Title: A Randomized, Observer-Blind, Controlled Phase 1/2 Trial to Evaluate the Safety, Tolerability and Immunogenicity of Different Doses of a Stand-alone Trivalent, Inactivated Poliomyelitis Vaccine from Sabin Strains in Healthy Infants, with a Safety and Tolerability Age-Step Down Lead-in in Healthy Adults followed by Healthy Toddlers

NCT Number: NCT03092791

Protocol Approve Date: 11 April 2017

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

A Randomized, Observer-Blind, Controlled Phase 1/2 Trial to Evaluate the Safety, Tolerability and Immunogenicity of Different Doses of a Stand-alone Trivalent, Inactivated Poliomyelitis Vaccine from Sabin Strains in Healthy Infants, with a Safety and Tolerability Age-Step Down Lead-in in Healthy Adults followed by Healthy Toddlers

IPV-102 Safety, Tolerability and Immunogenicity of TAK-195 in Healthy Infants, Toddlers and Adults

Sponsor:	Takeda Vaccines Inc., One Takeda Parkway Deerfield, IL 60015 USA
Study Identifier:	IPV-102
IND Number:	Not applicable EudraCT Number: Not applicable
Vaccine Name:	Investigational vaccine: Stand-alone Trivalent Sabin Inactivated Poliomyelitis Vaccine (sIPV) candidate Control vaccines: Adult cohort: Placebo Toddler and infant cohorts: Reference Inactivated Poliomyelitis Vaccine (IPV).
Date:	11 April 2017
Version:	2.0 The current version supersedes Version 1.0 dated 23 November 2016

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site. Contact information is also provided in Table 1.a.

The sponsor will provide investigators with emergency medical contact information cards to be carried by each subject's legally acceptable representative.

General advice on protocol procedures should be obtained through the monitor assigned to the trial site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Table 1.a Contact Information

Issue	Contact
Serious adverse event	PPD
Medical Monitor (medical advice on protocol, compound, and medical management of subjects)	
Responsible Medical Officer (carries overall responsibility for the conduct of the trial)	

1.2 Approval

REPRESENTATIVES OF TAKEDA

This trial will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical trial protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), ICH Harmonised Guideline, Integrated Addendum to ICH(R1): Guideline for Good Clinical Practice E6(R2) [1].
- All applicable laws and regulations, including, but not limited to those related to data privacy and clinical trial disclosure.

PPD

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the sponsor. I agree to conduct this trial in accordance with the requirements of this protocol and also protect the rights, safety, privacy, and well-being of trial subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), ICH Harmonised Guideline, Integrated Addendum to ICH(R1): Guideline for Good Clinical Practice E6(R2).
- All applicable laws and regulations, including, but not limited to those related to data privacy and clinical trial disclosure.
- Regulatory requirements for reporting serious adverse events defined in Section 10.4 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Appendix A – Responsibilities of the Investigator.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State)

_____

Location of Facility (Country)

1.3 Protocol Amendment Summary of Changes

This document describes the changes in reference to the Protocol Incorporating Amendment No.1.

The primary purpose of this substantial amendment is to update the protocol regarding the reference IPV to be used in the toddler and infant cohorts (controls) as locally licensed vaccine is not available. As pentavalent DTP-HBV-Hib vaccine is not licensed/available at the study sites, this vaccine will now also be sourced by Takeda and becomes a trial vaccine.

An error in the secondary endpoints for the infant cohort has also been corrected.

Full details on changes of text are given in Section 1.3.1

1.3.1 Amendment History

Date	Amendment Number	Amendment Type	Region
23 November 2016	Initial Protocol	Not applicable	Global
11 April 2017	1	Substantial	Global

1.3.2 Summary of Changes

Amendment to Protocol Version 1.0 23 November 2016	
Rationale for the Amendment: The primary purpose of this substantial amendment is to update the protocol regarding the reference IPV to be used in the toddler and infant cohorts (controls) as locally licensed vaccine is not available. As pentavalent DTP-HBV-Hib vaccine is not licensed/available at the study sites, this vaccine will now also be sourced by Takeda and becomes a trial vaccine. An error in the secondary endpoints for the infant cohort has also been corrected. Reference to ICH E6 guidance has been updated throughout.	
2.0	The Trial Summary had been adapted to reflect the changes in the body of the protocol.
2.1	Table 2a Errors in the table and footnotes have been corrected with additional cross-references added in the table where appropriate. The footnotes now read: ET: Early Termination. Use of (X) indicates samples or procedures that generally will not be performed but may be performed to investigate an AE, or at the time of premature discontinuation. (a) In women of childbearing potential, a pregnancy test will be performed on Day 1 prior to enrollment. (~~a~~***b***) Eligibility by review of relevant inclusion/exclusion criteria will be documented before enrollment. (~~b~~***c***) Physical exam ~~at~~ on Day 1 (Section 9.1.4). All subsequent physical examinations may be performed if deemed necessary and will be symptom-directed and should assess clinically significant changes from the baseline examination. For any procedures at the site, the investigator shall follow his/her standard practice. (~~c~~***d***)Vital signs: as defined in Section 9.1.5.

(e) After vaccination, subjects will be observed for at least 30 minutes including observation for immediate reactions and body temperature measurement.

(~~d~~***f***) Diary cards will be distributed on the day of vaccination, and will be collected at the return visit 7 days later.
(~~e~~***g***) Solicited local and systemic adverse events (AEs: Section 10.1.2) ***and unsolicited AEs*** will be recorded daily in diary cards for Days 1-7~~, and unsolicited AEs for Days 1-28~~, after vaccination.
(~~f~~***h***) AEs leading to Early Termination will be recorded by the investigator.
(~~g~~***i***) SAEs will be collected for the duration of the trial and will be reported to the Sponsor within 24 hours of the investigator becoming aware of the event.

Table 2b

Errors in the table and footnotes have been corrected with additional cross-references added in the table where appropriate. The footnotes now read:

ET: Early Termination. Use of (X) indicates samples or procedures that generally will not be performed but may be performed to investigate an AE, or at the time of premature discontinuation.

(a) Eligibility by review of relevant inclusion/exclusion criteria will be documented before enrollment.

(b) Only vaccines administered since the last visit should be recorded.

(~~b~~***c***) Physical exam on Day 1 (Section 9.1.4). All subsequent physical examinations may be performed if deemed necessary and will be symptom-directed and should assess clinically significant changes from the baseline examination. For any procedures at the site, the investigator shall follow his/her standard practice.

(~~c~~***d***) Vital signs: as defined in Section 9.1.5.

(~~d~~***e***) sIPV or reference IPV. ***After vaccination, subjects will be observed for at least 30 minutes including observation for immediate reactions and body temperature measurement.***

(~~e~~***f***) Diary cards will be distributed on the day of vaccination, and collected at the return visit on Day 29.

(~~f~~***g***) Solicited local and systemic adverse events (AEs: Section 10.1.2) will be recorded daily in diary cards for Days 1-7, and unsolicited AEs for Days 1-28.

(~~g~~***h***) AEs leading to Early Termination will be recorded by the investigator.

(~~h~~***i***) SAEs will be collected for the duration of the trial and will be reported to the Sponsor within 24 hours of the investigator becoming aware of the event.

(~~i~~***j***) Blood should be drawn prior to vaccination

Table 2c

Errors in the table and footnotes have been corrected with additional cross-references added in the table where appropriate. Information on vaccines administered will be collected at all visits. Adverse events will be collected on Days 36, 64, 372 and 393; an "X" has been added. Demographics will not be recorded at Day 365/Visit 9; ("X") removed. "Anchor to Study Visit 1" has been corrected to "Anchor to Study Visits". The footnotes now read:

ET: Early Termination. Use of (X) indicates samples or procedures that generally will not be performed but may be performed to investigate an AE, or at the time of premature

	discontinuation. (a) Eligibility by review of relevant inclusion/exclusion criteria will be documented before enrollment. ***Continuing eligibility (by review of relevant inclusion/exclusion criteria and criteria for delay of vaccination) will be documented before each vaccination.*** ***(b) Only vaccines administered since the last visit should be recorded.*** (~~b~~***c***) Physical exam on Day 1 (Section 9.1.4). All subsequent physical examinations may be performed if deemed necessary and will be symptom-directed and should assess clinically significant changes from the baseline examination. For any procedures at the site, the investigator shall follow his/her standard practice. (~~c~~***d***) Vital signs: as defined in Section 9.1.5. (~~d~~***e***) sIPV or reference IPV. ***Polio vaccine should be administered concomitantly with DTP-HBV-Hib on Days 1, 29 and 57. After vaccination, subjects will be observed for at least 30 minutes including observation for immediate reactions and body temperature measurement.*** (~~e~~***f***) Diary cards will be distributed on the day of each vaccination, and will be collected at the return visit 28 days later. (~~f~~***g***) Solicited local and systemic adverse events (AEs: Section 10.1.2) will be recorded daily in diary cards for Days 1-7, and unsolicited AEs for Days 1-28, after each vaccination. (~~g~~***h***) AEs leading to Early Termination will be recorded by the investigator. (~~h~~***i***) SAEs will be collected for the duration of the trial and will be reported to the Sponsor within 24 hours of the investigator becoming aware of the event. (~~i~~***j***) Blood should be drawn prior to vaccination.
3.3	National Program on Immunization (NPI) was added to the list of abbreviations
4.1	This trial will assess the safety and tolerability as well as the immunogenicity of Takeda's stand-alone sIPV candidate to identify the optimal formulation ~~that meets with the currently available standard of care~~ ***to take forward into advanced stage studies to show the immunogenicity and safety of the final candidate vaccine.***
4.2	Following a lead-in study of the safety and tolerability of the highest anticipated dosage in primed (after full primary poliovirus vaccination) adults followed by toddlers, the descriptive dosage-ranging study in infants will allow selection of the dosage to take forward into ***advanced stage*** studies ~~powered to show the non-inferiority of the final candidate vaccine against the current standard of care, i.e. licensed IPV vaccine.~~ This decision will be based on the WHO recommendations for assessment of IPV vaccines [4], and will use the seroconversion rate after completion of the three-dose primary schedule as primary measure. A control group will receive a ~~licensed,~~ reference IPV ~~to allow~~ ***for*** descriptive comparison ~~with the normal standard of care~~. In the infant dose ranging cohort**,** the control group will provide a comparator for the safety and tolerability of the different sIPV dosages. Assessing immunogenicity in the comparator control arm in the infant cohort will provide background information to show that the three groups ~~who~~ ***that*** receive the different dosages of sIPV all achieve adequate levels of immunity~~, similar to that provided by the current standard of care,~~ and so are not put at risk of poliovirus infection. The primary endpoint for the immunogenicity analysis is the seroconversion rate achieved in infants four weeks after the last of three primary doses of sIPV, in accordance with WHO recommendations for the assessment of IPV [4]. The study is not powered for statistical comparisons, and all comparisons will be descriptive. It is only designed to select

	a dosage formulation from consideration of an interim analysis performed on the data obtained 28 days after the third primary immunizations at Day 85. The selected formulation will be taken into larger phase 3 trials for advanced stage clinical development ***to show the immunogenicity and safety of the final candidate vaccine***.
5.1.2	Subsections in Section 5.1.2 ***Safety*** amended to ***Safety and tolerability***
5.2	*Immunogenicity, separately for poliovirus types 1, 2, and 3 for both Sabin and Salk strains* <u>Infant dose ranging cohort</u> ~~• SCR on Day 393 (28 days after booster vaccination).~~ • Seropositivity/seroprotection rate (SPR, defined as the percentage of subjects with antibody titers ≥ 8) on Days 85, 365, and 393 (28 days after booster vaccination).
6.1	B). Toddler lead-in cohort The second lead-in cohort of 60 healthy toddlers at 12–15 months of age inclusive, will be enrolled and randomized to two equal groups. Each group will receive, in an observer-blind fashion, a single intramuscular injection of high dose sIPV containing 3, 100, and 100 DU of poliovirus types 1, 2, and 3, respectively (Day 1), or ~~a licensed,~~ reference IPV. Polio vaccines previously received for primary immunization of these children will be recorded. Routine ~~infant~~ **childhood** vaccines other than poliovirus vaccine for booster immunization recommended for children at approximately 12 months of age according to ~~national guidelines~~ **the NPI** (eg, measles**-containing** vaccine) are to be given at least 4 weeks ~~after~~ **apart from** sIPV / reference IPV booster vaccination. ~~Routine infant vaccines according to the national immunization program~~ **NPI-recommended childhood vaccines other than poliomyelitis vaccine** will be given outside the trial.
	Individual titers pre and post booster vaccination will be assessed. Toddlers who receive sIPV and who have no neutralizing antibodies to any of the three poliovirus serotypes (titer <8) on Day 29 as well as those with no titer increase between Day 1 and Day 29 will be offered re-vaccination with a single dose of ~~a locally-available standard polio vaccine~~ ***the reference IPV*** (note: toddlers that have received bivalent OPV exclusively for primary immunization may not achieve seropositivity to poliovirus type 2. Therefore, subjects with documented primary immunization against serotypes 1 and 3 only who do not respond to serotype 2 post sIPV booster will not be offered re-vaccination).
	C). Infant dose ranging cohort Routine infant vaccines according to the ~~national immunization program~~ ***NPI*** other than poliovirus vaccine for primary immunization and for booster vaccination are to be given according to national guidelines outside the trial. Inactivated / oral routine infant vaccines should be given on the same day as sIPV / reference IPV. Injectable live-attenuated vaccines (eg, measles***-containing*** vaccine) should be given at least 4 weeks apart from sIPV / reference IPV. Infants who receive sIPV and who have no neutralizing antibodies to any of the three poliovirus serotypes (titer <8) on Day 393 will be offered re-vaccination with a ~~single~~ series of three ~~primary~~ immunizations ~~of a locally-available standard polio vaccine~~ ***of reference IPV*** <u>after the unblinding occurs and serological results become available, and outside of the IPV-102 clinical trial</u>.

6.2	The control groups ***in the toddler lead-in and infant dose ranging cohorts*** will provide background data on the safety of ~~standard~~ ***reference*** IPV immunizations in the study population against which to assess the safety and tolerability of sIPV.
7.3	After enrollment, subjects may encounter clinical circumstances that warrant a delay in the administration of trial vaccination. These situations are listed below. In the event that a subject meets a criterion for delay of vaccination, the subject may receive trial vaccination once the window for delay has passed as long as the subject is otherwise eligible for trial participation. • Individuals with a clinically significant active infection (as assessed by the investigator) or temperature ≥ 38.0°C / 100.4°F, within 3 days of intended trial vaccination (consider whether applicable as a criterion for delay or as an exclusion criterion, see Section 7.2). • Individuals who have received blood, blood products and/or plasma derivatives or any parenteral immunoglobulin preparation within the past 3 months prior to any dose (consider whether applicable as a criterion for delay or as an exclusion criterion, see 7.2). • Individuals who received any other vaccines within 28 days prior to planned vaccination or blood sampling. • ***Individuals who have used antipyretics/analgesic medications within 24 hours prior to planned vaccine administration.*** If vaccinations cannot be given within the visit window as defined by the protocol, the subject may receive the vaccination outside the visit window. This will be considered as a protocol deviation. All subjects should receive all vaccinations necessary to fulfill the locally recommended ***NPI*** schedule.
8.1	Takeda's stand-alone sIPV is a trivalent vaccine containing formaldehyde-inactivated Sabin poliovirus strains types 1, 2, and 3 formulated with CCI aluminum [as $Al(OH)_3$]. Additional excipients are: phosphate buffer at CCI as well as CCI 2-phenoxyethanol per 0.5 mL dose. Three formulations of the sIPV containing different antigen concentrations of the three Sabin strains will be used: • Low dose 'L': sIPV per poliovirus type 1, 2, and 3: DU 0.75:25:25, • Medium dose 'M': sIPV per poliovirus type 1, 2, and 3: DU 1.5:50:50 and • High dose 'H': sIPV per poliovirus type 1, 2, and 3: DU 3:100:100. ~~Licensed r~~***R***eference IPV: antigen content is assumed to comply with the ***corresponding*** product label ***(see the Pharmacy Manual)***. ***Pentavalent infant vaccine: DTP-HBV-Hib: antigen content is assumed to comply with the corresponding product label (see the Pharmacy Manual)***. The doses should be prepared at the time of administration by the unblinded administrator (and/or pharmacist) per the Pharmacy Manual.

