 1 to 5 year-old children as a safety lead-in. Inclusion of these cohorts allows safety, immunogenicity, and shedding results to be available several months earlier than is

possible for the 2018 lots. Safety data from subjects who received the 2016 candidate 2 lot in Stage I have been assessed by the DSMB members, together with the risk-benefit profile of candidate 2 (2016) and they unanimously supported the progress in each step of the interventions. Stage II will only begin when they consider the vaccine is safe in bOPV/IPV-primed children and support the further progress of the M5 study. These data from Stage I may also be used to advance programmatic considerations of nOPV2 development, in light of ongoing GPEI efforts, while allowing comparisons with the control to be conducted with the most relevant lots (2018).

A subsequent evaluation of the safety, immunogenicity, and shedding data will then be obtained in Stage II, which will be performed using the 2018 lots of vaccine candidates 1 and 2 when they are available.

RISK BENEFIT ANALYSIS

1.2.1 *Potential Risks*

OPV is safe and effective and has been used for decades in billions of doses, and Sabin mOPV2 is World Health Organization (WHO) prequalified and has recently been used in several clinical trials in Latin America. The nOPV2 candidates being used in the proposed study have been designed to be less likely to undergo reversion to a wild-type neurovirulence phenotype, and this has been confirmed in preclinical assessments, but it remains to be seen whether the attenuations affect the immunogenicity of the vaccine. There is no scientifically-plausible reason for the candidate vaccines to have caused the transient elevation of levels of enzymes (ALT, AST and CK) observed in the adult study (M4a), which are more likely to be linked to excessive exercise, but this will be monitored closely in the subsequent adult study (M4).

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). Preclinical data and clinical data from the Phase I adult study (M4a) support the theoretical improvements in genetic and phenotypic stability of both candidates, with no meaningful increase in neurovirulence observed. Preclinical and genetic stability analyses do not suggest any anticipated increase in the likelihood of VAPP with the vaccine candidates and lots used in this study.

Incremental exposure risk because of this study is negligible: in most countries, including those using only IPV, vaccine polio virus is routinely detected in sewage. IPV has recently been used as routine immunization in Panama, with bOPV (types 1 and 3) for booster in ongoing routine immunization.

Safety data from subjects who received the 2016 candidate 2 lot in Stage I have been assessed by the DSMB members, together with the risk-benefit profile of candidate 2 (2016) and they unanimously supported the progress in each step of the interventions.

1.2.2 *Potential Benefits*

Children who were previously vaccinated with polio vaccines and receive a new dose of nOPV2 in this study may benefit from boosting of immunity for poliovirus type 2.

This study is of major importance for global public health and will establish immunological responses to novel OPV2s and, if the data are supportive, assist in the selection of which novel candidate is taken for further development into a new polio vaccine in the future.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVES

The co-primary objectives of the study are:

- To assess the safety (incidence of serious adverse reactions [SARs] and severe adverse reactions [AEs; grade 3 according to CTCAE 4.03], important medical reactions [IMR] and any clinically-relevant clinical laboratory deviations) in infants and young children after administration of one or two doses of each dose level of all nOPV2 vaccine candidates and to contrast this with a control sample of similarly aged children receiving one or two doses of Sabin mOPV2 in a prior study (M2) designed to serve as a historical control for the current study.
- To assess and compare the immunogenicity (seroprotection rate against poliovirus type 2) of a single dose (at both 10^5 and 10^6 $CCID_{50}$ dose levels) of each of the two nOPV2 vaccine candidates (2018 lots) in infants at approximately 18–22 weeks of age after having been previously vaccinated with 3 doses of bOPV and 1 dose of IPV, relative to a control sample of infants receiving the same vaccination schedule followed by a single dose of Sabin mOPV2 in a prior study (M2) designed to serve as a historical control for the current study.

2.2 SECONDARY OBJECTIVES

Secondary objectives are to assess:

- To assess the safety expressed as incidence, severity and causality of any serious adverse event (SAE), any solicited AE, any unsolicited AEs, any important medical events (IME) and laboratory deviations with the exception of SAE, severe AEs/IME considered consistent with causal association to study vaccine and clinically-relevant clinical laboratory deviations (primary objective) following one or two doses of the nOPV2 candidates at the 10^6 $CCID_{50}$ dose level in healthy children aged 1 to 5 years, and of one or two doses of nOPV2 candidates at both 10^5 and 10^6 $CCID_{50}$ dose levels in infants at approximately 18–22 weeks of age after having been previously vaccinated with 3 doses of bOPV and 1 dose of IPV and contrast this safety with participants who received the same vaccination schedule followed by one or two doses of Sabin mOPV2 in a prior study (M2) designed to serve as a control for the current study.
- To assess the immunogenicity (median and geometric mean neutralizing antibody titers, seroconversion rates, seroprotection rates against poliovirus type 2) of one or two 10^6 $CCID_{50}$ doses of each of the nOPV2 vaccine candidate lots in healthy children aged 1 to 5 years, and contrast this immunogenicity with a control sample of similarly aged children receiving one or two doses of Sabin mOPV2 in a prior study (M2) designed to serve as a historical control for the current study.
- To assess the immunogenicity (median and geometric mean neutralizing antibody titers and seroconversion rates against poliovirus type 2) of one or two doses, and the seroprotection rates after two doses of each of the nOPV2 candidate lots at

both 10^5 and 10^6 $CCID_{50}$ dose levels at approximately 18–22 weeks of age in infants previously vaccinated with 3 doses of bOPV and 1 dose of IPV, and contrast this immunogenicity with a control sample of participants receiving the same vaccination schedule followed by one or two doses of Sabin mOPV2 in a prior study (M2) designed to serve as a control for the current study.

- To assess the immunogenicity (median and geometric mean neutralizing antibody titers, seroconversion rates, seroprotection rates against poliovirus type 2) of one or two doses (at both 10^5 and 10^6 $CCID_{50}$ dose levels) of nOPV2 vaccine candidate 2 (2016 lot) in infants at approximately 18–22 weeks of age.
- To assess the extent of viral shedding in stool at fixed time points following administration of one dose of the nOPV2 candidates (2016 and 2018 lots) at the 10^6 $CCID_{50}$ dose level in healthy children aged 1 to 5 years, and in infants at approximately 18–22 weeks of age, and contrast this shedding with a control sample of participants receiving the same vaccination schedule followed by one dose of Sabin mOPV2 in a prior study (M2) designed to serve as a control for the current study.
- To assess the potential for neurovirulence of virus isolated from a subset of stool samples of children aged 1 to 5 years, and infants at approximately 18–22 weeks of age after having been previously vaccinated with 3 doses of bOPV and 1 dose of IPV, following one dose of the nOPV2 candidates (2018 lots) at the 10^6 $CCID_{50}$ dose level, as measured in an animal model, and contrast this with a control sample of participants receiving the same vaccination schedule followed by one dose of Sabin mOPV2 in a prior study (M2) designed to serve as a control for the current study.

2.3 EXPLORATORY OBJECTIVES

Exploratory objectives may include:

- Assessment of the baseline humoral immunity to poliovirus type 2 as neutralizing antibodies in infants at approximately 6 weeks of age before any vaccination with either bOPV or IPV.
- Assessment of the priming by bOPV+IPV of immune responses to a single dose of both nOPV2 candidates (all lots) at 10^5 and 10^6 $CCID_{50}$ dose levels in infants at approximately 18–22 weeks of age relative to a control sample of infants receiving the same vaccination schedule followed by one or two doses of Sabin mOPV2 in a prior study (M2) designed to serve as a control for the current study.
- Investigation of the extent of viral shedding following the administration of two 10^6 $CCID_{50}$ doses of nOPV2 candidates (all lots) in healthy children aged 1 to 5 years and of 10^5 $CCID_{50}$ doses of nOPV2 candidates (all lots) in infants at approximately 18–22 weeks of age.
- Assessment of the genetic sequence heterogeneity and stability of virus isolated from a subset of stool samples of participants following one or two doses of the nOPV2 candidates (2018 lots) at 10^6 $CCID_{50}$ dose level in 1 to 5 year-olds, and at 10^5 and 10^6 $CCID_{50}$ dose levels, in infants at approximately 18–22 weeks of age

after having been previously vaccinated with 3 doses of bOPV and 1 dose of IPV, and contrast this heterogeneity profile with a control sample of participants receiving the same vaccination schedule followed by one or two doses of Sabin mOPV2 in a prior study designed to serve as a control for the current study. A similar exploratory assessment of genetic stability of samples from 1 to 5 year-olds and infants in Stage I administered with nOPV2 candidate 2 [2016] may be performed.

- Assessment of the immune response to parallel routine vaccinations through assessment of antibodies to hepatitis B (HBV) and *Haemophilus influenzae* type b (Hib) vaccine components after a full infant primary series and contrast these values with those in participants in a prior study (M2) designed to serve as a control for the current study.

3. STUDY ENDPOINTS

3.1 PRIMARY ENDPOINTS

The following endpoints will be evaluated by group and overall:

- Safety: incidence of Serious Adverse Reactions (SAR), severe AR and IMR, i.e. SAEs, severe AEs (grade 3), or IMEs considered consistent with a causal association with study vaccines as of the informed consent signature date and throughout the study period in all groups.
- Immunogenicity: seroprotection rate of type 2 polio neutralizing antibodies at Day 28 following a single 10^5 or 10^6 $CCID_{50}$ dose of nOPV2 candidates in all groups. Seroprotection rate is defined as the percentage of subjects with type 2-specific antibody titers ≥ 1:8 per group.

3.2 SECONDARY ENDPOINTS

The following safety and immunogenicity endpoints will be evaluated by time-point, group and overall.

Safety:

- Incidence of any SAEs, of any AEs grade 3, and of any IMEs as of the informed consent signature date and throughout the study period in all groups.
  (The following will be considered IMEs: medically significant events that do not meet any of the SAE criteria [see Section 11.1.3], but may require medical or surgical consultation or intervention to prevent one of the other serious outcomes listed in the SAE definition).
- Incidence of any mild and moderate solicited AEs (fever, vomiting, abnormal crying, drowsiness, loss of appetite and irritability) for 7 days after the first dose in all groups and for 7 days after the second dose in all groups receiving two doses.
- Incidence of any mild and moderate unsolicited AEs throughout the study period by causal association with study vaccines.

- Incidence and description of deviations from normal clinical laboratory assessments at Day 0 and 28 days after first dose of nOPV2 in all groups, Day 7 after the first dose of nOPV2 candidates in all groups, and at 28 days after the second dose of nOPV2 candidates in all groups receiving two doses.

Immunogenicity:

- Median and geometric mean antibody titers of type 2 polio neutralizing antibodies at Day 0 and at 28 days after the first dose of nOPV2 in all groups, and 28 days after the second dose of nOPV2 in all groups receiving two doses.
- Seroconversion rate at Day 28, 28 days after the first dose of nOPV2 in all groups, and at Day 56, 28 days after the second dose of nOPV2 in in all groups receiving two doses. Seroconversion is defined as a change from seronegative to seropositive, or in seropositive subjects as an antibody titer increase of ≥ 4 fold over Day 0 titer corrected for maternal antibody titers where applicable/age-appropriate.
- Seroprotection rate of type 2 polio neutralizing antibodies at Day 0 in all groups, at 28 days after the first dose of nOPV2 in all 1 to 5 year-old groups, and at Day 56, 28 days after the second dose of nOPV2 in all 1 to 5 year-old groups and two-dose infant groups.

Shedding of poliovirus

- Descriptive analysis of viral shedding as determined using RT-PCR (viral identity) and 50% cell culture infective dose ($CCID_{50}$; titer) after viral extraction from a subset of stool samples taken at fixed time points following the first dose from all 1 to 5 year-old groups and all infant groups administered the 10^6 $CCID_{50}$ dose.
- Potential for neurovirulence (as measured in an animal model) of shed virus extracted from a subset of stool samples following the first dose from both 1 to 5 year-old groups and both infant groups administered the 10^6 $CCID_{50}$ dose of each of the 2018 lots of nOPV2 candidates 1 and 2, respectively.

3.3 EXPLORATORY ENDPOINTS:

- Median and geometric mean antibody titers of type 2 polio neutralizing antibodies in infants at 6 weeks of age (Day -84) before receiving their first bOPV vaccination to provide a measure of maternal antibodies.
- Descriptive and exploratory analysis of 1 to 5 year-olds and 18–22 week-old infants developing a polio type 2 seroconversion within 1 week of nOPV2 exposure, i.e. 7 days after their first dose of nOPV2.
- Descriptive analysis of viral shedding following a second dose in 1 to 5 year-olds, and infant groups administered two 10^6 $CCID_{50}$ doses of each nOPV2 candidate.
- Descriptive analysis of viral shedding in all infant groups administered one 10^5 $CCID_{50}$ dose of each nOPV2 candidate.