8.1.1	In this protocol, study medication refers to the trivalent polio vaccine sIPV, the reference IPV, ***pentavalent infant vaccine,*** and placebo. Study medication outer cartons/kits will be packaged and labelled with a tamper seal. The inner primary packaging will be unblinded and dose preparation will be carried out by unblinded site personnel. This trial will involve the use of three sIPV trivalent polio vaccine formulations for intramuscular administration that were manufactured and filled at Takeda's manufacturing plant in Hikari, Japan. ***In addition***, a reference IPV (toddler and infant cohorts ~~only~~) and placebo (adult cohort ~~only~~) ***will be provided for control groups and a pentavalent DTP-HBV-Hib vaccine will be provided for the infant dose ranging cohort to complete childhood immunizations. In case the reference IPV and / or the pentavalent vaccine cannot be sourced locally, Takeda will import these vaccines from a country/countries where the respective vaccine(s) is/are licensed.***
8.1.1.1	Study medications described in this protocol (sIPV, reference IPV***, pentavalent infant vaccine,*** and placebo) will be supplied by the sponsor. The Takeda sIPV single-dose vials will be supplied in a labeled, single-use vial and carton (0.5 mL) dose for intramuscular injection, preferably in the right limb. Each vial and carton will contain a label that includes pertinent trial information and caution statements. The label text will be in the specific country language, depending on local requirements. The vaccine to be used will be identifiable by a unique identification number and managed by the interactive response technology (IRT) system. ~~Depending on the IPV in use in the country selected for the study, t~~***T***he reference IPV will be presented in a blinded or open label carton. Should the primary container/packaging be open label, unblinded pharmacy and administration teams at the site will be required for dose preparation, administration and accountability. Each reference IPV and carton will contain a label ~~that includes pertinent trial information and caution statements~~. The label text, ***which includes pertinent trial information and caution statements,*** will be in the specific country language, depending on local requirements ***and will be included in the Pharmacy Manual and in the ICF for the toddler lead-in and infant dose ranging cohorts***. The placebo (saline control) will be 0.9% sodium chloride for injection without preservatives. ***Vaccination against D, T, P, HBV and Hib will be given as pentavalent combination vaccine (DTP-HBV-Hib). The pentavalent infant vaccine will be sourced as trial vaccine.*** All doses should be prepared at the time of administration by the unblinded administrator (and/or pharmacist) per the Pharmacy Manual.
8.1.1.2	*Routine ~~Infant~~ Vaccines for Primary Immunizations and Booster Vaccinations* ~~Appropriate medication for the local vaccination schedule~~ ***NPI-recommended routine vaccines (other than poliomyelitis vaccine and pentavalent vaccine, see above)*** will be sourced locally by the site and administered in accordance with the approved package labeling. Additional injectable routine infant vaccines given concomitantly will be administered in a limb different from that of the sIPV / reference IPV vaccination.
8.1.3	An additional cross-reference has been added, with its corresponding footnote: ***(b) Subjects will also receive DTP-HBV-Hib vaccine at the same visit; pentavalent vaccine will be administered in a limb different from that of the sIPV / reference IPV vaccination.***

8.4	~~The trial vaccine blind will be maintained using IRT.~~ ***This trial is an observer-blind study. The subjects, data collectors (eg investigator), and data evaluators (eg trial statisticians) are blinded to the material administered. The investigational product assignment will be maintained by the unblinded site staff designee.*** ***All care must be taken to ensure that the unblinded reports and documents are shared only with unblinded personnel and properly stored in a secured area, accessible only by authorized personnel.***
8.5	If any subject is unblinded, the subject must be withdrawn from the trial, and their data no longer evaluated. However, further doses of ~~trial~~ vaccine are to be administered to ensure completion of the ~~nationally~~ ***NPI*** recommended schedule, and they should be monitored for safety parameters.
8.6	The investigator or designee must ensure that the sponsor-supplied vaccine is used in accordance with the approved protocol and is administered only to subjects enrolled in the trial. To document appropriate use of sponsor-supplied vaccines (sIPV, reference IPV***,*** ~~and~~ placebo***, and DTP-HBV-Hib***), the investigator must maintain records of all sponsor-supplied vaccine delivery to the site, site inventory, administration and use by each subject, and return to the sponsor or designee.
	The investigator must record the current inventory of all sponsor-supplied vaccines (sIPV, reference IPV***,*** ~~and~~ placebo***, and DTP-HBV-Hib***) on a sponsor-approved vaccine accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied vaccines, expiry date and amount. The IRT should include all required information as a separate entry for each subject to whom sponsor-supplied vaccine is administered.

9.1.2	Demographic information to be obtained will include ~~age~~ ***date of birth***, sex, and race as described by the subject or the subject's LAR. Medical History will also be collected, including but not limited to any medical history that may be relevant to subject eligibility for trial participation such as gestational age and birth weight ***(for infants in the dose ranging cohort only)***, prior vaccinations, concomitant medications, and previous and ongoing illnesses or injuries. Relevant medical history can also include any medical history that contributes to the understanding of an AE that occurs during trial participation, if it represents an exacerbation of an underlying disease/preexisting problem. All medications, vaccines and blood products taken or received by the subjects within: a) Medications: 4 weeks prior to the start of the trial b) Vaccines: 4 weeks prior to the start of the lead-in study. Infants in the dose ranging study should only have received any routine vaccines recommended ***by the NPI*** at birth. Information on previous polio vaccinations should be collected for toddlers in the lead-in cohort. c) Blood products: 4 weeks prior to the start of the trial are to be recorded on the Prior and Concomitant Medications eCRF. The use of antipyretics and/or analgesic medications within 24 hours prior to vaccination must be identified and the reason for their use (prophylaxis versus treatment) must be described in the source documents or the eCRF. Trial vaccination should be delayed if subjects have used antipyretics/analgesic medications within 24 hours prior to vaccine administration.
9.1.5	Vital signs to be measured in this study are respiratory and heart rates, ~~height and weight,~~ ***and*** temperature (preferably measured as oral temperature for the adult cohort and rectal temperature for the toddler and infant cohorts). ***For the adult lead-in cohort, height and weight are measured at enrollment only; for the toddler lead-in cohort, height and weight are measured at enrollment and at the last study visit. For the infant dose ranging cohort, height and weight are measured at each visit.***
9.1.8	For female subjects of childbearing potential, ~~urine~~ pregnancy testing will be performed on Day 1 prior to ~~vaccination~~ ***enrollment***. Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy and donation of ova. Women of childbearing potential will receive guidance with respect to the avoidance of pregnancy as part of the trial procedures (Section 2.1).
9.1.9	Should a pregnancy occur after the administration of a blinded trial vaccine, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive ~~unblended~~ ***unblinded*** treatment information, the individual blind should be broken by the investigator and procedures must be followed as described in Section 8.5.

9.3.1	1. Confirm informed consent and complete signing of informed consent form. 2. Demographics. ~~a)~~***3.*** Prior and concomitant medication. This should include the vaccines that will be concomitantly administered with the trial vaccine at this visit. ~~b)~~***4.*** Medical history. ~~3. Review of systems: Review of systems is a structured interview that queries the subject (adult cohort) or the subject's LAR (toddler and infant cohorts) as to any complaints the subject has experienced across each organ system.~~ 4***5***. "~~Complete~~" physical examination and temperature. ***Physical examination.*** ~~5~~***6***. Vital signs. ~~6~~***7***. Review of eligibility criteria. ~~7~~***8***. Enrollment***/randomization***. ~~9. Randomization.~~ 9. Blood sampling for toddler lead-in and infant dose ranging cohorts. Blood should be taken from the subject in the infant cohort using an aseptic venipuncture technique for serological immunogenicity testing.
9.3.9	No post-trial care will be provided, except to ensure that all subjects in the toddler lead-in and infant dose ranging cohorts receive their complete number of polio vaccine doses as recommended by the ~~national schedule~~***NPI***, and that toddlers from both the lead-in cohort and the dose ranging cohort (after their booster dose) who received the trial sIPV vaccine are seropositive or have demonstrated a vaccine response which shows seroprotection. Toddlers from the lead-in cohort who do not meet these criteria will be offered a single dose of ~~a locally available standard polio vaccine~~ ***the reference IPV*** (note: toddlers that have received bivalent OPV exclusively for primary immunization may not achieve seropositivity to poliovirus type 2. Therefore, subjects with documented primary immunization against serotypes 1 and 3 only who do not respond to serotype 2 post sIPV booster will not be offered re-vaccination). Toddlers in the dose ranging cohort, who received sIPV as infants in their primary series and their toddler booster dose, and who have no neutralizing antibodies to any of the three poliovirus serotypes (titer <8) on Day 393 will be offered re-vaccination with a ~~single~~ series of three ~~primary i~~mmunizations of ~~a locally available standard polio vaccine~~ ***the reference IPV*** after the unblinding occurs and serological results become available, and outside of the IPV-102 clinical trial.
11.2.1	~~Details of the independent DMC will be captured in a charter prior to the start of the trial.~~ ***The DMC will have study-specific responsibilities to review IPV-102 data and decide on the enrollment of the toddler and infant cohorts after reviewing 7 days of safety and tolerability follow-up post vaccination in adults in the lead-in cohort. In addition, the DMC will evaluate the overall tolerability and safety of Takeda's sIPV on an ongoing basis. The DMC will be entitled to stop enrollment of additional subjects or to stop administration of additional sIPV doses. The composition, role and responsibilities of the DMC are presented in a separate DMC Charter.***
15.0	ICH Harmonized ~~Tripartite~~ Guideline for GCP
Appendix D	To permit flexibility in testing, Viroclinics Biosciences has been added to the contract laboratories in the Serology Plan.

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2.0 TRIAL SUMMARY

Name of Sponsor(s):	**Product Name:**
Takeda Vaccines, Inc. One Takeda Parkway Deerfield, IL 60015 USA	Stand-alone Trivalent Sabin Inactivated Poliomyelitis Vaccine (sIPV) (TAK-195)

Trial Title: A Randomized, Observer-Blind, Controlled Phase 1/2 Trial to Evaluate the Safety, Tolerability and Immunogenicity of Different Doses of a Stand-alone Trivalent, Inactivated Poliomyelitis Vaccine from Sabin Strains in Healthy Infants, with a Safety and Tolerability Age-Step Down Lead-in in Healthy Adults followed by Healthy Toddlers.

IND No.: Not applicable	**EudraCT No.:** Not applicable	
Study Identifier: IPV-102	**Phase:** 1/2	**Trial Blinding Schema:** Observer-blind

Background and Rationale:

Poliomyelitis is an acute infectious disease caused by any of 3 poliovirus serotypes (types 1, 2, or 3), spread by fecal-to-oral and oral-to-oral routes. Approximately 25% of those infected develop transient minor symptoms including fever, headache, malaise, nausea, vomiting, and sore throat, and on rare occasions is complicated with signs suggestive of aseptic meningitis. After infection, an average of 1 in 200 susceptible individuals develops paralytic poliomyelitis - depending on age and serotype - of whom 5-10% suffer viral destruction of bulbar cells resulting in respiratory paralysis and death.

Immunity acquired following infection is considered to provide serotype-specific lifelong protection against paralytic poliomyelitis. Similarly, induction of circulating antibodies through vaccination is an excellent indicator of protection against clinical disease, so post-vaccination seropositivity rates are considered to equate with seroprotection rates. Currently, two types of vaccines against poliomyelitis are available to control the disease in most parts of the world: injectable Inactivated Poliomyelitis Vaccine (IPV), and live Oral Poliomyelitis Vaccine (OPV). The introductions of IPV in 1955 (Jonas Salk) and OPV in 1963 (Albert Sabin) have led to a near eradication in poliomyelitis worldwide. Since the Global Polio Eradication Initiative (GPEI) was initiated by the World Health Assembly (WHA) in 1988, cases of polio have decreased by over 99%. One of the three serotypes, poliovirus type 2, was officially declared to be globally eradicated in September 2015, the last case being reported in 1999, and no cases of type 3 wild poliovirus have been reported since November 2012. Wild type 1 poliovirus is currently circulating in only three countries, Afghanistan, Pakistan and Nigeria.

With the global eradication of wild-type 2 poliovirus, trivalent OPV has been withdrawn globally since April 2016, and only bivalent OPVs (types 1 and 3) are now in use. Currently, OPV is used in polio-endemic countries, in countries at high risk for importation of polio and/or intermediate-to-high potential for transmission. OPV has several advantages over IPV: it is easy to administer in resource-poor settings, it allows for the vaccine virus to spread to contacts resulting in contact immunity beyond the vaccinated individual, and it elicits a better intestinal immunity. In addition, it is safer and, hence, easier and cheaper to manufacture as it does not involve the amplification of wild poliovirus, which reduces production costs. However, on rare occasions, the attenuated Sabin strains can cause vaccine-associated paralytic poliomyelitis (VAPP). A further risk is the occurrence of mutations that can revert the attenuated strain into a neurovirulent form of poliovirus leading to circulating vaccine-derived poliovirus (cVDPV), with the potential of outbreaks of VAPP. For this reason, OPV is not suitable for long-term control of polio and IPV will be the cornerstone towards final eradication.

The GPEI Polio Eradication and Endgame Strategic Plan 2013–2018 is a comprehensive, long-term strategy that calls for all countries to introduce at least one dose of IPV into their national routine immunization schedules together with the replacement of trivalent OPV with bivalent OPV from April 2016, before the eventual withdrawal of all forms of OPV immunization. The GPEI recommendation that all children receive at least one dose of IPV with the introduction of bOPV which will help to:

- ***Reduce the risk of poliovirus type 2-associated VAPP as well as a potential re-emergence of type 2 cVDPV.*** With withdrawal of OPV type 2, IPV maintains immunity against type 2 poliovirus, leading to lower risk of re-emergence or reintroduction of wild or vaccine-derived type 2 poliovirus.
- ***Interrupt transmission in the case of outbreaks.*** In the event of a type 2 outbreak and use of monovalent OPV type 2, people primed with IPV would be expected to have a stronger immune response, thus facilitating outbreak control and interruption of polio transmission.
- ***Hasten polio eradication.*** IPV will boost immunity against poliovirus types 1 and 3 in OPV-immunized children, to further accelerate eradication of these two wild viruses.

The costs per vaccine dose of IPV and the current production capacity limit the wide use and availability of IPV, particularly in low-income countries. A major component of the strategy to achieve a polio-free world is to make IPV vaccines more affordable and more widely accessible, eg, by antigen dose-sparing strategies (eg, formulations containing fractional antigen doses through the addition of an adjuvant and/or by administration by intradermal delivery), immunization schedule reduction (fewer vaccine doses), and/or approaches to reduce vaccine production costs.