- Descriptive analysis of viral shedding in all infant groups administered two 10^5 $CCID_{50}$ doses of each nOPV2 candidate.
- Exploratory endpoints may also include assessment of the genetic stability of shed virus at one or more time points following two doses 10^6 $CCID_{50}$ of each nOPV2 candidate**,** following one dose of candidate 2 (2016), or one or two 10^5 $CCID_{50}$ doses of all nOPV2 candidates.
- Exploratory endpoints may also include assessment of the potential for neurovirulence of shed virus at one or more time points following two 10^6 $CCID_{50}$ doses of nOPV2 candidates, following one dose of candidate 2 (2016), or one or two10^5 $CCID_{50}$ doses of nOPV2 candidates.
- Assessment of antibody levels and proportions displaying protective levels against HBV antigen (≥ 10 mIU/mL) and PRP antigen (≥ 0.15 µg/mL) in all infant groups 4 weeks after the last dose of DTPw-HBV-Hib (coincides with Day 0 serum sample for polio antibodies).

4. STUDY DESIGN

4.1 OVERVIEW OF STUDY DESIGN

This will be a single center, age de-escalation, partly-randomized study in cohorts of healthy children aged 1 to 5 years (cohort A) and bOPV-IPV vaccinated healthy infants from age 6 weeks (cohort B), performed in two consecutive stages as follows:

Stage I

- **Group A2H2[2016]:** 50 IPV and/or OPV vaccinated participants aged 1 to 5 years administered two 10^6 $CCID_{50}$ doses of candidate 2 (2016), separated by 28 days.

Age de-escalation will be based on general safety data (solicited and unsolicited AEs and clnically significant abnormal laboratory values) through 14 days post dose 1 in 1 to 5 year-olds presented to the DSMB. After the DSMB recommendation to proceed, the younger cohort will be randomized to the following groups:

- **Group B2L1[2016]:** 162 infants enrolled at 6 weeks of age (-7 to +14 days) vaccinated with 3 doses of bOPV at 6, 10 and 14 weeks of age and 1 dose of IPV at 14 weeks of age, followed at 18–22 weeks of age with one 10^5 $CCID_{50}$ dose of candidate 2 (2016).
    - **Group B2L2[2016]:** a sub-group of 50 infants will be randomly selected from B2L1[2016] to receive a second 10^5 $CCID_{50}$ dose of candidate 2 (2016), 28 days later.

Following completion of post-dose 1 safety assessment from the first 50 subjects from group B2L1[2016] and after the DSMB recommends to proceed, infants will be randomized to groups B2H1[2016] and B2H2[2016]. Dose escalation will be based on general safety data (solicited and unsolicited AEs and clnically significant abnormal laboratory values) through 14 days post dose 1 in first 50 subjects from group B2L1[2016].

- **Group B2H1[2016]:** 162 infants enrolled at 6 weeks of age (-7 to +14 days) vaccinated with 3 doses of bOPV at 6, 10 and 14 weeks of age and 1 dose of IPV at 14 weeks of age, followed at 18–22 weeks of age with one 10^6 $CCID_{50}$ dose of candidate 2 (2016).
    - **Group B2H2[2016]:** a sub-group of 50 infants will be randomly selected from B2H1[2016] to receive a second 10^6 $CCID_{50}$ dose of candidate 2 (2016), 28 days later.

Stage II

Stage II will be performed following completion in Stage I of the enrollment and a minimum of 14 days safety follow-up in at least 50 subjects of group B2H2 after administration of 10^6 $CCID_{50}$ nOPV2 candidate 2 [2016], and with the recommendation of the DSMB. In Stage II the process will be repeated in the same fashion as in Stage I, subject to any programmatic changes necessitated by observations in Stage I, with randomized enrollment to candidate within age group and dose level. Enrolment of

subjects for Stage II may begin before the above-defined completion threshold but no administrations of nOPV2 are to be perfomed before this threshold is achieved.
Following completion of Stage I, with administration of nOPV2 candidate 2 (2016), with the agreement of the DSMB and when the 2018 lots of nOPV2 candidates 1 and 2 are available, the process will be repeated in the same fashion in Stage II with new cohorts of 1–5 year old children and 18–22 week-old infants randomly allocated to receive either nOPV2 candidate 1 or nOPV2 candidate 2 (2018 lots) in the following groups:

- **Group A1H2[2018]:** 50 IPV and/or OPV vaccinated participants aged 1 to 5 years administered with two 10^6 $CCID_{50}$ doses of candidate 1 (2018) separated by 28 days.
- **Group A2H2[2018]:** 50 IPV and/or OPV vaccinated participants aged 1 to 5 years administered with two 10^6 $CCID_{50}$ doses of candidate 2 (2018) separated by 28 days.

Age de-escalation will be based on general safety data (solicited and unsolicited AEs and clinically significant abnormal laboratory values) through 14 days post dose 1 in 1 to 5 year-olds presented to the DSMB. After the DSMB recommendation to proceed, the younger cohort will be enrolled and randomized to the following groups:

- **Group B1L1[2018]:** 162 infants enrolled at 6 weeks of age (-7 to +14 days) administered with 3 doses of bOPV at 6, 10 and 14 weeks of age and 1 dose of IPV at 14 weeks of age, followed at 18–22 weeks of age with one 10^5 $CCID_{50}$ dose of candidate 1 (2018).
    - **Group B1L2[2018]:** a sub-group of 50 infants will be randomly selected to receive a second 10^5 $CCID_{50}$ dose of candidate 1 (2018), 28 days later.

Following completion of post-dose 1 safety assessment from the first fifty subjects from each group B1L1(2018) and after the DSMB recommends to proceed, infants will be randomized to groups B1H1(2018), B1H2(2018). Dose escalation will be based on general safety data (solicited and unsolicited AEs and clinically significant abnormal laboratory values) through 14 days post-dose 1 in group B1L1(2018).

- **Group B1H1[2018]:** 162 infants enrolled at 6 weeks of age (-7 to +14 days) vaccinated with 3 doses of bOPV at 6, 10 and 14 weeks of age and 1 dose of IPV at 14 weeks of age, followed at 18–22 weeks of age with one 10^6 $CCID_{50}$ dose of candidate 1.
    - **Group B1H2[2018]:** a sub-group of 50 infants will receive a second 10^6 $CCID_{50}$ dose of candidate 1, 28 days later.

4.2 DISCUSSION OF STUDY DESIGN

There will be no randomization of 1 to 5 year-olds in Cohort A of Stage I, as all subjects will receive two 10^6 $CCID_{50}$ doses of the 2016 lot of candidate 2. In Cohort B of Stage I the first 50 subjects will receive the 10^5 $CCID_{50}$ dose and subjects will be randomized to receive either one or two doses of the respective vaccine dosage. Only one candidate vaccine will be used in Stage I, so clinical staff will not be blinded to candidate.

In Stage II, for the assessment of both candidates prepared in 2018, randomization to candidate will be performed in both 1 to 5 year-old and infant cohorts to increase the likelihood that known and unknown subject attributes (e.g., demographic and baseline characteristics) are evenly balanced across candidate and one and two dose groups. Randomization of infants to 2018 lots in Stage II will be conducted within dose level (randomized to candidate and number of doses within low dose, then separate randomization to candidate and number of doses within high dose).

5. SELECTION OF STUDY POPULATION

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

5.1 INCLUSION CRITERIA

1. For Cohort A children enrolled at 1 to 5 years of age who have previously been fully vaccinated according to MoH recommendations with OPV and/or IPV.
2. For Cohort B infants enrolled at 6 weeks of age (-1, + 2 weeks) with birth weight >2,500 gm. To be eligible to continue into the experimental phase of the study infants must be vaccinated with 3 doses of bOPV and one dose of IPV prior to administration of the study vaccine at 18–22 weeks of age to take into account the visit windows for enrollment (age 6 weeks, -1 or + 2 weeks) and subsequent OPV vaccination windows (± 1 week). The last polio vaccine must have been administered at least 4 weeks prior to the first dose of study vaccine. Subjects in Cohort B who do not complete the three routine vaccination visits will be replaced in the study, and their parents/guardians will be encouraged to complete the primary vaccinations series.
3. Healthy children 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 to be in the study as established by the medical history and physical examination.
4. 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. For all participants the presence of anyone under 10 years of age in the subject's household (living in the same house or apartment unit) who does not have complete "age appropriate" vaccination status with respect to poliovirus vaccines at the time of study vaccine administration. For household members younger than 18 months age appropriate vaccination is at least three (3) doses of IPV. For household members between 18 months and 10 years "age appropriate" vaccination is at least three (3) doses of IPV or tOPV plus one (1) booster dose of any antipolio vaccine.
2. For all participants having a member of the subject's household (living in the same house or apartment unit) who is under 6 months of age at the moment of study vaccine administration.
3. For all participants having a member of the subject's household (living in the same house or apartment unit) who has received OPV in the previous 3 months before study vaccine administration.

4. For Cohort A: receipt of polio vaccines within the 3 months prior to the administration of the study vaccine (number of previous polio vaccine doses to be documented). Any other vaccine 4 weeks before study entry.
5. For Cohort A: any participating children attending day care or pre-school during their participation in the study until one month after their last nOPV2 administration.
6. For Cohort B: any receipt of polio vaccines prior to administration of the study vaccine other than 3 doses of bOPV and 1 dose of IPV.
7. Any confirmed or suspected immunosuppressive or known immunodeficient condition including human immunodeficiency virus (HIV) infection in the potential participant or any member of the subject's household.
8. Family history of congenital or hereditary immunodeficiency.
9. Major congenital defects or serious uncontrolled chronic illness (neurologic, pulmonary, gastrointestinal, hepatic, renal, or endocrine).
10. Known allergy to any component of the study vaccines or to any antibiotics, that share molecular composition with the nOPV2 vaccines.
11. Uncontrolled coagulopathy or blood disorder contraindicating intramuscular injections (of IPV).
12. Administration of immunoglobulins and/or any blood products since birth or planned administration during the study period.
13. Acute severe febrile illness at 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.).
14. 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.

5.3 CRITERIA FOR ELIMINATION FROM THE PER-PROTOCOL POPULATION

Subjects with clinically relevant deviations for hematology and chemistry parameters will be excluded from the per-protocol analysis population (see Section 10.1). These subjects will continue in the study for safety follow-up and intention to treat analysis but will not receive further vaccine doses.

Subjects that receive any other vaccine (with the exception of influenza) during the whole study period will be removed from the per-protocol population, but not the total vaccinated population. These subjects will only contribute safety data to the total vaccinated population prior to administration of the non-study vaccine, 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:

- Serious adverse event, severe adverse event (grade 3) or IME after vaccination considered to be consistent with a causal association to any of the study vaccines.
- 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, and the subject is in a group scheduled to receive a second nOPV2 vaccination, 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 vaccines: novel monovalent OPV type 2 (nOPV2) candidates 1 and 2 are produced by Bio Farma, Indonesia. Lots used will be nOPV2 candidate 2 (lot 2016), nOPV2 candidate 1 (lot 2018) and nOPV2 candidate 2 (lot 2018).

Other vaccines: licensed bOPV and IPV for pre-vaccination of subjects in infant cohorts B prior to administration of the study vaccine. DTPw-HB-Hib will be provided by the sponsor. Pneumococcal conjugate and Rotavirus vaccines will be provided by the local National Immunization Program.

6.1 PHYSICAL DESCRIPTION OF THE STUDY VACCINES

The nOPV2 candidate vaccines will be provided to the sites in vials presented as an aqueous yellow-red solution for oral use. Vials will be filled at concentrations for each candidate so that each dose of the nOPV2 vaccine candidate 1 (2018) and nOPV2 vaccine candidates 2 (2016 and 2018) will contain approximately 10^6 or 10^5 $CCID_{50}$, dependent on study group. Both vaccines will be administered orally.

6.2 CHARACTERIZATON OF VACCINE LOTS

In mouse neurovirulence testing of the two candidate bulks, both 2018 candidates displayed limited virulence, with paralysis rates that are the same or lower than rates observed with the 2016 material. Further testing of the candidates is ongoing, including monkey neurovirulence testing and confirmation of temperature sensitivity, and the use of 2018 candidates will only be initiated when the results of these tests are known and confirm the relative safety of both vaccine lots.