Current IPVs are based on virulent wild-type poliovirus strains and are considered as very safe and effective. However, the use of wild-type poliovirus for vaccine manufacturing carries the risk of accidental re-introduction of wild poliovirus into the environment and will be discouraged in the post eradication era. Moreover, containment requirements for all polioviruses will increase from level-2 to an equivalent of level-3 further increasing production costs. An alternative way to manufacture safe and affordable IPV is the development and application of production processes that avoid wild-type poliovirus.

The objective of the Takeda program is to supply affordable Sabin-based IPV (sIPV) to GAVI countries as part of the Polio Eradication and Endgame Strategic Plan. As a basis for developing and producing IPV based on non-virulent Sabin strains (types 1, 2, and 3), Takeda CCI [redacted] previously manufactured and tested Sabin-based IPV (sIPV) in Japan as part of a combination vaccine candidate (DTaP-sIPV). Takeda's approach to a more affordable sIPV is to reduce vaccine production costs using a new technology platform. In addition, Takeda will leverage on existing manufacturing capacities as the company has an established manufacturing facility in Hikari, Japan, which is production-ready and has capacity for inventory build-up in preparation of delivery and access globally.

The primary indication for sIPV is the immunization of infants and toddlers (primary series + booster) against poliomyelitis caused by any of the three polio strains.

This trial will assess the safety and tolerability as well as the immunogenicity of Takeda's stand-alone trivalent sIPV candidate to identify the optimal formulation to take forward into advanced stage studies to show the immunogenicity and safety of the final candidate vaccine. The trial will be conducted in accordance with the protocol, ICH-GCP Guidelines and applicable regulatory requirements.

Trial Design:

This is a Phase 1/2, randomized, observer-blind, safety, tolerability, and dose ranging trial on a stand-alone trivalent inactivated poliomyelitis vaccine derived from Sabin strains in healthy infants with a lead-in in healthy adults followed by healthy toddlers.

The trial will start with an adult cohort (n = 40) in a safety and tolerability lead-in of the highest dosage of sIPV compared with placebo. Unblinded safety and tolerability assessments post vaccination will be reviewed by an independent Data Monitoring Committee (DMC) who will recommend whether or not vaccination of younger cohorts can proceed. The toddler lead-in cohort (n = 60) is designed to evaluate the safety and tolerability of the highest dosage of sIPV given as booster vaccination compared with the reference IPV. Blinded safety data from this cohort will be reviewed internally by Takeda before initiating the recruitment of the infant dose ranging cohort.

In the adult lead-in cohort, 40 healthy adults, 18-49 years of age inclusive, will be recruited to receive in an observer-blind fashion a single intramuscular injection of high dose sIPV containing 3, 100, and 100 D-antigen units (DU) of poliovirus types 1, 2, and 3, respectively (Day 1), or placebo. Subjects must have completed primary immunization against poliomyelitis according to local recommendations. Safety and tolerability will be assessed 7 days post vaccine administration.

The total follow-up duration will be 7 days for adults in this cohort; they will have 2 clinical visits.

In the toddler lead-in cohort, 60 toddlers at 12 to 15 months of age inclusive, will be recruited to receive in an observer-blind fashion a single intramuscular injection of high dose sIPV containing 3, 100, and 100 DU for poliovirus types 1, 2, and 3, respectively (Day 1), or the reference IPV. Polio vaccines previously received for primary immunization will be recorded. Other routine vaccines for toddler immunizations as recommended by the locally applicable National Program on Immunization (NPI) for children shall be given at least 4 weeks apart from the sIPV / reference IPV booster vaccination. Safety and tolerability will be assessed 7 and 28 days post IPV administration. In addition, a final safety visit will be scheduled for 6 months post IPV booster administration.

Individual poliovirus neutralizing antibody titers pre and post booster vaccination will be assessed. Toddlers who receive sIPV and who have no neutralizing antibodies to any of the three poliovirus serotypes (titer <8) on Day 29 as well as those with no titer increase between Day 1 and Day 29 will be offered re-vaccination with a single dose of the reference IPV (note: toddlers that have received bivalent OPV exclusively for primary immunization may not achieve seropositivity to poliovirus type 2. Therefore, subjects with documented primary immunization against serotypes 1 and 3 only who do not respond to serotype 2 post- sIPV booster will not be offered re-vaccination).

The total follow-up duration will be 182 days for toddlers in the lead-in cohort, who will have 2 clinical visits and 2 telephone contacts.

In the infant dose ranging cohort, a total of 240 infants at 6 to 8 weeks of age, inclusive, with no previous history of poliomyelitis vaccination, will be enrolled and randomized to 4 equal study arms to receive 3 doses 4 weeks apart (on Day 1, Day 29, and Day 57) of either i) low concentration (0.75, 25, and 25 Du, formulation 'L', Arm 1), ii) medium concentration (1.5, 50, and 50 DU, formulation 'M', Arm 2), iii) high concentration (3, 100, and 100 DU, formulation 'H', Arm 3) sIPV, or iv) or a reference IPV (controls, Arm 4). The 3-dose primary IPV administrations will be performed concomitantly with routine NPI-recommended infant vaccinations. Solicited adverse events (AEs) will be assessed for 7 days and unsolicited adverse events for 28 days after each of the three vaccinations. Additional safety assessments will be performed 6 months (Day 183) and 12 months post first dose (Day 365) of the primary immunization. Serious adverse events (SAEs) will be recorded throughout the entire study period. Neutralizing antibodies to each of the three poliovirus types will be assessed before the first vaccination, and 28 days after the second and third primary vaccinations on Day 57 and Day 85.

Twelve months (Day 365) after first dose received for primary immunization, all subjects recruited in the dose ranging cohort will receive a booster vaccination containing the same sIPV formulation that was allocated for

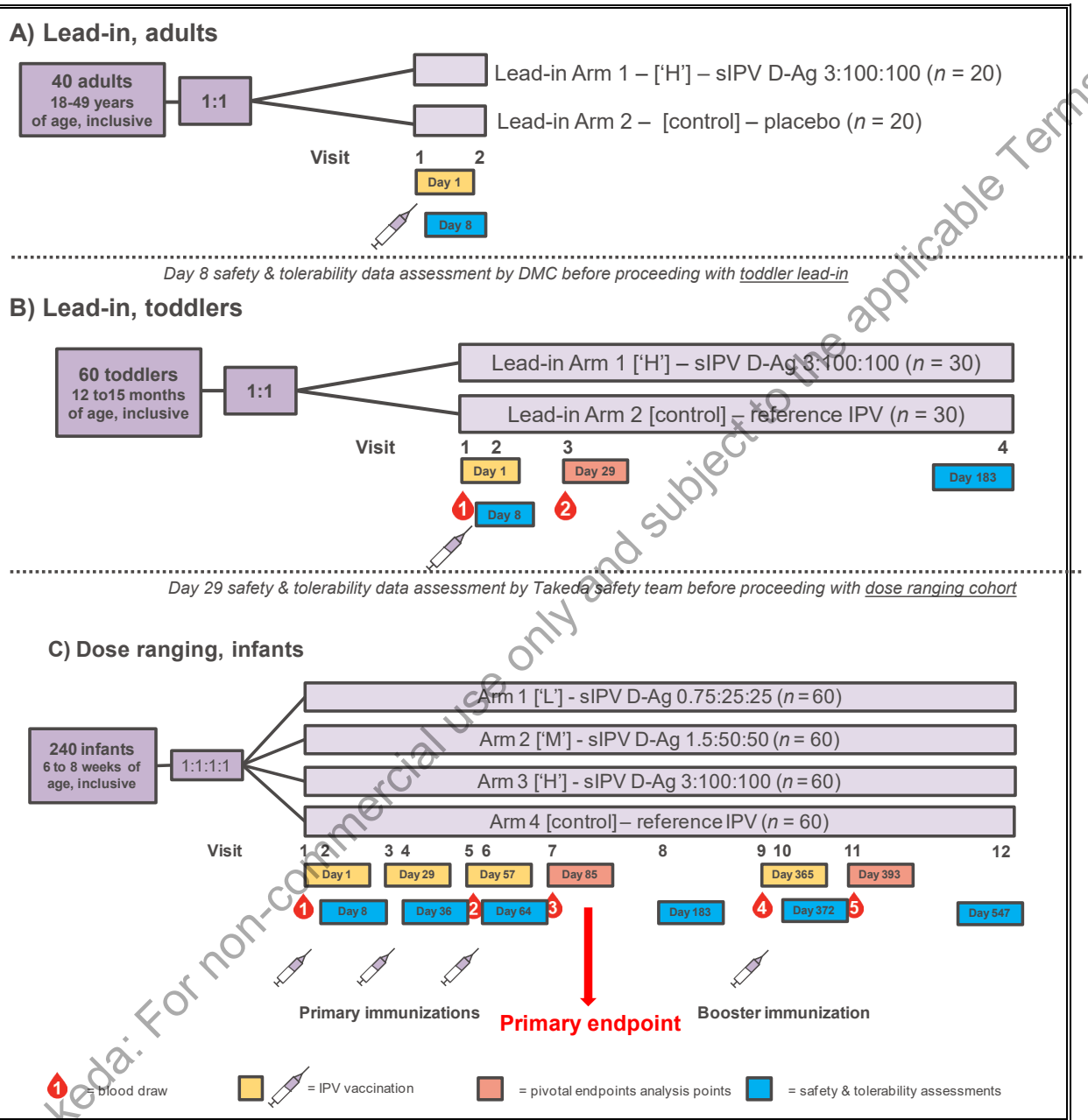
their primary immunization (Arms 1-3) or the reference IPV (Arm 4), concomitantly with NPI-recommended booster vaccinations. Solicited adverse events will be assessed for 7 days and unsolicited adverse events for 28 days after this booster vaccination, and SAEs will be recorded throughout the entire study period. Neutralizing antibodies to each of the three poliovirus types will be assessed before (Day 365) and 28 days after the booster vaccination (Day 393). Infants who receive sIPV and who have no neutralizing antibodies to any of the three poliovirus serotypes (titer <8) on Day 393 will be offered re-vaccination with a single series of three primary immunizations of the reference IPV after the unblinding occurs and serological results become available, and outside of the IPV-102 clinical trial.

Total follow-up duration will be 546 days for infants in the dose ranging cohort, who will have 6 clinical visits and 6 telephone contacts.

Primary evaluation of the trial objectives is planned at Day 85, 28 days after the third dose of a series of three IPV (sIPV or reference IPV) doses given for primary immunization in the infant dose ranging cohort.

An interim analysis will be performed when the safety, tolerability and immunogenicity data until Day 85 (28 days after the third dose of the primary immunization series) are available. The interim analysis will be performed by a separate set of unblinded statisticians who will have access to individual treatment assignments, but will not be involved in subsequent study conduct. Other personnel involved in the conduct of the study, including those at Takeda, the contract research organization (CRO), and the study sites, will remain blinded to the individual subject data (including treatment assignments) until unblinding after database lock post Day 547.

The figure below illustrates numbers of subjects as well as planned procedures / visits for the adult and toddler lead-in cohorts and the infant dose ranging cohort.



Primary Objective:

Infant dose ranging cohort only

To select for further development, the optimal antigen concentrations of the three Sabin poliovirus strains (types 1, 2, and 3) of the stand-alone trivalent sIPV by comparing the three sIPV study arms based on two parameters:

- the safety and tolerability profile after each dose of primary immunization
- the seroconversion rates (SCR) for poliovirus types 1, 2, and 3 for both Sabin and Salk strains, after the final dose of a three dose primary immunization series (Day 85)

Secondary Objectives:

Safety and tolerability:

Adult lead-in cohort

- To compare the safety and tolerability profile in the high dose sIPV arm with the control arm in adults after a single vaccination.

Toddler lead-in cohort

- To compare the safety and tolerability profile in the high dose sIPV arm with the reference IPV (control) arm in toddlers after a single booster vaccination.

Infant dose ranging cohort

- To compare the safety and tolerability profile of each sIPV study arm with the reference IPV (control) arm after each primary immunization.
- To compare the safety and tolerability profile between sIPV study arms, and between each sIPV study arm and the reference IPV (control) arm, after booster vaccination.

Immunogenicity:

Infant dose ranging cohort

- To compare between each sIPV study arm and the reference IPV (control) arm, the SCR separately for poliovirus types 1, 2, and 3 for both Sabin and Salk strains, after the final dose out of a series of three doses for primary immunization (Day 85).
- To compare between sIPV study arms, and between each sIPV study arm and the reference IPV (control) arm, the seropositivity/seroprotection rates (SPR) separately for poliovirus types 1, 2, and 3 for both Sabin and Salk strains, after the final dose out of a series of three doses for primary immunization (Day 85).
- To compare between sIPV study arms, and between each sIPV study arm and the reference IPV (control) arm, the geometric mean titers (GMT) separately for poliovirus types 1, 2, and 3 for both Sabin and Salk strains, after the final dose out of a series of three doses for primary immunization (Day 85).
- To compare between sIPV study arms, and between each sIPV study arm and the reference IPV (control) arm, the SPR and GMT separately for poliovirus types 1, 2, and 3 for both Sabin and Salk strains, before the sIPV booster vaccination (Day 365).
- To compare between sIPV study arms, and between each sIPV study arm and the reference IPV (control) arm, the vaccine response rate (VRR), SPR, and GMT separately for poliovirus types 1, 2, and 3 for both Sabin and Salk strains, after the sIPV booster vaccination (Day 393).

Exploratory Objectives:

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[redacted]

Subject Populations:

Adult lead-in cohort:

Healthy subjects: yes

Planned Minimum Age: 18 years

Planned Number of Subjects: 40

Planned Number of Arms: 2 (randomly allocated, *n* = 20 per arm)

- Arm 1: sIPV formulation 'H', high concentration (3.0, 100, and 100 DU)
- Arm 2: placebo

Toddler lead-in cohort:

Healthy subjects: yes

Planned Minimum Age: 12 months

Planned Number of Subjects: 60

Planned Number of Arms: 2 (randomly allocated, *n* = 30 per arm)

- Arm 1: sIPV formulation 'H', high concentration (3.0, 100, and 100 DU)
- Arm 2: reference IPV.

Infant dose ranging cohort:

Healthy subjects: yes

Planned Minimum Age: 6 weeks

Planned Number of Subjects: 240

Planned Number of Arms: 4 (randomly allocated, *n* = 60 per arm)

- Arm 1: sIPV formulation 'L', low concentration (0.75, 25, and 25 DU)
- Arm 2: sIPV formulation 'M', medium concentration (1.5, 50, and 50 DU)
- Arm 3: sIPV formulation 'H', high concentration (3.0, 100, and 100 DU)
- Arm 4: reference IPV.

Criteria for Inclusion:

Adult Lead-in Cohort

- Male and female adults aged 18 to 49 years, inclusive, at the time of enrollment.
- Individuals who are in good health at the time of entry into the trial as determined by medical history, physical examination (including vital signs) and clinical judgment of the investigator.
- The subject signs and dates a written, informed consent form (ICF) and any required privacy authorization prior to the initiation of any trial procedures, after the nature of the trial has been explained according to local regulatory requirements.
- Individuals who can comply with trial procedures and are available for the duration of follow-up.
- Completed primary immunization against poliomyelitis according to local recommendations.