Deep sequencing analyses of the 2016 candidate 2 lot and the 2018 lots provides supportive information to the neurovirulence testing, including that (1) the modified sites incorporated in the candidates are preserved and (2) there are no detected mutations in domain V of the virus, the primary attenuation site for Sabin-derived strains. As anticipated, there were some noted changes from the 2016 preparations, which included a reduction in the level of one variant (VP1 E295K) for both candidates. Increases in levels of other variants were noted including low levels (1–2%) of a VP1-143 reversion in candidate 1. This reversion occurs readily in replication *in vivo* for Sabin-2 and also was observed in both candidates in shed virus samples from the M4a trial. The increases in these variants are not expected to impact safety (as confirmed by mouse and monkey neurovirulence testing) or immunogenicity.

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

Both vaccine candidates are 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 vaccine 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 vaccine must be stored as specified at delivery and in the original packaging.

The nOPV2 candidate vaccines 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 vaccine 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 vaccine 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 vaccine 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 in the study (LSLV), any used and unused study vaccine will be returned to the Sponsor, or 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

All subjects will receive one of the three nOPV2 candidate lots.

In Stage I, 1–5 year-old OPV-IPV pre-vaccinated subjects in Cohort A will be enrolled to receive two 10^6 $CCID_{50}$ doses (N=50) of nOPV2 candidate 2 lot 2016: **Group A2H2[2016]**.

Following DSMB approval previously enrolled infants in Cohort B at 18–22 weeks of age who have received 3 doses of bOPV and 1 dose of IPV will be assigned to **Group B2L1[2016]** (N=162) to receive one 10^5 $CCID_{50}$ dose of nOPV2 candidate 2 (2016). A randomly selected sub-group (N=50) will receive a second dose of this vaccine 28 days after the first: **Group B2L2[2016]**. After the DSMB have considered the safety data from the first fifty participants in Group B2L1[2016] and given approval**,** the following group of 18–22 week-old infants (N=162) will then be assigned to receive one 10^6 $CCID_{50}$ dose of nOPV2 candidate 2: **Group B2H1[2016]**, and a randomly selected sub-group (N=50) will receive a second dose of this vaccine 28 days after the first: **Group B2H2[2016]**).

In Stage II, this procedure will be repeated with the 2018 lots of candidates 1 and 2:

Initially 100 OPV-IPV pre-vaccinated Cohort A subjects will be enrolled and randomized to two equal groups to receive two 10^6 $CCID_{50}$ doses (N=50) of nOPV2 candidate 1 (**Group A1H2[2018]**) or nOPV2 candidate 2 (**Group A2H2[2018]**). Enrollment of Stage II 1 to 5 year-olds may proceed upon completion of Stage I, i.e. complete enrolment and the availability of a minimum of 14 days safety follow-up in at least 50 subjects of group **B2H2[2016]** after administration of 10^6 $CCID_{50}$ nOPV2 (2016), regardless of the enrollment status of the 2016 infant cohort.

Following DSMB approval infants enrolled in Cohort B at 18–22 weeks of age after receiving 3 doses of bOPV and 1 dose of IPV will be randomly assigned to **Group B1L1[2018]** (N=162) to receive one 10^5 $CCID_{50}$ dose of nOPV2 candidate 1 (2018) or **Group B2L1[2018]** (N=162) to receive one 10^5 $CCID_{50}$ dose of nOPV2 candidate 2 (2018). Randomly selected sub-groups (N=50) will receive a second dose of the respective vaccine 28 days after the first: **Group B1L2[2018] and Group B2L2[2018]**.

After the DSMB have given approval based on consideration of the safety data from the first fifty participants in each **Groups B1L2[2018]** and **B2L2[2018]**, the following groups of 18–22 week-old infants (N=162) will then be assigned to receive either one 10^6 $CCID_{50}$ dose of nOPV2 candidate 1 (2018): **Group B1H1[2018]**, or one 10^6 $CCID_{50}$ dose of nOPV2 candidate 2 (2018): **Group B2H1[2018]**, and randomly selected sub-group (N=50) will receive a second dose of the respective vaccines 28 days after the first: **Groups B1H2[2018]** and **Group B2H2[2018]**. Enrollment of subjects into infant groups in Stage II may proceed to build up the cohorts and to receive their three doses of bOPV and one dose of IPV, but they will not receive any nOPV2 candidate until receipt of a positive recommendation from the DSMB based on safety data from Stage I.

Allocation of each subject in Stage II from Cohorts A and B, within candidate and dose level groups to the different one-dose or two-dose candidate 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 be balanced using randomly permuted blocks across the groups.

6.7 DOSE AND ADMINISTRATION

For all lots (2016 and 2018) one 10^5 $CCID_{50}$ dose of vaccine (0.1 ml) is contained in two drops, which are delivered using the dropper supplied with the vaccine.

For the 2016 lot of candidate 2 one 10^6 $CCID_{50}$ dose of vaccine (0.3 ml) is contained in six drops, which are delivered using the dropper supplied with the vaccine.

For both 2018 lots (candidates 1 and 2) one 10^6 $CCID_{50}$ dose of vaccine is contained in 1.0 ml which may be delivered from a syringe, or using a syringe to measure the dose into a spoon.

The vaccinees will remain under medical supervision for at least 30 min following the administration of each 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. In the older age Cohort (Group A), subjects are not allowed to receive any other vaccines during the whole study period and 4 weeks prior to study vaccination. Influenza vaccine will be allowed in all groups according to National Immunization Recommendations.

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 in Cohort B will concomitantly receive with bOPV/IPV the DTPw-HB-Hib, Pneumococcal conjugate and Rotavirus vaccines which will be provided by the Sponsor and the local National Immunization Program. In infants who receive nOPV2 at 18-22 weeks, no other vaccines can be administered 3 weeks before or 72 days after nOPV2 with the exception of influenza vaccine according to the National Immunization Program.

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 intake of concomitant medication will be monitored continuously from informed consent until the last study-related activity 28 days after the last vaccination. Any subsequent SAEs and IMEs occurring up to six months after the last vaccination will be solicited by telephone contact with parents.

After the pre-dose procedures, including recruitment, administration of routine vaccinations and collection of baseline information and biological samples outlined in the Time and Events Schedule, the subjects will receive the first dose of study vaccine according to the procedure described in Section 6.6, followed by further assessments as outlined in the Time and Events Schedules. The subjects will be kept under medical supervision for at least 30 minutes after vaccination.

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 back up.

Unscheduled visits can be planned for instance:

- To obtain additional information to ensure safety to the subject. Additional blood and urine samples may be taken at the discretion of the Investigator.

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*

Neutralizing Type 2 Poliovirus Antibody Titers

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 type 2 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.

Immunogenicity criteria

For an overview of endpoints, see Section 3.

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

- Median and geometric mean titers.
- Seroprotection: defined as poliovirus type 2-specific titers ≥1:8.
- Seroconversion: defined as a change from seronegative to seropositive, and in seropositive subjects, as an antibody titer increase of ≥4 fold over baseline, corrected for maternal antibody titer where applicable/age-appropriate. Seroconversion will be computed from Day 0 for all subjects, and from Day -84 for infant subjects.

8.3 VIRAL SHEDDING

Stool samples will be collected at the time points outlined in the Time and Events Schedule. As a measure of intestinal immunity, shedding of type 2 poliovirus in a pre-selected subset of stools will be evaluated using:

- RT-PCR (viral identity).
- $CCID_{50}$ determination (titer).

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

8.4 NEUROVIRULENCE

Phenotypic neurovirulence of shed virus will be evaluated in a subset of stool samples, using a transgenic mice assay (TgPVR mice).[8] Stool samples collected for viral extraction will be collected as outlined in the Time and Events Schedule and stored.

For the neurovirulence testing of virus derived from stool samples of clinical trial participants vaccinated with oral polio vaccines, a modified transgenic mouse neurovirulence test (mTgmNVT) may be applied. The TgmNVT that will be used is adapted from the WHO SOP (Neurovirulence Testing of Oral Polio Vaccine Using TgPVR21 Transgenic Mice) used for vaccine release. In the mTgmNVT, blinded, cell culture-amplified virus material (from stool) is titrated and then diluted to a fixed target dose/inoculum selected to detect reversion of the Sabin-2 strain. The inoculum is intraspinally injected into transgenic mice susceptible to poliovirus. Control virus is tested concurrently in the TgmNVT to assess the validity of a given test.

The inoculated mice are observed daily for the presence of clinical signs of poliovirus infection (weakness, paresis, and paralysis). After the observation period of 14 days, the in-vivo phase is ended. Mice are euthanized and a clinical end score (paralyzed or non-paralyzed) is assigned to each mouse. Results are reported as percent paralysis observed per sample. Samples that induce paralysis above a critical threshold may be further tested in a multi-dose format of the TgmNVT for further characterization.

NV data from this study will be combined with data from the historical control study (M2) to draw comparisons between shed virus from Sabin-2 and the 2018 lots of novel vaccine candidates.

Stool samples that remain after protocol-specific assessments have been performed may be used for further exploratory work on polio. No human DNA or RNA analysis will be performed.

8.5 SAFETY EVALUATIONS

The safety assessment in this study will be based on AEs and clinical laboratory tests, as described in the following sections.

8.5.1 *Adverse Events*

Adverse events will be monitored continuously from the time of informed consent signature until the last study-related activity 28 days after the last vaccination. Any subsequent SAEs and IMEs occurring up to six months after the last vaccination will be solicited by telephone contact with parents. At regular intervals during the study, parents will be asked non-leading questions to determine the occurrence of any AEs. All AEs reported spontaneously during the course of the study will be recorded as well.

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

Solicited AEs will be recorded for 7 days following each vaccine dose of study vaccine using a Diary Card.

8.5.2 *Clinical Laboratory Tests*

Blood samples of up to 6 mL in both Cohorts will be collected at the time points indicated in the Time and Events Schedules.

Standard laboratory tests as outlined in Appendix 1 will be performed by a local laboratory.

The Investigator must review the laboratory report, document this review, and record any change occurring during the study he/she considers to be clinically relevant in the source documents and in the AE section of the eCRF. Laboratory values outside the normal range will be flagged and their clinical relevance will be assessed by the Investigator. A copy of all laboratory reports must be filed in the subject's medical records.

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.

8.6 EXPLORATORY EVALUATIONS

8.6.1 *Sequencing*

Viral sequencing methods (e.g. deep sequencing) may be performed on selected stool samples taken at one or more of the time points specified in the Time and Events Schedule to explore the heterogeneity of shed virus, including reversion at known sites of attenuation, as well as attenuating modifications introduced to enhance genetic stability. Sequence information on shed virus may be compared with the results of neurovirulence testing, if available.

8.7 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 and they are not withdrawn before the final study safety visit 6 months after their last vaccination.

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, i.e. the proportions of the B cohort infant groups with seroprotective type 2 polio neutralizing antibodies at Day 28 following the first doses of the two nOPV2 candidates at both dose levels.

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.

All statistical methods shall be detailed in a Statistical Analysis Plan (SAP) that will be finalized before database lock.

Data obtained in Stage II from candidates 1 and 2 (2018 lots) from this study will be combined with data from the historical control study (M2) to enable assessments and comparisons described in the study objectives. In general, data from this study will be presented alongside these historical components, as if the data were collected simultaneously.

Unless otherwise specified, descriptive statistics include mean, standard deviation (SD), 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 confidence intervals (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 confidence intervals will be used for rate differences.

Data obtained in Stage I from candidate 2 (2016) from this study will be analyzed descriptively, and summarized in an interim report.

10.1.1 *Study Populations*

The following populations will be considered for analysis:

- Total Vaccinated population, defined as all subjects who received at least one dose of study vaccine.
- Per-Protocol (PP) population, consisting of all eligible study participants who are in the Total Vaccinated population and who receive all of the immunizations scheduled for the group to which they are allocated and excludes those subjects who received any therapy that could significantly affect the subject's immune status and those subjects who meet criteria outlined in Section 5.3. The per-protocol population will be adapted by time point to allow subjects to contribute data to per-protocol 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 Total Vaccinated population will be used for safety/tolerability analysis and analysis of demographics. Immunogenicity and viral shedding analyses will be primarily conducted in the per-protocol population.

10.1.2 *Analysis Sequence*

An interim analysis of safety, immunogenicity, and viral shedding will be conducted following completion of a minimum of 28 days of safety follow-up following each dose in 1 to 5 year-old and infant groups administered candidate 2 (2016) in Stage I.

In order to enable data review and candidate/dose selection decisions which may impact future clinical development plans prior to completion of the extended safety follow-up phase, the analysis of Stage II will proceed in two part.

In the first part, an interim statistical report and interim summary document will be produced based on a database freeze initiated following collection of all immunogenicity endpoints and 28 days of both viral shedding and general safety follow-up following the last dose of 2018 candidates administered to the last subject. This interim document will be unblinded to group, and will contain final summaries of safety, immunogenicity and viral shedding primary and secondary endpoints, although safety endpoints will be limited to the 28-day period after each vaccination only. This document will contain formal comparisons of these endpoints to corresponding endpoints collected in the historical control study, M2.