Toddler lead-in cohort:

- Male and female toddlers, aged 12 to 15 months, inclusive, at the time of enrollment.
- Toddlers in good health at the time of entry into the trial as determined by medical history, physical examination (including vital signs) and clinical judgment of the investigator.
- The toddler's legally authorized representative (LAR) signs and dates a written ICF and any required privacy authorization prior to the initiation of any trial procedures, after the nature of the trial has been explained according to local regulatory requirements.
- Toddlers and their LAR can comply with trial procedures, are available for the duration of the trial, and a suitable telephone contact is available.
- Completed primary immunization against poliomyelitis, preferably with IPV, according to local recommendations.

Infant dose ranging cohort**:**

- Male and female infants, aged 6 to 8 weeks (42 – 55 days, inclusive) at the time of enrollment.
- Infants in good health at the time of entry into the trial as determined by medical history, physical examination (including vital signs) and clinical judgment of the investigator.
- Infants must have been born full term (37-42 weeks of gestation).
- The infant's LAR signs and dates a written ICF and any required privacy authorization prior to the initiation of any trial procedures, after the nature of the trial has been explained according to local regulatory requirements.
- Infants and their LAR can comply with trial procedures, are available for the duration of follow-up, and a suitable telephone contact is available.

Criteria for Exclusion:

Adult lead-in cohort

- Individuals with body mass index (BMI) greater than or equal to 35 kg/m2 (= weight in kg / [height in meters * height in meters].
- Individuals with history of substance or alcohol abuse within the past 2 years.
- Female subjects who are pregnant or breastfeeding

Toddler lead-in cohort:

- Last polio vaccination (either inactivated or oral) received within 5 months prior to first trial visit.
- Household member/sibling who had received or is/are scheduled to receive OPV in the previous 3 months until 5 weeks post subject's inclusion in the study.
- Prior vaccination with booster dose of diphtheria, tetanus, pertussis (acellular or whole cell), polio (either inactivated or oral), or *Haemophilus influenzae* type b (Hib) vaccines.

Infant dose ranging cohort:

- Infants with low birth weight according to local standards.
- Prior vaccination with polio vaccines (either inactivated or oral).
- Household member/sibling that had received or is/are scheduled to receive OPV in the previous 3 months until 5 weeks after the third dose of the primary immunization series.
- Prior vaccination with any diphtheria, tetanus, pertussis (acellular or whole cell), *Haemophilus influenzae* type b (Hib) vaccine or polio vaccine (OPV or IPV). Note, BCG at birth and prior vaccination with Hepatitis B vaccine given at least 28 days prior to first trial visit are not exclusion criteria.

All cohorts:

- Known hypersensitivity or allergy to any of the vaccine components (including excipients) or standard infant vaccines.
- Any significant chronic infection.
- Any clinically significant active infection (as assessed by the investigator) or temperature ≥38.0°C/100.4°F, within 3 days of intended trial vaccination.
- Subjects who received any vaccine within 28 days prior to enrollment in this trial.
- Any serious chronic or progressive disease according to the judgment of the investigator (eg, cardiac, renal or hepatic disease).
- Individuals with history, eg, convulsions/febrile convulsions, or any illness, that, in the opinion of the investigator, might interfere with the results of the trial or pose additional risk to the subjects due to participation in the trial.

The full list of exclusion criteria is included in protocol.

Trial Vaccine(s):

Investigational Vaccine:

Takeda's stand-alone sIPV is a trivalent vaccine containing formaldehyde-inactivated Sabin poliovirus strains types 1, 2, and 3 formulated with CCI aluminum [as $Al(OH)_3$] for protection against poliomyelitis caused by any of the three circulating poliovirus types by generation of neutralizing antibodies. Additional excipients are: phosphate buffer at CCI as well as CCI 2-phenoxyethanol per 0.5 mL dose. The vaccine will be manufactured and filled at Takeda's manufacturing plant in Hikari, Japan. Vaccine will be provided in single-dose vials for intramuscular injection.

Three formulations of the sIPV containing different antigen concentrations of the three Sabin strains (types 1, 2 and 3) will be assessed in this trial:

- Low dose 'L': sIPV per poliovirus type 1, 2, and 3: D-Ag units (DU) 0.75:25:25
- Medium dose 'M': sIPV per poliovirus type 1, 2, and 3: D-Ag units (DU) 1.5:50:50
- High dose 'H': sIPV per poliovirus type 1, 2, and 3: D-Ag units (DU) 3:100:100

Subjects in the adult and toddler lead-in cohorts will receive high dose sIPV.

Control Vaccines:

Adult lead-in cohort:

Subjects in the control arm of the adult lead-in cohort will receive placebo.

Toddler lead-in and infant dose ranging cohorts:

Subjects in the control arms of the toddler lead-in cohort and infant dose ranging cohort will receive stand-alone trivalent IPV (reference IPV). The reference IPV will be sourced and provided by Takeda as trial vaccine. The reference IPV will be selected based on supportive evidence for its use in infants as young as 6 weeks.

Routine vaccines for primary immunizations and booster vaccinations:

Toddler lead-in cohort:

Routine childhood vaccines other than poliomyelitis vaccine for booster immunization recommended for children at approximately 12 months of age according to the NPI (eg, measles-containing vaccine) are to be given at least 4 weeks apart from sIPV / reference IPV booster vaccination. NPI-recommended childhood vaccines other than poliomyelitis vaccine will be given outside the trial.

Infant dose ranging cohort:

Vaccination against diphtheria (D), tetanus (T), pertussis (P), hepatitis B (HBV) and *Haemophilus influenzae* type b (Hib) will be given as pentavalent combination vaccine (DTP-HBV-Hib). The pentavalent vaccine will be sourced and provided by Takeda as trial vaccine.

All other routine infant vaccines (other than poliomyelitis vaccine and pentavalent vaccine) for primary immunization and for booster vaccination at approximately 12 months of age will be given concordant with NPI recommendations outside the trial. Inactivated / oral routine infant vaccines should be given on the same day as sIPV / reference IPV. Injectable live-attenuated vaccines (eg, measles-containing vaccine) should be given at least 4 weeks apart from sIPV / reference IPV.

Route of administration: sIPV / reference IPV / placebo will be administered by IM injection, preferably in the right limb. Additional injectable inactivated routine infant vaccines given concomitantly to infants in the dose ranging cohort will be administered in a limb/limbs different from the one used for sIPV / reference IPV vaccination.

Duration of the Trial:	**Period of Evaluation:**
Adult lead-in cohort: approximately 1 week	Adult lead-in cohort: 7 days
Toddler lead-in cohort: approximately 6 months	Toddler lead-in cohort: 182 days
Infant dose ranging cohort: approximately 18 months	Infant dose ranging cohort: 546 days

Main Criteria for Evaluation and Analyses:

The co-primary endpoints for this trial are in the infant dose ranging cohort only:

Safety:

- Percentage of subjects with solicited local reactions on a symptom by symptom basis, in each severity category, during the 7-day period (including day of vaccination) after each primary immunization dose of sIPV.
- Percentage of subjects with solicited systemic AEs on a symptom by symptom basis, in each severity category, during the 7-day period (including day of vaccination) after each primary immunization dose of sIPV.
- Percentage of subjects with a body temperature ≥ 38°C (defined as fever) during the 7-day period (including day of vaccination) after each primary immunization dose of sIPV.
- Percentage of subjects experiencing non-serious unsolicited AEs during the 28-day period (including day of vaccination) after each primary immunization dose of sIPV.
- Percentage of subjects experiencing SAEs throughout the entire trial duration in the sIPV study arms.

Immunogenicity, separately for poliovirus types 1, 2, and 3 for both Sabin and Salk strains for the three study arms:

- SCR = percentage of subjects in each arm who seroconvert, which is defined as:
  i) initially seronegative infants (titer <8 at Day 1) having a titer ≥ 8 at Day 85, or

ii) initially seropositive infants (titer ≥ 8 at Day 1) with a 4-fold rise in antibody titers over the expected level of maternal antibodies at Day 85, calculated using a decline from the Day 1 titer with a half-life of 28 days.

Secondary endpoints:

Safety and tolerability:

Infant dose ranging cohort

- Percentage of subjects with solicited local reactions on a symptom by symptom basis, in each severity category, during the 7-day period (including day of vaccination) after each primary immunization dose of sIPV or IPV.
- Percentage of subjects with solicited systemic AEs on a symptom by symptom basis, in each severity category, during the 7-day period (including day of vaccination) after each primary immunization dose of sIPV or IPV.
- Percentage of subjects with a body temperature ≥ 38°C (defined as fever) during the 7-day period (including day of vaccination) after each primary immunization dose of sIPV or IPV.
- Percentage of subjects experiencing non-serious unsolicited AEs during the 28-day period (including day of vaccination) after each primary immunization dose of sIPV or IPV.
- Percentage of subjects experiencing SAEs throughout the entire trial duration in the sIPV and IPV study arms.
- Percentage of subjects with solicited local reactions on a symptom by symptom basis, in each severity category, during the 7-day period (including day of vaccination) after booster vaccination.
- Percentage of subjects with solicited systemic AEs on a symptom by symptom basis, in each severity category, during the 7-day period (including day of vaccination) after booster vaccination.
- Percentage of subjects with a body temperature ≥ 38°C (defined as fever) during the 7-day period (including day of vaccination) after booster vaccination.
- Percentage of subjects experiencing non-serious unsolicited AEs during the 28-day period (including day of vaccination) after booster vaccination.

Toddler lead-in cohort

- Percentage of subjects with solicited local reactions on a symptom by symptom basis, in each severity category, during the 7-day period (including day of vaccination) after booster vaccination.
- Percentage of subjects with solicited systemic AEs on a symptom by symptom basis, in each severity category, during the 7-day period (including day of vaccination) after booster vaccination.
- Percentage of subjects with a body temperature ≥ 38°C (defined as fever) during the 7-day period (including day of vaccination) after booster vaccination.
- Percentage of subjects experiencing non-serious unsolicited AEs during the 28-day period (including day of vaccination) after booster vaccination.
- Percentage of subjects experiencing SAEs throughout the entire trial duration.

Adult lead-in cohort

- Number of subjects with solicited local reactions on a symptom by symptom basis, in each severity category, during the 7-day period (including day of vaccination) after a single dose of sIPV or placebo.

- Number of subjects with solicited systemic AEs on a symptom by symptom basis, in each severity category, during the 7-day period (including day of vaccination) after a single dose of sIPV or placebo.
- Number of subjects with a body temperature ≥ 38°C (defined as fever) during the 7-day period (including day of vaccination) after a single dose of sIPV or placebo.
- Number of subjects experiencing non-serious unsolicited AEs during the 7-day period (including day of vaccination) after a single dose of sIPV or placebo.
- Number of subjects experiencing SAEs during the 7-day period (including day of vaccination) after a single dose of sIPV or placebo.

Immunogenicity, separately for poliovirus types 1, 2, and 3 for both Sabin and Salk strains:

Infant dose ranging cohort

- Seropositivity/seroprotection rate (SPR, defined as the percentage of subjects with antibody titers ≥ 8) on Days 85, 365, and 393 (28 days after booster vaccination).
- GMT on Days 85, 365, and 393 (28 days after booster vaccination).
- VRR on Day 393 (28 days after booster vaccination) defined as subjects:
  - i) seronegative prior to booster vaccination (titer <8) having a titer ≥8, or
  - ii) seropositive prior to booster vaccination (titer ≥8) having a 4-fold rise in antibody titers.

Exploratory endpoints:

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[redacted]

Statistical Considerations:

Analysis sets

Safety Set: The Safety Set will consist of all subjects who received at least one dose of the trial vaccine.

Full Analysis Set (FAS): The FAS will include all subjects who were randomized and received at least one dose of the trial vaccines.

Per–Protocol Set (PPS): The PPS will include all subjects in the FAS who have no major protocol violations. The major protocol violation criteria will be defined in the Statistical Analysis Plan (SAP). Subjects with major

protocol violations will be identified as part of the blinded data review prior to the unblinding of subject's investigational trial vaccine assignment. The categories of major protocol violations include: (1) not meeting selected entry criteria, (2) receiving a wrong trial vaccine or an incorrect regimen, (3) receiving prohibited therapies, and (4) other major protocol violations that may be identified during blinded data reviews.

All summaries and analyses of safety data will be based on subjects in the Safety Set. The primary immunogenicity analyses will be based on the PPS, and additional sensitivity analyses will be based on the FAS.

Analysis of Demographics and Other Baseline Characteristics
Summaries of age, gender, race, and other baseline characteristics will be presented by formulation arm.

Immunogenicity Analysis

Descriptive statistics for the primary, secondary, and exploratory immunogenicity endpoints, including estimates and 95% confidence intervals for SCR, SPR, VRR, and GMT will be provided by study arm and by poliovirus type. For the dose ranging cohort only, estimates and 95% confidence intervals for differences in SCR, SPR, and VRR, as well as ratios in GMT, will be provided for each pair of study arms by poliovirus type.

Safety Analysis
Reactogenicity will be assessed for 7 days following each vaccination (including day of vaccination) via daily collection of solicited AEs, including local reactions (injection site: pain, erythema, induration, and swelling) and systemic adverse events of headache, asthenia, malaise, arthralgia and myalgia for the adult lead-in cohort and irritability/fussiness, drowsiness, loss of appetite for the toddler lead-in and infant dose ranging cohorts. In addition, body temperature (preferably measured as oral temperature in the adult lead-in cohort and as rectal temperature in the toddler lead-in and infant dose ranging cohorts) as indicator of reactogenicity will be collected (with fever defined as body temperature ≥ 38°C).

For each solicited AE and fever, the percentage of subjects will be summarized by event severity for each day for the 7 days after each vaccination and overall. For subjects with more than 1 episode of the same event, the maximum severity will be used for tabulations.

Unsolicited AEs, and SAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT) for each formulation arm.

Sample Size Justification:

This trial is designed to be descriptive and is not based on testing formal null hypotheses, and therefore the sample size was not determined based on formal statistical power calculations.

Interim Analysis:

An interim analysis will be performed on data from Day 85 (28 days after the last dose of the primary immunization series in the infant dose ranging cohort)**.** The interim analysis will be performed by a separate set of unblinded statisticians and programmers who will have access to individual treatment assignments but will not be involved in subsequent study conduct. Results of the interim analysis will be used to inform the choice of antigen dose to be used in subsequent phase 3 studies of the sIPV.

More details on the analyses will be provided in the SAP.

Independent Data Monitoring Committee:

An independent program level DMC will be established. The DMC will have study-specific responsibilities to review IPV-102 data and decide on the enrollment of the toddler and infant cohorts after reviewing 7 days of safety and tolerability follow-up post vaccination in adults in the lead-in cohort. In addition, the DMC will evaluate the overall tolerability and safety of Takeda's sIPV on an ongoing basis. The DMC will be entitled to stop enrollment of additional subjects or to stop administration of additional sIPV doses. The composition, role and responsibilities of the DMC are presented in a separate DMC Charter.