The second stage will be initiated following study completion for all subjects. The final statistical report and Clinical Study Report (CSR) will augment the interim reports with the additional safety follow-up and concomitant therapies collected in the extended follow-up phase. For example, tables of unsolicited adverse events which had originally been limited to the 28-day post-final-dose period will have a corresponding additional table to account for all events observed throughout the study period, including the extended 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).

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

10.1.4 *Immunogenicity Data*

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

Neutralizing Type 2 Poliovirus Antibody Titers

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

- Seroprotection rates with 95% confidence intervals (CIs) will be computed.
- Seroconversion rates with 95% confidence intervals (CIs) will be computed from Day 0 at post-nOPV2 vaccination time points.
- Seroconversion rates with 95% confidence intervals (CIs) will be computed from Day -84 for infant groups.

- Median of log2 and geometric mean antibody titers will be computed along with 95% CIs.
- Plots of the reverse cumulative distribution of antibody titers will be generated.

Viral Shedding

Summaries of the detection of candidate vaccine via quantitative PCR and viral titer (log_{10} $CCID_{50}$/g of stool) among those positive for virus will be computed by group and time point, for a subset of stool samples. A viral shedding index endpoint (SIE) will be calculated as the average of log_{10}-transformed values of viral concentration in stool samples as determined using quantitative PCR (viral identity) and $CCID_{50}$ (titer) from selected stool samples taken following each vaccine dose, and this index will be summarized by group.

Descriptive analysis and plots of the reverse cumulative distribution of the viral shedding index will be generated.

10.1.5 *Neurovirulence Data*

Neurovirulence data will be obtained from the transgenic mouse assay applied to virus isolated from select stool samples in this study. Assessment in the mouse neurovirulence model requires a minimally sufficient quantity of virus (≥4.0 log_{10} $CCID_{50}$ per gram) to be present in stool samples. Data from each sample tested will be summarized by group. For each candidate separately (2018 lots), if 5 or more such samples are available for 1 to 5 year-old and/or infant cohorts as well as from corresponding cohorts from the historical control study M2, these data will be combined in order to directly compare the neurovirulence of samples from candidate vaccines to the control vaccine. Additional assessment of samples from Stage I using candidate 2 (2016) may also be performed. The proportion of mice paralyzed and the odds ratio of paralysis from the single-dose assay will be the primary means of comparison of NV of shed virus between each candidate and the Sabin mOPV2 control samples. The statistical hypothesis that will be tested will be that of superiority (lower neurovirulence) of at least one 2018 lot of candidate vaccine to Sabin 2, with respect to the frequency of mouse paralysis observed in the assay. Exploratory analysis of additional samples, or samples from additional groups will also be considered.

The SAP will provide additional detail on the selection of samples, as well as the summary and comparison of these data.

10.1.6 *Safety Data*

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

Safety parameters will be tabulated and analyzed descriptively, in the safety population, according to the actual vaccine received.

Adverse Events

Analyses described below will be performed for solicited and unsolicited AEs by severity using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 published by NIH in 2010, as well as for SAEs and IMEs.[9]

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 Medical Dictionary for Regulatory Activities (MedDRA).

All AEs will be summarized by time-point, group, severity and occurrence in relation to vaccination, and overall. Determination of causal association to the study vaccines will be assigned using the new individual causality assessment algorithm published by WHO in 2013.[10] All SAEs and severe 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 or severe AE will be classified as consistent or inconsistent with causal association to immunization; those which meet the definition of causality will be defined as Serious Adverse Reactions (SAR). Those SAE or severe AEs 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 a severe or serious AE. Summaries, listings, and narratives may be provided, as appropriate. Unsolicited adverse events occurring within 28 days of any vaccine administration will be summarized, as will any data obtained on SAEs or IMEs reported during the extended safety follow-up or obtained in the follow-up telephone call at the end of the study.

Clinical Laboratory Tests

Each continuous biochemistry and hematology laboratory test will be evaluated by means of descriptive statistics (i.e., number of subjects, mean, SD, median, minimum, and maximum) on the actual values, at each assessment time point and by group. Changes from baseline will also be summarized by assessment time point and by group.

Relative changes in clinical laboratory test values compared to values at baseline will be evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (toxicity grades) or in accordance with the normal ranges of the clinical laboratory (below, within, or above normal range) for parameters for which no toxicity grades are defined.

A listing of subjects with any clinical laboratory test result outside the reference ranges will be provided.

10.1.7 *Exploratory*

10.1.8 *Viral sequencing methods*

Viral sequencing (e.g. deep sequencing) may be performed on selected stool samples taken at one or more of the time points specified in the Time and Events Schedule to explore the heterogeneity of shed virus, including reversion at known sites of attenuation, as well as attenuating modifications introduced to enhance genetic stability. Sequence information on shed virus may be compared with the results of neurovirulence testing, if available.

10.1.9 *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 trial 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 trial data.

10.2 DETERMINATION OF SAMPLE SIZE

As in the historical control comparator study M2, this study has safety and Day 28 post-initial vaccination seroprotection rate as primary endpoints. Each age group will be monitored for safety; the primary immunogenicity endpoint, however will be limited to the infant groups administered the 2018 lots of both vaccine candidates, to which both 1- and 2-dose groups will contribute. The primary comparisons will entail comparisons of post-first-dose data from the four infant groups administered 10^5 and 10^6 dose levels of candidate 1 (2018) and candidate 2 (2018), to the corresponding infant cohort from study M2. Data obtained for candidate 2 (2016) material will be summarized, and not involved in direct comparisons with the historical control.

The sample size for the older children (Groups A1H2[2018], A2H2[2016], and A2H2[2018]) is chosen to provide adequate safety data prior to age de-escalation. Forty-five subjects are required to have 90% probability of observing at least one occurrence of an adverse event, when the true adverse event rate is 5%. Allowing for a 10% non-evaluability/dropout rate requires 50 subjects for the safety evaluations. Immunogenicity will be assessed as a secondary endpoint in the older cohort.

For the primary immunogenicity endpoint, it is assumed that the seroprotection rate following administration of a single dose of Sabin mOPV2 and 2018 lots of candidate nOPV2 vaccines in this population will be ≥ 95%. In the historical control comparator study, M2, a total of 91 per-protocol subjects (a 20% dropout rate from the enrolled population) were available for the immunogenicity endpoint in the younger cohort. For the current study, 129 evaluable (per-protocol) subjects per vaccine candidate and per dose level are required such that 90% power is available to declare non-inferiority to the Sabin 2 control, using the lower confidence bound of the Miettinen-Nurminen score confidence interval for inference (one-sided alpha = 0.025 for each candidate vaccine and dose level, separately, non-inferiority margin 10%). Therefore, assuming a 20% dropout rate the required enrollment is 162 subjects. Since the safety endpoint requires 50 subjects, and all subjects contribute to the immunogenicity endpoint, 50 randomly-chosen subjects will be assigned to receive two doses, and the remaining 112 subjects will receive only a single dose of each candidate vaccine.

Sample sizes for the 2016 candidate 2 groups in Stage I were selected based on the same criteria, prior to availability of the 2018 material.

Multiplicity is addressed in two ways. First, because there are two candidates, immunogenicity non-inferiority is assessed using the Bonferroni-corrected one-sided type I error rate of 0.025 (0.05/2). Second, multiplicity between dose levels for each candidate is addressed by considering fixed-sequence testing; that is, the 10^6 $CCID_{50}$ dose will be tested for non-inferiority first at level alpha = 0.025. If the non-inferiority criterion is met for a given vaccine candidate, the 10^5 $CCID_{50}$ dose level will also be tested for non-inferiority at level alpha = 0.025 for that vaccine candidate.

11. ADVERSE EVENT REPORTING

11.1 DEFINITIONS

11.1.1 *Adverse Events*

An Adverse Event Following Immunization (AEFI), has been defined by the working group on vaccine pharmacovigilance of the Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organization (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 adverse event 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 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 CRF.

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 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 1, to facilitate the assessments of the level of functional impairment for each experienced AE.

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.

Space will be provided in both the electronic diary for the recording of any other symptoms (unsolicited AEs) experienced during this period.

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.

Important medical events (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 important medical events 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 trial 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 NIH CTCAE grading terminology by organ system[9]:

Table 1 Intensity scales for solicited symptoms

Adverse Event	Intensity grade	Parameter
Fever	0	<37.5°C
	1	37.5°C to 38.0°C
	2	38.1°C to 39.0°C
	3	>39.0°
Vomiting	0	None
	1	1 episode per 24 hours
	2	2 - 5 episodes per 24 hours
	3	≥6 episodes per 24 hours or requiring parenteral hydration
Abnormal crying	0	None
	1	<1 hour
	2	1 - 3 hours
	3	>3 hours
Drowsiness	0	None
	1	Sleepier than usual or less interested in surroundings
	2	Not interested in surroundings or did not wake up for a feed/meal
	3	Sleeping most of the time or difficult to wake up
Loss of appetite	0	None
	1	Eating less than normal
	2	Missed 1 or 2 feeds/meals completely
	3	Refuses ≥3 feeds/meals or refuses most feeds/meals
Irritability	0	None
	1	Easily consolable
	2	Requiring increased attention
	3	Inconsolable

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.

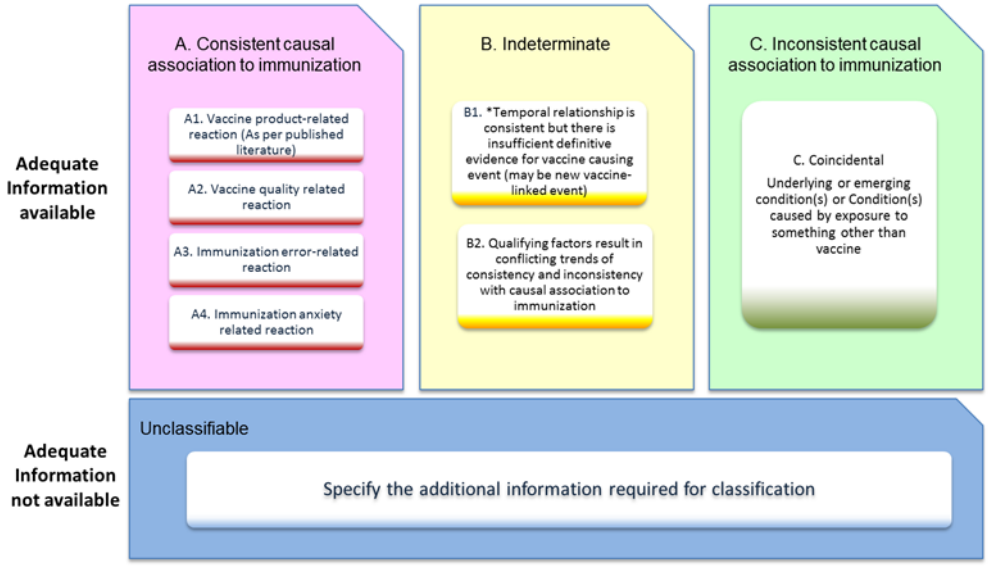
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities (In adults, such an AE would, for example, prevent attendance at work and would necessitate the administration of corrective therapy.)

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.

11.3 CAUSALITY ASSESSMENT

The investigator is obligated to assess the relationship between investigational vaccine and the occurrence of each 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.[10] When appropriate information is available the investigator should arrive to the following possible conclusions:



*B1 : Potential signal and maybe considered for investigation

Serious Adverse Events (SAE) considered to be causally related to the vaccination will be termed Serious Adverse Reactions (SAR).

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 (S)AEs 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, VaxTrials 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 last subject's last visit [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 Data Safety Monitoring Board (DSMB) will monitor the safety aspects of this trial. 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 Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice 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 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 vaccine.

- 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 vaccine.
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually).
- Reports of AEs that are serious, unlisted, and associated with the investigational product (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 candidates 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 VAXTRIALS.

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 [DCF]) for resolution by the clinical staff, and 3- the clinical data manager can generate a query for resolution by the clinical staff.

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 Good Clinical Research Practice Guidelines and Recommendations, 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 IMP. 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 coordinating 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 (ICTRP).

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.

14. REFERENCES

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APPENDIX 1: Overview of Laboratory Assessments

Hematology	Chemistry	Coagulation
Hemoglobin Hematocrit Red blood cells (RBC) White blood cells (WBC) with differential Lymphocytes Monocytes Neutrophils Eosinophils Basophils Platelets	Total bilirubin Direct bilirubin[a] Creatinine Alanine aminotransferase Aspartate aminotransferase Creatine phosphokinase Gamma-glutamyl transferase	Prothrombin time Activated partial thromboplastin time Fibrinogen

[a] Assay if total bilirubin is above normal range.