2.1 Schedule of Trial Procedures

Table 2.a Adult Lead-In Cohort

Day		Day 1	Day 8	ET
Anchor to Study Visit 1		-/-	Visit 1 + 7 days	
Visit Number		1	2	
Acceptable Visit Window (before/after) (days)		NA	0/+4	
Clinical Visit (at site)		X	X	
Signed Informed Consent Form		X		
Pregnancy Test[a]		X		
Assessment of Eligibility Criteria[b]		X		
Demographics		X		
Medical History		X		
Prior Medications		X		
Concomitant Medications		X	X	(X)
Physical Examination	**Complete**[c]	X		
	Symptom Directed[c]		(X)	(X)
Vital Signs[d]		X	(X)	(X)
Randomization		X		
IPV/placebo administration[e]		X		
Diary Card	**Distribution**[f]	X		
	Collection[f]		X	(X)
Adverse Events[g]		X	X	(X)[h]
Serious Adverse Events[i]		X	X	(X)

ET: Early Termination. Use of (X) indicates samples or procedures that generally will not be performed but may be performed to investigate an AE, or at the time of premature discontinuation.
(a) In women of childbearing potential, a pregnancy test will be performed on Day 1 prior to enrollment.
(b) Eligibility by review of relevant inclusion/exclusion criteria will be documented before enrollment.
(c) Physical exam on Day 1 (Section 9.1.4). All subsequent physical examinations may be performed if deemed necessary and will be symptom-directed and should assess clinically significant changes from the baseline examination. For any procedures at the site, the investigator shall follow his/her standard practice.
(d) Vital signs: as defined in Section 9.1.5.
(e) After vaccination, subjects will be observed for at least 30 minutes including observation for immediate reactions and body temperature measurement.
(f) Diary cards will be distributed on the day of vaccination, and will be collected at the return visit 7 days later.
(g) Solicited local and systemic adverse events (AEs: Section 10.1.2) and unsolicited AEs will be recorded daily in diary cards for Days 1-7 after vaccination.
(h) AEs leading to Early Termination will be recorded by the investigator.
(i) SAEs will be collected for the duration of the trial and will be reported to the Sponsor within 24 hours of the investigator becoming aware of the event.

Table 2.b. Toddler Lead-In Cohort

Day		Day 1	Day 8	Day 29	Day 183	ET
Anchor to Study Visit 1		-/-	Visit 1 + 7 days	Visit 1 + 28 days	Visit 1 + 182 days	
Visit Number		1	2	3	4	
Acceptable Visit Window (before/after) (days)		NA	0/+4	0/+4	0/+4	
Clinical Visit (at site)		X		X		
Telephone Contact			X		X	(X)
Signed Informed Consent Form		X				
Assessment of Eligibility Criteria[a]		X				
Demographics		X				
Medical History		X				
Prior Medications		X				
Concomitant Medications		X	X	X	X[b]	(X)[b]
Physical Examination	**Complete**[c]	X				
	Symptom Directed[c]			(X)		(X)
Vital Signs[d]		X		X		(X)
Randomization		X				
IPV administration[e]		X				
Diary Card	**Distribution**[f]	X				
	Collection[g]			X		(X)
Adverse Events[h]		X	X	X		(X)[h]
Serious Adverse Events[i]		X	X	X	X	(X)
Blood Draw (5 mL)		X[j]		X		

ET: Early Termination. Use of (X) indicates samples or procedures that generally will not be performed but may be performed to investigate an AE or at the time of premature discontinuation.
(a) Eligibility by review of relevant inclusion/exclusion criteria will be documented before enrollment.
(b) Only vaccines administered since the last visit should be recorded.
(c) Physical exam on Day 1 (Section 9.1.4). All subsequent physical examinations may be performed if deemed necessary and will be symptom-directed and should assess clinically significant changes from the baseline examination. For any procedures at the site, the investigator shall follow his/her standard practice.
(d) Vital signs: as defined in Section 9.1.5.
(e) sIPV or reference IPV. After vaccination, subjects will be observed for at least 30 minutes including observation for immediate reactions and body temperature measurement.
(f) Diary cards will be distributed on the day of vaccination, and collected at the return visit on Day 29.
(g) Solicited local and systemic adverse events (AEs: Section 10.1.2) will be recorded daily in diary cards for Days 1-7, and unsolicited AEs for Days 1-28.
(h) AEs leading to Early Termination will be recorded by the investigator.
(i) SAEs will be collected for the duration of the trial and will be reported to the Sponsor within 24 hours of the investigator becoming aware of the event.
(j) Blood should be drawn prior to vaccination.

Table 2.c. Infant Dose Ranging Cohort

Day		Day 1	Day 8	Day 29	Day 36	Day 57	Day 64	Day 85	Day 183	Day 365	Day 372	Day 393	Day 547	ET
Anchor to Study Visits		-/-	Visit 1 + 7 days	Visit 1 + 28 days	Visit 3 + 7 days	Visit 3 + 28 days	Visit 5 + 7 days	Visit 5 + 28 days	Visit 1 + 182 days	Visit 1 + 364 days	Visit 9 + 7 days	Visit 9 + 28 days	Visit 9 + 182 days	
Visit Number		1	2	3	4	5	6	7	8	9	10	11	12	
Acceptable Visit Window (before/after) (days)		NA	0/+4	0/+4	0/+4	0/+4	0/+4	0/+4	-7/+7	-7/+14	0/+4	0/+4	-7/+14	
Clinical Visit (at site)		X		X		X		X		X		X		
Telephone Contact			X		X		X		X		X		X	
Signed Informed Consent Form		X												
Assessment of Eligibility Criteria [a]		X												
Demographics		X												
Medical History		X												
Prior Medications		X												
Concomitant Medications[b]		X	X	X	X	X	X	X	X[b]	X[b]	X[b]	X[b]	X[b]	(X)
Physical Exam	**Complete** [c]	X												
	Symptom Directed [c]			(X)		(X)		(X)		(X)		(X)		(X)
Vital Signs [d]		X		X		X				X				(X)
Randomization		X												
IPV administration [e]		X		X		X				X				
Diary Card	**Distribution** [f]	X		X		X				X				
	Review/Collection			X		X		X				X		
Adverse Events [g]		X	X	X	X	X	X	X		X	X	X		(X)[h]
Serious Adverse Events [i]		X	X	X	X	X	X	X	X	X	X	X	X	(X)
Blood Draw (5 mL)		X[j]				X[j]		X		X[j]		X		

ET: Early Termination. Use of (X) indicates samples or procedures that generally will not be performed but may be performed to investigate an AE, or at the time of premature discontinuation.

(a) Eligibility by review of relevant inclusion/exclusion criteria will be documented before enrollment. Continuing eligibility (by review of relevant inclusion/exclusion criteria and criteria for delay of vaccination) will be documented before each vaccination.

(b) Only vaccines administered since the last visit should be recorded.

(c) Physical exam on Day 1 (Section 9.1.4). All subsequent physical examinations may be performed if deemed necessary and will be symptom-directed and

should assess clinically significant changes from the baseline examination. For any procedures at the site, the investigator shall follow his/her standard practice.
(d) Vital signs: as defined in Section 9.1.5.
(e) sIPV or reference IPV. Polio vaccine should be administered concomitantly with DTP-HBV-Hib on Days 1, 29 and 57. After vaccination, subjects will be observed for at least 30 minutes including observation for immediate reactions and body temperature measurement.
(f) Diary cards will be distributed on the day of each vaccination, and will be collected at the return visit 28 days later.
(g) Solicited local and systemic adverse events (AEs: Section 10.1.2) will be recorded daily in diary cards for Days 1-7, and unsolicited AEs for Days 1-28, after each vaccination.
(h) AEs leading to Early Termination will be recorded by the investigator.
(i) SAEs will be collected for the duration of the trial and will be reported to the Sponsor within 24 hours of the investigator becoming aware of the event.
(j) Blood should be drawn prior to vaccination

3.0 TRIAL REFERENCE INFORMATION

3.1 Trial-Related Responsibilities

The sponsor will perform all trial-related activities with the exception of those identified in the Trial-Related Responsibilities template. The identified vendors in the template for specific trial-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Principal Investigator/Coordinating Investigator

The sponsor will select a Signatory Principal Investigator / Coordinating Investigator from the investigators who participate in the trial. Selection criteria for this investigator will include significant knowledge of the trial protocol, the investigational vaccine, their expertise in the therapeutic area and the conduct of clinical research as well as trial participation. The Signatory Principal Investigator / Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the trial.

3.3 List of Abbreviations

AE	Adverse Event
Al(OH)3	Aluminum Hydroxide
bOPV	bivalent Oral Poliomyelitis Vaccine
CI	Confidence Interval
eCRF	electronic Case Report Form
CRO	Contract Research Organization
cVDPV	circulating Vaccine-Derived Poliovirus
DTaP	Diphtheria, Tetanus, acellular Pertussis combination vaccine
DTaP-IPV	Diphtheria, Tetanus, acellular Pertussis, Inactivated Poliomyelitis combination vaccine
DMC	Data Monitoring Committee
DU	D-Antigen Units
EC	Ethics Committee
EDC	Electronic Data Capture
EMA	European Medicines Agency
EPI	Expanded Programme on Immunization
FAS	Full Analysis Set
FSFV	First Subject First Visit
GAVI	Global Alliance for vaccines and Immunization
GCP	Good Clinical Practice
GMT	Geometric Mean Titer
GPEI	Global Polio Eradication Initiative
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IM	Intramuscular
IPV	Inactivated Poliomyelitis Vaccine
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intention-To-Treat
IUD	Intrauterine Device
JPRI	Japanese Poliomyelitis Research Institute
LAR	Legally Authorized Representative

LLN	Lower Limit of Normal
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
NPI	National Program on Immunization
OPV	Oral Poliomyelitis Vaccine
PP	Per Protocol
PPS	Per-Protocol Analysis Set
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCR	Seroconversion Rate
sIPV	Sabin-based Inactivated Poliomyelitis Vaccine
SOC	System Organ Class
SOP	Standard Operating Procedure
SPR	Seropositivity/Seroprotection Rate
SUSAR	Suspected Unexpected Serious Adverse Reaction
ULN	Upper Limit of Normal
VAPP	Vaccine-Associated Paralytic Poliomyelitis
WHA	World Health Assembly
WHO	World Health Organization
VRR	Vaccine Response Rate

3.4 Corporate Identification

TV	Takeda Vaccines, Inc.
VBU	Vaccines Business Unit

4.0 INTRODUCTION

4.1 Background

Poliomyelitis is an acute infectious disease caused by any of 3 poliovirus serotypes (types 1, 2, or 3), spread by fecal-to-oral and oral-to-oral routes. Approximately 25% of those infected develop transient minor symptoms including fever, headache, malaise, nausea, vomiting, and sore throat, and on rare occasions is complicated with signs suggestive of aseptic meningitis. After infection, an average of 1 in 200 susceptible individuals develops paralytic poliomyelitis—depending on age and serotype—of whom 5–10% suffer viral destruction of bulbar cells resulting in respiratory paralysis and death [2].

Immunity acquired following infection is considered to provide serotype-specific lifelong protection against paralytic poliomyelitis [3]. Similarly, induction of circulating antibodies through vaccination is an excellent indicator of protection against clinical disease, so post-vaccination seropositivity rates are considered to equate with seroprotection rates [4]. Currently, two types of vaccines against poliomyelitis are available to control the disease in most parts of the world: injectable Inactivated Poliomyelitis Vaccine (IPV), and live Oral Poliomyelitis Vaccine (OPV). The introductions of IPV in 1955 (Jonas Salk) and OPV in 1963 (Albert Sabin) have led to a significant decrease in poliomyelitis worldwide. Since the Global Polio Eradication Initiative (GPEI) was initiated by the World Health Assembly (WHA) in 1988, cases of polio have decreased by over 99%. One of the three serotypes, poliovirus type 2, was officially declared to be globally eradicated in September 2015, the last case being reported in 1999, and no cases of type 3 wild poliovirus have been reported since November 2012. Wild type 1 poliovirus is currently circulating in only three countries, Afghanistan, Pakistan and Nigeria [5].

With the global eradication of wild-type 2 poliovirus, trivalent OPV has been withdrawn globally since April 2016 and only bivalent OPVs (types 1 and 3) are now in use. Currently, OPV is used in polio-endemic countries, in countries at high risk for importation of polio and/or intermediate-to-high potential for transmission. OPV has several advantages over IPV: it is easy to administer in resource-poor settings, it allows for the vaccine virus to spread to contacts resulting in contact immunity beyond the vaccinated individual, it elicits a better intestinal immunity. In addition, it is safer and, hence, easier and cheaper to manufacture as it does not involve the amplification of wild poliovirus which reduces production costs. However, on rare occasions, the attenuated Sabin strains cause vaccine-associated paralytic poliomyelitis (VAPP). A further risk is the occurrence of mutations that can revert the attenuated strain into a neurovirulent form of poliovirus leading to circulating vaccine-derived poliovirus (cVDPV) with the potential of outbreaks of VAPP. For this reason, OPV is not suitable for long-term control of polio and IPV will be the cornerstone towards final eradication.

The GPEI Polio Eradication and Endgame Strategic Plan 2013–2018 [6] is a comprehensive, long-term strategy that calls for all countries to introduce at least one dose of IPV into their national routine immunization schedules together with the replacement of trivalent OPV with bivalent OPV from April 2016, before the eventual withdrawal of all forms of OPV immunization.

The GPEI recommendation that all children receive at least one dose of IPV with the introduction of bOPV [6] will help to:

- ***Reduce the risk of poliovirus type 2-associated VAPP as well as a potential re-emergence of type 2 cVDPV.*** With withdrawal of OPV type 2, IPV maintains immunity against type 2 poliovirus, leading to lower risk of re-emergence or reintroduction of wild or vaccine-derived type 2 poliovirus.
- ***Interrupt transmission in the case of outbreaks.*** In the event of a type 2 outbreak and use of monovalent OPV type 2, people primed with IPV would be expected to have a stronger immune response, thus facilitating outbreak control and interruption of polio transmission.
- ***Hasten polio eradication.*** IPV will boost immunity against poliovirus types 1 and 3 in OPV-immunized children, to further accelerate eradication of these two wild viruses.

The costs per vaccine dose of IPV and the current production capacity limit the wide use and availability of IPV, particularly in low-income countries [7]. One of the major components of the strategy for achieving a polio-free world is to make IPV vaccines more affordable and more widely accessible by antigen dose-sparing strategies (eg, formulations containing fractional antigen doses through the addition of an adjuvant and/or by administration by intradermal delivery), immunization schedule reduction (fewer vaccine doses), and/or approaches to reduce vaccine production costs.

Current IPVs are based on virulent wild-type poliovirus strains and are considered as very safe and effective [2]. However, the use of wild-type poliovirus for vaccine manufacturing carries the risk of accidental environmental re-introduction of wild poliovirus and will be discouraged in the post eradication era. Moreover, containment requirements for all polioviruses will increase from level-2 to an equivalent of level-3 that are likely to further increase production costs. An alternative way to manufacture safe and affordable IPV is the development and application of production processes that avoid wild-type poliovirus [8].

Takeda Sabin-based IPV (sIPV) vaccine candidate

The objective of the Takeda program is to supply affordable sIPV to GAVI countries as part of the Polio Eradication and Endgame Strategic Plan. As a basis for developing and producing IPV based on non-virulent Sabin strains (types 1, 2, and 3), CCI [redacted]. Takeda has previously manufactured and tested sIPV in Japan as part of a combination vaccine candidate (DTaP- sIPV). Takeda's approach to more affordable sIPV is to reduce vaccine production costs using a new technology production platform. In addition, Takeda will leverage on existing manufacturing capacities as the company has an established manufacturing facility in Hikari, Japan, which is production-ready and has capacity for inventory build-up in preparation of delivery and access globally.

Clinical experience with sIPV

Takeda's previous experience with sIPV is limited to its use as a component of a Takeda candidate diphtheria-tetanus-acellular pertussis-IPV combination vaccine (DTaP-IPV, TAK-361S). CCI

[redacted]

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[redacted]

The primary indication for IPV is the immunization of infants and toddlers (primary series + booster) against poliomyelitis caused by any of the three polio strains. Based on the experience with TAK-361S, Takeda is looking to develop a stand-alone sIPV that can be used to supplement GAVI vaccination initiatives that currently rely on OPV to provide protection against poliomyelitis, to ensure such coverage through and beyond the polio eradication era when all OPV will be withdrawn.

This trial will assess the safety and tolerability as well as the immunogenicity of Takeda's stand-alone sIPV candidate to identify the optimal formulation to take forward into advanced stage studies to show the immunogenicity and safety of the final candidate vaccine.

4.2 Rationale for the Proposed Trial

With the imminent global eradication of wild-type polioviruses, the routine vaccination of infants and toddlers with IPV will be necessary for several years to maintain sufficient population immunity to prevent polio disease outbreaks due to circulating vaccine-derived poliovirus (cVDPV). Current constraints on cost, capacity and safety of manufacturing of IPV can be alleviated by use of stand-alone vaccines such as Takeda's sIPV, particularly for GAVI-supported countries to complement other Expanded Programme on Immunization (EPI)-recommended vaccines. This phase 1/2 trial is intended to show the safety, tolerability and provide a first indication of antigen dosage of Takeda's sIPV in the target population of unvaccinated infants.

Following a lead-in study of the safety and tolerability of the highest anticipated dosage in primed (after full primary poliovirus vaccination) adults followed by toddlers, the descriptive dosage-ranging study in infants will allow selection of the dosage to take forward into advanced stage studies. This decision will be based on the WHO recommendations for assessment of IPV vaccines [4], and will use the seroconversion rate after completion of the three-dose primary schedule as primary measure.

In the adult and toddler lead-ins, the focus will be to ensure no unanticipated reactions or AEs are observed following one dose of the highest dosage formulation, which will be administered as a booster in adults and children who have previously been primed with a full primary poliomyelitis vaccination series according to the local recommendations. Immunogenicity will not be assessed in the adult cohort. In the toddler lead-in cohort, immunogenicity will be assessed after children receive this "booster" dose of sIPV to ensure they all have antibodies against at least serotypes 1 and 3 (as immune response to type 2 poliovirus may be incomplete in toddlers who had received their primary immunization with bOPV). A control group will receive a reference IPV for descriptive comparison.

In the infant dose ranging cohort, the control group will provide a comparator for the safety and tolerability of the different sIPV dosages. Assessing immunogenicity in the comparator control arm in the infant cohort will provide background information to show that the three groups that receive the different dosages of sIPV all achieve adequate levels of immunity and so are not put at risk of poliovirus infection.

The primary endpoint for the immunogenicity analysis is the seroconversion rate achieved in infants four weeks after the last of three primary doses of sIPV, in accordance with WHO recommendations for the assessment of IPV [4]. The study is not powered for statistical comparisons, and all comparisons will be descriptive. It is only designed to select a dosage formulation from consideration of an interim analysis performed on the data obtained 28 days after the third primary immunizations at Day 85. The selected formulation will be taken into

larger phase 3 trials for advanced stage clinical development to show the immunogenicity and safety of the final candidate vaccine.

The trial will be conducted in accordance with the protocol, ICH-GCP Guidelines and applicable regulatory requirements.

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

Infant dose ranging cohort only

To select for further development, the optimal antigen concentrations of the three Sabin poliovirus strains (types 1, 2, and 3) of the stand-alone trivalent sIPV by comparing the three sIPV study arms based on two parameters:

- the safety and tolerability profile after each dose of primary immunization
- the seroconversion rates (SCR) for poliovirus types 1, 2, and 3 for both Sabin and Salk strains, after the final dose of a three dose primary immunization series (Day 85)

5.1.2 Secondary Objectives

Safety and tolerability

Adult lead-in cohort

- To compare the safety and tolerability profile in the high dose sIPV arm with the control arm in adults after a single vaccination.

Toddler lead-in cohort

- To compare the safety and tolerability profile in the high dose sIPV arm with the reference IPV (control) arm in toddlers after a single booster vaccination.

Infant dose ranging cohort

- To compare the safety and tolerability profile of each sIPV study arm with the reference IPV (control) arm after each primary immunization.
- To compare the safety and tolerability profile between sIPV study arms, and between each sIPV study arm and the reference IPV (control) arm, after booster vaccination.

Immunogenicity

Infant dose ranging cohort

- To compare between each sIPV study arm and the reference IPV (control) arm, the SCR separately for poliovirus types 1, 2, and 3 for both Sabin and Salk strains, after the final dose out of a series of three doses for primary immunization (Day 85).
- To compare between sIPV study arms, and between each sIPV study arm and the reference IPV (control) arm, the seropositivity/seroprotection rates (SPR) separately for poliovirus types 1, 2, and 3 for both Sabin and Salk strains, after the final dose out of a series of three doses for primary immunization (Day 85).

- To compare between sIPV study arms, and between each sIPV study arm and the reference IPV (control) arm, the geometric mean titers (GMT) separately for poliovirus types 1, 2, and 3 for both Sabin and Salk strains, after the final dose out of a series of three doses for primary immunization (Day 85).
- To compare between sIPV study arms, and between each sIPV study arm and the reference IPV (control) arm, the SPR and GMT separately for poliovirus types 1, 2, and 3 for both Sabin and Salk strains, before the sIPV booster vaccination (Day 365).
- To compare between sIPV study arms, and between each sIPV study arm and the reference IPV (control) arm, the vaccine response rate (VRR), SPR, and GMT separately for poliovirus types 1, 2, and 3 for both Sabin and Salk strains, after the sIPV booster vaccination (Day 393).

5.1.3 Exploratory Objectives

CCI

[redacted]

5.2 Endpoints

Primary endpoints (infant dose ranging cohort)

Safety and tolerability

- Percentage of subjects with solicited local reactions on a symptom by symptom basis, in each severity category, during the 7-day period (including day of vaccination) after each primary immunization dose of sIPV.
- Percentage of subjects with solicited systemic AEs on a symptom by symptom basis, in each severity category, during the 7-day period (including day of vaccination) after each primary immunization dose of sIPV.
- Percentage of subjects with a body temperature ≥ 38°C (defined as fever) during the 7-day period (including day of vaccination) after each primary immunization dose of sIPV.

- Percentage of subjects experiencing non-serious unsolicited AEs during the 28-day period (including day of vaccination) after each primary immunization dose of sIPV.
- Percentage of subjects experiencing SAEs throughout the entire trial duration in the sIPV study arms.

Immunogenicity, separately for poliovirus types 1, 2, and 3 for both Sabin and Salk strains, in the three study arms

- SCR = percentage of subjects in each arm who seroconvert, which is defined as:
  i. initially seronegative infants (titer <8 at Day 1) having a titer ≥8 at Day 85, or
  ii. initially seropositive infants (titer ≥8 at Day 1) with a 4-fold rise in antibody titers over the expected level of maternal antibodies at Day 85, calculated using a decline from the Day 1 titer with a half-life of 28 days.

Secondary Endpoints

Safety and tolerability

Infant dose ranging cohort

- Percentage of subjects with solicited local reactions on a symptom by symptom basis, in each severity category, during the 7-day period (including day of vaccination) after each primary immunization dose of sIPV or IPV.
- Percentage of subjects with solicited systemic AEs on a symptom by symptom basis, in each severity category, during the 7-day period (including day of vaccination) after each primary immunization dose of sIPV or IPV.
- Percentage of subjects with a body temperature ≥ 38°C (defined as fever) during the 7-day period (including day of vaccination) after each primary immunization dose of sIPV or IPV.
- Percentage of subjects experiencing non-serious unsolicited AEs during the 28-day period (including day of vaccination) after each primary immunization dose of sIPV or IPV.
- Percentage of subjects experiencing SAEs throughout the entire trial duration in the sIPV and IPV study arms.
- Percentage of subjects with solicited local reactions on a symptom by symptom basis, in each severity category, during the 7-day period (including day of vaccination) after booster vaccination.
- Percentage of subjects with solicited systemic AEs on a symptom by symptom basis, in each severity category, during the 7-day period (including day of vaccination) after booster vaccination.

- Percentage of subjects with a body temperature ≥ 38°C (defined as fever) during the 7-day period (including day of vaccination) after booster vaccination.
- Percentage of subjects experiencing non-serious unsolicited AEs during the 28-day period (including day of vaccination) after booster vaccination.

Toddler lead-in cohort

- Percentage of subjects with solicited local reactions on a symptom by symptom basis, in each severity category, during the 7-day period (including day of vaccination) after booster vaccination.
- Percentage of subjects with solicited systemic AEs on a symptom by symptom basis, in each severity category, during the 7-day period (including day of vaccination) after booster vaccination.
- Percentage of subjects with a body temperature ≥ 38°C (defined as fever) during the 7-day period (including day of vaccination) after booster vaccination.
- Percentage of subjects experiencing non-serious unsolicited AEs during the 28-day period (including day of vaccination) after booster vaccination.
- Percentage of subjects experiencing SAEs throughout the entire trial duration.

Adult lead-in cohort

- Number of subjects with solicited local reactions on a symptom by symptom basis, in each severity category, during the 7-day period (including day of vaccination) after a single dose of sIPV or placebo.
- Number of subjects with solicited systemic AEs on a symptom by symptom basis, in each severity category, during the 7-day period (including day of vaccination) after a single dose of sIPV or placebo.
- Number of subjects with a body temperature ≥ 38°C (defined as fever) during the 7-day period (including day of vaccination) after a single dose of sIPV or placebo.
- Number of subjects experiencing non-serious unsolicited AEs during the 7-day period (including day of vaccination) after a single dose of sIPV or placebo.
- Number of subjects experiencing SAEs during the 7-day period (including day of vaccination) after a single dose of sIPV or placebo.

Immunogenicity, separately for poliovirus types 1, 2, and 3 for both Sabin and Salk strains

Infant dose ranging cohort

- Seropositivity/seroprotection rate (SPR, defined as the percentage of subjects with antibody titers ≥ 8) on Days 85, 365, and 393 (28 days after booster vaccination).

- GMT on Days 85, 365, and 393 (28 days after booster vaccination).
- Vaccine response rate (VRR) on Day 393 (28 days after booster vaccination) defined as subjects:
  i. seronegative prior to booster vaccination (titer <8) having a titer ≥ 8, or
  ii. seropositive prior to booster vaccination (titer ≥ 8) having a 4-fold rise in antibody titers.

Exploratory Endpoints

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[redacted]

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

This observer-blind, randomized trial has three separately enrolled cohorts starting with an adult cohort (n = 40) in a safety and tolerability lead-in of the highest dosage of sIPV compared with placebo. Unblinded safety and tolerability assessments over the first 7 days post vaccination will be reviewed by an independent Data Monitoring Committee (DMC) who will recommend whether or not vaccination of younger cohorts can proceed. The toddler lead-in cohort (n = 60) is designed to evaluate the safety and tolerability of the highest dosage of sIPV given as booster vaccination compared with the reference IPV. Blinded safety data from this cohort will be reviewed internally by Takeda before initiating the recruitment of the infant dose ranging cohort.

A schematic of the trial design is included as Figure 6.a. A schedule of trial procedures is provided in Section 2.1.

A). Adult lead-in cohort

The first lead-in cohort will consist of 40 healthy adults, 18-49 years of age inclusive. Subjects will be enrolled and randomized to two equal groups to receive, in an observer-blind fashion, a single intramuscular injection of high dose sIPV containing 3, 100, and 100 DU of poliovirus types 1, 2, and 3, respectively (Day 1), or placebo. To be eligible, subjects must have completed primary immunization against poliomyelitis according to local recommendations.

Safety and tolerability will be assessed 7 days post vaccine administration.

B). Toddler lead-in cohort

The second lead-in cohort of 60 healthy toddlers at 12–15 months of age inclusive, will be enrolled and randomized to two equal groups. Each group will receive, in an observer-blind fashion, a single intramuscular injection of high dose sIPV containing 3, 100, and 100 DU of poliovirus types 1, 2, and 3, respectively (Day 1), or reference IPV. Polio vaccines previously received for primary immunization of these children will be recorded. Routine childhood vaccines other than poliovirus vaccine for booster immunization recommended for children at approximately 12 months of age according to the NPI (eg, measles-containing vaccine) are to be given at least 4 weeks apart from sIPV / reference IPV booster vaccination. NPI-recommended childhood vaccines other than poliomyelitis vaccine will be given outside the trial.

Safety and tolerability will be assessed 7 and 28 days post IPV administration. In addition, a final safety contact is scheduled for six months post IPV administration.

Individual titers pre and post booster vaccination will be assessed. Toddlers who receive sIPV and who have no neutralizing antibodies to any of the three poliovirus serotypes (titer <8) on Day 29 as well as those with no titer increase between Day 1 and Day 29 will be offered re-vaccination with a single dose of the reference IPV (note: toddlers that have received bivalent OPV exclusively for primary immunization may not achieve seropositivity to poliovirus type 2. Therefore, subjects with documented primary immunization against serotypes 1 and 3 only who do not respond to serotype 2 post sIPV booster will not be offered re-vaccination).

C). Infant dose ranging cohort

A cohort of 240 healthy infants at 6 to 8 weeks of age, inclusive, with no previous history of poliomyelitis vaccination, will be enrolled and randomized to four equal groups. Each group will receive three vaccinations, at four week intervals, with one of the three different dosages of sIPV or the reference IPV, in an observer-blind fashion.

Safety and tolerability will be assessed 7 and 28 days post each vaccination with a further safety contact scheduled for six months post sIPV / reference IPV administration (Day 183).

Blood samples drawn before the first vaccination (Day 1) and 28 days after the second (Day 57) and third (Day 85) doses will be used to assess neutralization antibodies.

All children will then receive a fourth (booster) dose of sIPV or reference IPV 12 months (Day 365) after their last primary series vaccination.

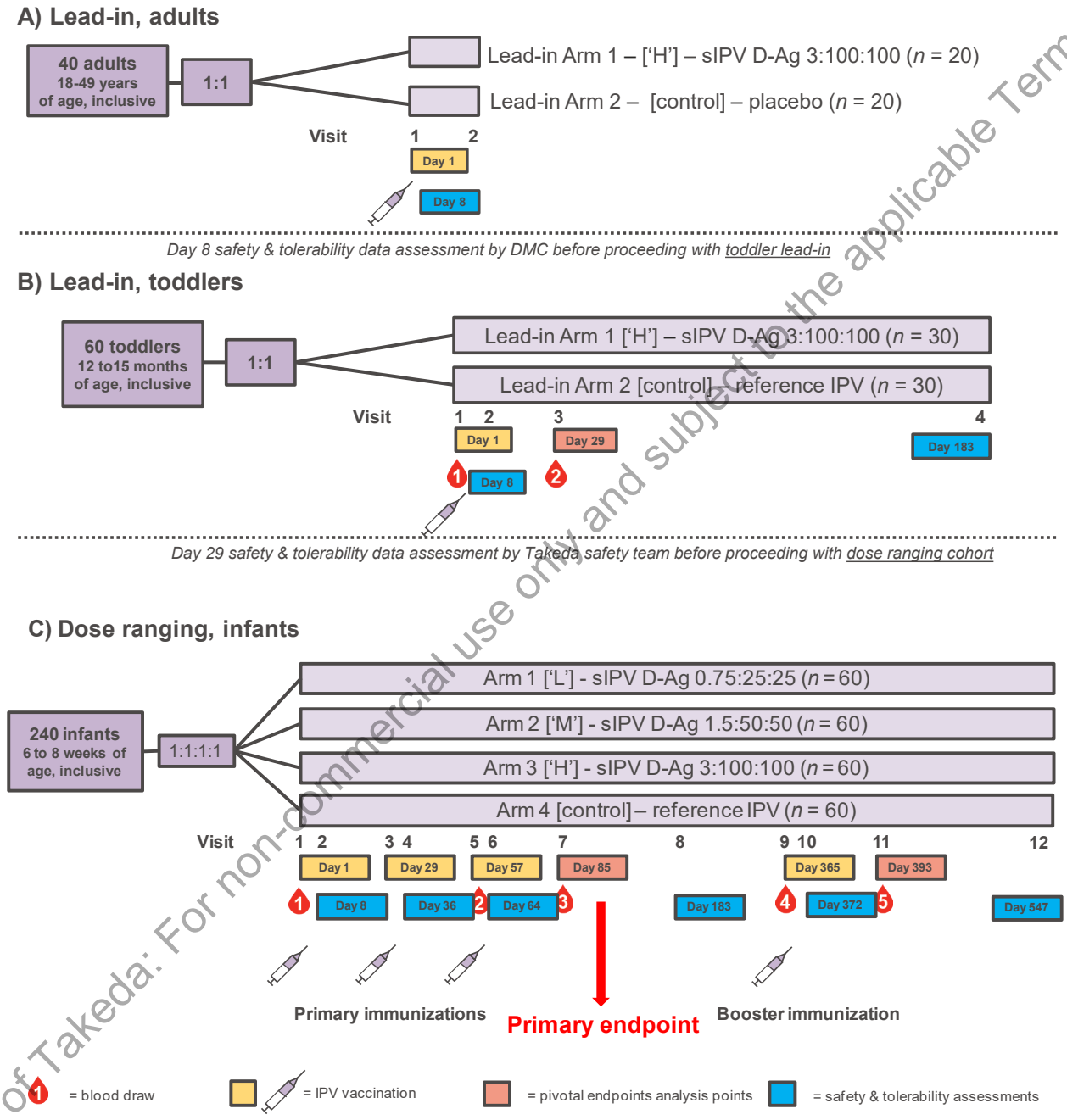
Routine infant vaccines according to the NPI other than poliovirus vaccine for primary immunization and for booster vaccination are to be given according to national guidelines outside the trial. Inactivated / oral routine infant vaccines should be given on the same day as sIPV / reference IPV. Injectable live-attenuated vaccines (eg, measles-containing vaccine) should be given at least 4 weeks apart from sIPV / reference IPV.

Safety and tolerability will be assessed for 7 and 28 days post booster vaccination with a further safety contact scheduled one year post sIPV / reference IPV administration (Day 547).

Infants who receive sIPV and who have no neutralizing antibodies to any of the three poliovirus serotypes (titer <8) on Day 393 will be offered re-vaccination with a series of three immunizations of reference IPV after the unblinding occurs and serological results become available, and outside of the IPV-102 clinical trial.

Blood samples drawn before (Day 365) and 28 days after booster vaccination (Day 393) will be used to assess neutralization antibodies.

Figure 6.a Schematic of Trial Design



6.2 Justification for Trial Design, Dose, and Endpoints

- The infant population is the target population for the stand-alone sIPV.
- Previous clinical experience with the sIPV component in DTaP-IPV (TAK-361S) does not suggest any safety issues, even though the sIPV will be produced with a slightly modified manufacturing process. The adult and toddler lead-ins will confirm this.
- The sample size is not based on a statistical comparison, but on the availability of data from ≥ 50 infants per group assuming an attrition rate of 10–15% (see Section 13.3).
- The control groups in the toddler lead-in and infant dose ranging cohorts will provide background data on the safety of reference IPV immunizations in the study population against which to assess the safety and tolerability of sIPV. Similarly, it may also confirm that adequate levels of protective immunity are achieved, the local rates having been shown to lead to maintain polio eradication in the study region.
- The study schedule (6, 10 and 14 weeks) and administration route (intramuscular injection) are the expected ones to be used in the target population for the vaccine (GAVI regions).
- The primary endpoint, seroconversion using neutralization assays, is the WHO recommended parameter for assessment of new IPVs [4].
- Seroconversion and the presence of neutralizing antibodies (seropositivity) are accepted to provide protection against type-specific poliomyelitis.
- CCI [redacted].

The collection of solicited reactions, symptoms and AEs following vaccination are consistent with vaccine evaluation studies.

6.3 Duration of Subject's Expected Participation in the Entire Trial

Adults enrolled in the first lead-in cohort will be involved for 1 week (from Day 1 to Day 8).

Toddlers enrolled in the second lead-in cohort will be involved for 6 months until their final follow up safety visit (Day 183).

Infants enrolled in the dose ranging cohort will be involved for 18 months (Day 547) until their final follow up safety visit.

6.4 Premature Termination or Suspension of Trial or Investigational Site

6.4.1 Criteria for Premature Termination or Suspension of the Trial

The trial will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the trial.

- New information or other evaluation regarding the safety or efficacy of the investigational vaccine that indicates a change in the known risk/benefit profile, such that the risk/benefit is no longer acceptable for subjects participating in the trial.
- The DMC recommends that the trial should be suspended or terminated.
- Significant deviation from Good Clinical Practice (GCP) that compromises the ability to achieve the primary trial objectives or compromises subject safety.

6.4.2 Criteria for Premature Termination or Suspension of Investigational Sites

A trial site may be terminated prematurely or suspended if the site (including the investigator) is found in significant deviation from GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the trial, or as otherwise permitted by the contractual agreement.

6.4.3 Procedures for Premature Termination or Suspension of the Trial or the Participation of Investigational Site(s)

In the event that the sponsor, an institutional review board (IRB)/independent ethics committee (IEC) or regulatory authority elects to terminate or suspend the trial or the participation of an investigational site, a trial-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or trial suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to randomization.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria:

Adult Lead-in Cohort

1. Male and female adults aged 18 to 49 years, inclusive, at the time of enrollment.
2. Individuals who are in good health at the time of entry into the trial as determined by medical history, physical examination (including vital signs) and clinical judgment of the investigator.
3. The subject signs and dates a written, informed consent form (ICF) and any required privacy authorization prior to the initiation of any trial procedures, after the nature of the trial has been explained according to local regulatory requirements (Appendix B).
4. Individuals who can comply with trial procedures and are available for the duration of follow-up.
5. Completed primary immunization against poliomyelitis according to local recommendations.

Toddler Lead-in Cohort

1. Male and female toddlers, aged 12 to 15 months, inclusive, at the time of enrollment.
2. Toddlers in good health at the time of entry into the trial as determined by medical history, physical examination (including vital signs) and clinical judgment of the investigator.
3. The toddler's legally authorized representative (LAR) signs and dates a written ICF and any required privacy authorization prior to the initiation of any trial procedures, after the nature of the trial has been explained according to local regulatory requirements (Appendix B).
4. Toddlers and their LAR can comply with trial procedures, are available for the duration of the trial, and a suitable telephone contact is available.
5. Completed primary immunization against poliomyelitis, preferably with IPV, according to local recommendations.

Infant Dose Ranging Cohort

1. Male and female infants, aged 6 to 8 weeks (42–55 days, inclusive) at the time of enrollment.
2. Infants are in good health at the time of entry into the trial as determined by medical history, physical examination (including vital signs) and clinical judgment of the investigator.
3. Infants must have been born full term (37-42 weeks of gestation).

4. The infant's LAR signs and dates a written ICF and any required privacy authorization prior to the initiation of any trial procedures, after the nature of the trial has been explained according to local regulatory requirements (Appendix B).
5. Infants and their LAR can comply with trial procedures, are available for the duration of follow-up, and a suitable telephone contact is available.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the trial:

Adult Lead-in Cohort

1. Individuals with body mass index (BMI) greater than or equal to 35 kg/m2 (= weight in kg / [height in meters * height in meters].
2. Individuals with history of substance or alcohol abuse within the past 2 years.
3. Female subjects who are pregnant or breastfeeding.
4. If female subject of childbearing potential, sexually active, and has not used any of the "acceptable contraceptive methods" for at least 2 months prior to trial entry:
   a) Of childbearing potential is defined as status post onset of menarche and not meeting any of the following conditions: menopausal for at least 2 years, status after bilateral tubal ligation for at least 1 year, status after bilateral oophorectomy, or status after hysterectomy.
   b) Acceptable birth control methods are defined as one or more of the following:
      I. Hormonal contraceptive (such as oral, injection, transdermal patch, implant, cervical ring).
      II. Barrier (condom with spermicide or diaphragm with spermicide) each and every time during intercourse.
      III. Intrauterine device (IUD).
      IV. Monogamous relationship with vasectomized partner. Partner must have been vasectomized for at least 6 months prior to the subject's trial entry.
5. If female subject of childbearing potential and sexually active, refusal to use an "acceptable contraceptive method" through to 1 month after the last dose of trial vaccine. In addition, they must be advised not to donate ova during this period (Section 9.1.8).
6. Any positive or indeterminate pregnancy test.

Toddler Lead-in Cohort

1. Last polio vaccination (either inactivated or oral) received within 5 months prior to first trial visit.
2. Household member/sibling who had received or is/are scheduled to receive OPV in the previous 3 months until 5 weeks post subject's inclusion in the study.

3. Prior vaccination with booster dose of diphtheria, tetanus, pertussis (acellular or whole cell), polio (either inactivated or oral), or *Haemophilus influenzae* type b (Hib) vaccines.

Infant Dose Ranging Cohort

1. Infants with low birth weight according to local standards.
2. Prior vaccination with polio vaccines (either inactivated or oral).
3. Household member/sibling that had received or is/are scheduled to receive OPV in the previous 3 months until 5 weeks after the third dose of the primary immunization series.
4. Prior vaccination with any diphtheria, tetanus, pertussis (acellular or whole cell), *Haemophilus influenzae* type b (Hib) vaccine or polio vaccine (OPV or IPV). Note, BCG at birth and prior vaccination with Hepatitis B vaccine given at least 4 weeks prior to first trial visit are not exclusion criteria.

All Cohorts

1. Known hypersensitivity or allergy to any of the vaccine components (including excipients) or standard infant vaccines, as summarized in Section 6.1.
2. Any significant chronic infection.
3. Any clinically significant active infection (as assessed by the investigator) or temperature ≥38.0°C (>100.4°F), within 3 days of intended trial vaccination.
4. Subjects who received any vaccine within 28 days prior to enrollment in this trial.
5. Any serious chronic or progressive disease according to the judgment of the investigator (eg, cardiac, renal or hepatic disease).
6. Individuals with history, eg, convulsions/febrile convulsions, or any illness, that, in the opinion of the investigator, might interfere with the results of the trial or pose additional risk to the subjects due to participation in the trial.
7. Known or suspected impairment/alteration of immune function, including:
   a) Chronic use of oral steroids (equivalent to 20 mg/day prednisone for ≥12 weeks/≥2 mg/kg body weight/day for ≥2 weeks) within 60 days prior to Day 1 (use of inhaled, intranasal, or topical corticosteroids is allowed).
   b) Receipt of parenteral steroids (equivalent to 20 mg/day prednisone ≥12 weeks/≥2 mg/kg body weight/day for ≥2 weeks) within 60 days prior to Day 1.
   c) Administration of immunoglobulins and/or any blood or blood products within the 3 months preceding the administration of the trial vaccine or planned administration during the trial (consider whether applicable as an exclusion criterion or criterion for delay, see Section 7.3).
   d) Receipt of immunostimulants within 60 days prior to Day 1.
   e) Genetic immunodeficiency.

8. Individuals with a known bleeding diathesis, or any condition that may be associated with a prolonged bleeding time.
9. Individuals participating in any clinical trial with another investigational product 30 days prior to first trial visit or intent to participate in another clinical trial at any time during the conduct of this trial.
10. Individuals with first degree relatives involved in the trial conduct.

There may be instances when individuals meet all entry criteria except one that relates to transient clinical circumstances (eg, temperature elevation or recent use of excluded medication). Under these circumstances, eligibility for trial enrollment may be considered if the appropriate window for delay has not passed, inclusion/exclusion criteria have been rechecked, and if the subject is confirmed to be eligible.

7.3 Criteria for Delay of Vaccination and/or Blood Sampling

After enrollment, subjects may encounter clinical circumstances that warrant a delay in the administration of trial vaccination. These situations are listed below. In the event that a subject meets a criterion for delay of vaccination, the subject may receive trial vaccination once the window for delay has passed as long as the subject is otherwise eligible for trial participation.

- Individuals with a clinically significant active infection (as assessed by the investigator) or temperature ≥ 38.0°C / 100.4°F, within 3 days of intended trial vaccination (consider whether applicable as a criterion for delay or as an exclusion criterion, see Section 7.2).
- Individuals who have received blood, blood products and/or plasma derivatives or any parenteral immunoglobulin preparation within the past 3 months prior to any dose (consider whether applicable as a criterion for delay or as an exclusion criterion, see Section 7.2).
- Individuals who received any other vaccines within 28 days prior to planned vaccination or blood sampling.
- Individuals who have used antipyretics/analgesic medications within 24 hours prior to planned vaccine administration.

If vaccinations cannot be given within the visit window as defined by the protocol, the subject may receive the vaccination outside the visit window. This will be considered as a protocol deviation. All subjects should receive all vaccinations necessary to fulfill the locally recommended NPI schedule.

There are also circumstances under which receipt of further vaccines is a contraindication in this trial. These circumstances include anaphylaxis or severe hypersensitivity reactions following the initial vaccination. If these reactions occur, the subject must not receive additional vaccinations but is encouraged to continue in trial participation for safety reasons.

7.4 Criteria for Early Study Termination of a Subject

Under some circumstances, a subject's trial participation may be terminated early. This means that no further trial procedures (including data collection) will be performed on that subject beyond the specific date of early termination. The primary reason for early termination of the subject from the trial should be recorded in the electronic case report form (eCRF "end of study visit" page) using the following categories. For screen failure subjects, refer to Section 9.1.10.

1. Adverse Event: The subject has experienced an AE (irrespective of being related / unrelated to the Trial Vaccine or trial-related procedures) that requires early termination because continued participation imposes an unacceptable risk to the subject's health and / or the subject is unwilling to continue participation because of the AE. If the subject (adult cohort) or the subject's LAR (toddler and infant cohorts) is unwilling to continue because of the AE the primary reason for early termination in this case will be 'withdrawal due to AE' and not 'withdrawal of consent', see below. Any ongoing AEs leading to early termination should be followed by the investigator until resolution or stabilization.
2. Lost to follow-up: The subject did not return to the clinic and at least three attempts to contact the subject (adult cohort) or the subject's LAR (toddler and infant cohorts) were unsuccessful. Attempts to contact the subject or the subject's LAR must be documented.
3. Withdrawal of consent: The subject (adult cohort) or the subject's LAR (toddler and infant cohorts) wishes to withdraw from the trial. The primary reason for early termination will be 'withdrawal of consent" if the subject is withdrawn from participation due to a non-medical reason (ie, reason other than AE). The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded.
4. Premature study termination by sponsor, a regulatory agency, the EC/IRB, or any other authority.

   If the clinical study is prematurely terminated by the sponsor, the investigator is to promptly inform the study subjects and local EC/IRB and should assure appropriate follow up for the subjects. The primary reason for early termination in this case will be 'trial termination".
5. Subject's death during trial participation.
6. Other.

   Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.5 Criteria for Premature Discontinuation of Trial Vaccine Administration

Early study termination of a subject will by default prevent the subject from continued Trial Vaccine administration, as the subject will no longer be participating in the study. In addition to early termination (see Section 7.4) criteria, other situations may apply in which subjects may continue participating in the trial (eg, contributing safety data according to protocol) but Trial

Vaccine administration is discontinued selectively. Regardless of the reasons for discontinuation of Trial Vaccine administration, this must be documented as protocol deviation. Even if the subject is deemed ineligible to receive Trial Vaccine, all efforts should be made to continue the collection of safety data according to protocol. In addition, the one primary reason for premature discontinuation of Trial Vaccine application should be recorded in the electronic case report form (eCRF, "end of Trial Vaccine application" page) using the following categories.

1. Adverse Event: The subject has experienced an AE (irrespective of being related / unrelated to the Trial Vaccine or trial-related procedures) for which subsequent Trial Vaccine applications impose an unacceptable risk to the subject's health, but the subject may continue trial participation for safety, or a subset of other study procedures.
2. Lost to follow-up: The subject did not return to the clinic and at least three attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
3. Withdrawal of consent: The subject (adult cohort) wishes to withdraw from the trial or the subject's LAR (toddler and infant cohorts) wishes to withdraw the subject from the trial. The primary reason for early termination will be 'withdrawal of consent" if the subject is withdrawn from participation due to a non-medical reason (ie, reason other than AE). The reason for withdrawal, if provided, should be recorded in the eCRF.
4. Premature study termination by sponsor, a regulatory agency, the IEC/IRB, or any other authority.

   If the clinical study is prematurely terminated by the sponsor, the investigator is to promptly inform the study subjects and local IEC/IRB and should assure appropriate follow up for the subjects. The primary reason for early termination in this case will be 'trial termination".
5. Subject´s death during trial participation.
6. Protocol deviation: A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. The subject may remain in the trial unless continuation in the trial jeopardizes the subject's health, safety or rights (see Section 7.4).
7. Other.

   Note: The specific reasons should be recorded in the "specify" field of the eCRF.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all vaccines and materials provided directly by the sponsor, and/or sourced by other means, that are required by the trial protocol, including important sections describing the management of clinical trial material.

8.1 Trial Vaccines and Materials

Takeda's stand-alone sIPV is a trivalent vaccine containing formaldehyde-inactivated Sabin poliovirus strains types 1, 2, and 3 formulated with CCI aluminum [as $Al(OH)_3$]. Additional excipients are: phosphate buffer at CCI as well as CCI 2-phenoxyethanol per 0.5 mL dose. Three formulations of the sIPV containing different antigen concentrations of the three Sabin strains will be used:

- Low dose 'L': sIPV per poliovirus type 1, 2, and 3: DU 0.75:25:25,
- Medium dose 'M': sIPV per poliovirus type 1, 2, and 3: DU 1.5:50:50 and
- High dose 'H': sIPV per poliovirus type 1, 2, and 3: DU 3:100:100.

Reference IPV: antigen content is assumed to comply with the corresponding product label (see the Pharmacy Manual).

Pentavalent infant vaccine: DTP-HBV-Hib: antigen content is assumed to comply with the corresponding product label (see the Pharmacy Manual).

The doses should be prepared at the time of administration by the unblinded administrator (and/or pharmacist) per the Pharmacy Manual.

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, study medication refers to the trivalent polio vaccine sIPV, the reference IPV, pentavalent infant vaccine, and placebo. Study medication outer cartons/kits will be packaged and labeled with a tamper seal. The inner primary packaging will be unblinded and dose preparation will be carried out by unblinded site personnel.

This trial will involve the use of three sIPV trivalent polio vaccine formulations for intramuscular administration that were manufactured and filled at Takeda's manufacturing plant in Hikari, Japan. In addition, a reference IPV (toddler and infant cohorts) and placebo (adult cohort) will be provided for control groups and a pentavalent DTP-HBV-Hib vaccine will be provided for the infant dose ranging cohort to complete childhood immunizations. In case the reference IPV and / or the pentavalent vaccine cannot be sourced locally, Takeda will import these vaccines from a country/countries where the respective vaccine(s) is/are licensed.

8.1.1.1 Investigational Drug

Study medications described in this protocol (sIPV, reference IPV, pentavalent infant vaccine, and placebo) will be supplied by the sponsor.

The Takeda sIPV single-dose vials will be supplied in a labeled, single-use vial and carton (0.5 mL) dose for intramuscular injection, preferably in the right limb. Each vial and carton will contain a label that includes pertinent trial information and caution statements. The label text will be in the specific country language, depending on local requirements. The vaccine to be used will be identifiable by a unique identification number and managed by the interactive response technology (IRT) system.

The reference IPV will be presented in a blinded or open label carton. Should the primary container/packaging be open label, unblinded pharmacy and administration teams at the site will be required for dose preparation, administration and accountability. Each reference IPV and carton will contain a label. The label text, which includes pertinent trial information and caution statements, will be in the specific country language, depending on local requirements and will be included in the Pharmacy Manual and in the ICF for the toddler lead-in and infant dose-ranging cohorts.

The placebo (saline control) will be 0.9% sodium chloride for injection without preservatives.

Vaccination against D, T, P, HBV and Hib will be given as pentavalent combination vaccine (DTP-HBV-Hib). The pentavalent infant vaccine will be sourced as trial vaccine.

All doses should be prepared at the time of administration by the unblinded administrator (and/or pharmacist) per the Pharmacy Manual.

8.1.1.2 Routine Vaccines for Primary Immunizations and Booster Vaccinations

NPI-recommended routine vaccines (other than poliomyelitis vaccine and pentavalent vaccine, see above) will be sourced locally by the site and administered in accordance with the approved package labeling. Additional injectable routine infant vaccines given concomitantly will be administered in a limb different from that of the sIPV / reference IPV vaccination.

Refer to Section 8.4 for investigational vaccine blind maintenance.

8.1.2 Storage

Vaccine will be shipped in refrigerated containers. From receipt and prior to use, the vaccine must be stored at 2°C to 8°C in a refrigerator.

All clinical trial material must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. All sponsor-supplied vaccines must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the vaccine storage area must be maintained every working day. Temperature excursions must be reported to the sponsor as soon as possible and use of these vaccines requires sponsor approval.

8.1.3 Dose and Regimen

Each subject who meets all the inclusion criteria and none of the exclusion criteria will be randomly assigned to receive either sIPV or reference IPV/placebo via the IRT. In all parts of the

study (adult lead-in, toddler lead-in and infant dose ranging), trial vaccines should be prepared by site personnel who are unblinded while maintaining the blind for other study personnel.

Table 8.a describes the dose(s) that will be provided to each group.

Table 8.a Sponsor-Supplied Vaccines and Reference

Treatment Group	Dose	Treatment Description	Timing			
		Vaccine	Dose 1[(b)]	Dose 2[(b)]	Dose 3[(b)]	Dose 4
A) Adult lead-in						
Arm 1	High-dose[(a)]	sIPV H	Day 1	-	-	-
Arm 2	Placebo	Placebo	Day 1	-	-	-
B) Toddler lead-in						
Arm 1	High-dose[(a)]	sIPV H	Day 1	-	-	-
Arm 2	Reference IPV	IPV Reference	Day 1	-	-	-
C) Infant dose ranging						
Arm 1	Low-dose[(a)]	sIPV L	Day 1	Day 29	Day 57	Day 365
Arm 2	Medium-dose[(a)]	sIPV M	Day 1	Day 29	Day 57	Day 365
Arm 3	High-dose[(a)]	sIPV H	Day 1	Day 29	Day 57	Day 365
Arm 4	Reference IPV	IPV Reference	Day 1	Day 29	Day 57	Day 365

(a) Low-dose = 0.75, 25, and 25 DU; Medium-dose = 1.5, 50, and 50 DU; High-dose = 3, 100, and 100 DU
(b) Subjects will also receive DTP-HBV-Hib vaccine at the same visit; pentavalent vaccine will be administered in a limb different from that of the sIPV / reference IPV vaccination.

8.2 Trial Vaccine Assignment and Dispensing Procedures

Each subject will be assigned a unique study number supplied by the sponsor. Subjects will be assigned to receive their treatment according to the schedule allocated to the study site. The investigator or investigator's designee will access the IRT to obtain the subject number at screening.

Vaccination will be performed by suitably qualified and authorized study personnel. Blinded personnel must not be present during dose preparation or at point of administration. An unblinded nurse or administrator will be required to administer the vaccines to the infants and toddlers.

If sponsor-supplied vaccine is lost or damaged, the site can request a replacement via IRT (refer to IRT manual separately). Expired vaccines must not be administered.

PRECAUTIONS TO BE OBSERVED IN ADMINISTERING THE TRIAL VACCINE:

Prior to vaccination, a subject must be determined to be eligible for trial vaccination and it must be clinically appropriate in the judgment of the investigator to vaccinate. Eligibility for vaccination prior to first trial vaccine administration is determined by evaluating the entry criteria outlined in this protocol (Sections 7.1 and 7.2).

Eligibility for subsequent trial vaccination is determined by following the criteria outlined in Section 7.0.

Trial vaccines should not be administered to individuals with known hypersensitivity to any component of the vaccines.

Standard immunization practices are to be observed and care should be taken to administer the injection intramuscularly. In addition, WHO recommendations to reduce anxiety and pain at the time of vaccination should be followed [9]. Before administering the vaccine, the vaccination site is to be disinfected with a skin disinfectant (eg, 70% alcohol). Allow the skin to dry. DO NOT inject intravascularly.

As with all injectable vaccines, trained medical personnel and appropriate medical treatment should be readily available in case of anaphylactic reactions following vaccination. For example, epinephrine 1:1000, diphenhydramine, and/or other medications for treating anaphylaxis should be available.

8.3 Randomization Code Creation and Storage

Randomization personnel of the sponsor or designee will generate the randomization schedule for the adult lead-in, the toddler lead-in and the infant dose ranging cohorts. Randomization information will be stored in a secured area, accessible only by authorized personnel. At the Randomization Visit, all qualified subjects will be randomized to one of the 2 (adult and toddler lead-ins) or 4 (infant dose ranging) arms in a 1:1 or a 1:1:1:1 ratio, respectively, using IRT.

8.4 Trial Vaccine Blind Maintenance

This trial is an observer-blind study. The subjects, data collectors (eg investigator), and data evaluators (eg trial statisticians) are blinded to the material administered. The investigational product assignment will be maintained by the unblinded site staff designee.

All care must be taken to ensure that the unblinded reports and documents are shared only with unblinded personnel and properly stored in a secured area, accessible only by authorized personnel.

8.5 Unblinding Procedure

The trial vaccine blind shall not be broken by the investigator unless information concerning the trial vaccine is necessary for the medical treatment of the subject. In the event of a medical emergency, if possible, the medical monitor should be contacted before the trial vaccine blind is broken to discuss the need for unblinding.

For unblinding a subject, the trial vaccine blind can be obtained by the investigator, by accessing the IRT. The sponsor's Pharmacovigilance Department must be notified as soon as possible if the trial vaccine blind is broken by the investigator and the completed SAE form must be sent within 24 hours. The date, time, and reason the blind is broken must be recorded in the source document and the same information (except the time) must be recorded on the eCRF.

If any subject is unblinded, the subject must be withdrawn from the trial, and their data no longer evaluated. However, further doses of vaccine are to be administered to ensure completion of the NPI-recommended schedule, and they should be monitored for safety parameters.

8.6 Accountability and Destruction of Sponsor-Supplied Vaccines

Vaccine supplies will be counted and reconciled at the site before being returned to the sponsor or designee as noted below. Sites will maintain source documents in addition to entering data in the IRT.

The investigator or designee must ensure that the sponsor-supplied vaccine is used in accordance with the approved protocol and is administered only to subjects enrolled in the trial. To document appropriate use of sponsor-supplied vaccines (sIPV, reference IPV, placebo and DTP-HBV-Hib), the investigator must maintain records of all sponsor-supplied vaccine delivery to the site, site inventory, administration and use by each subject, and return to the sponsor or designee.

Upon receipt of sponsor-supplied vaccine(s), the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, the trial vaccine is received within the labeled storage conditions (ie, no cold chain break has occurred during transit), and is in good condition. If quantity and conditions are acceptable, investigator or designee will acknowledge receipt of the shipment.

If there are any discrepancies between the packing list versus the actual product received, the sponsor or designee must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator must maintain 100% accountability for all sponsor-supplied vaccines [including challenge agents, ancillary materials, as applicable] received and administered during their entire participation in the trial. Proper vaccine accountability includes, but is not limited to:

- Verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the vaccine lot (or Vaccine Med ID or job number) used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The investigator must record the current inventory of all sponsor-supplied vaccines (sIPV, reference IPV, placebo and DTP-HBV-Hib) on a sponsor-approved vaccine accountability log.

The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied vaccines, expiry date and amount. The IRT should include all required information as a separate entry for each subject to whom sponsor-supplied vaccine is administered.

Prior to site closure or at appropriate intervals throughout the trial, before any clinical trial materials are returned to the sponsor or its designee for destruction, a representative from the sponsor or its designee will perform clinical trial material accountability and reconciliation. The investigator will retain a copy of the documentation regarding clinical trial material accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

The pharmacist (or designated individual) at each site will be responsible for vaccine accountability and will document receipt, use, return, or destruction of trial vaccines. Vaccine accountability documentation will be reviewed by the unblinded monitor during clinical monitoring visits.

9.0 TRIAL PLAN

9.1 Trial Procedures

The following sections describe the trial procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Trial Procedures is located in Section 0.

9.1.1 Informed Consent Form

The requirements of the informed consent form are described in Section 15.2.

Informed consent from the subject or the subject's LAR must be obtained prior to the subject entering into the trial, and before any protocol-directed procedures are performed.

A unique subject number will be assigned to each subject after informed consent is obtained from the IRT. If all eligibility criteria are fulfilled, this subject number will be used throughout the trial. Subject numbers assigned to subjects who fail screening should not be reused (Section 9.1.10).

9.1.2 Demographics, Medical History and Prior Medications

Demographic information to be obtained will include date of birth, sex, and race as described by the subject or the subject's LAR.

Medical History will also be collected, including but not limited to any medical history that may be relevant to subject eligibility for trial participation such as gestational age and birth weight (for infants in the dose ranging cohort only), prior vaccinations, concomitant medications, and previous and ongoing illnesses or injuries. Relevant medical history can also include any medical history that contributes to the understanding of an AE that occurs during trial participation, if it represents an exacerbation of an underlying disease/preexisting problem.

All medications, vaccines and blood products taken or received by the subjects within:

a) Medications: 4 weeks prior to the start of the trial

b) Vaccines: 4 weeks prior to the start of the lead-in study. Infants in the dose ranging study should only have received any routine vaccines recommended by the NPI at birth. Information on previous polio vaccinations should be collected for toddlers in the lead-in cohort.

c) Blood products: 4 weeks prior to the start of the trial

are to be recorded on the Prior and Concomitant Medications eCRF. The use of antipyretics and/or analgesic medications within 24 hours prior to vaccination must be identified and the reason for their use (prophylaxis versus treatment) must be described in the source documents or the eCRF. Trial vaccination should be delayed if subjects have used antipyretics/analgesic medications within 24 hours prior to vaccine administration.

Medications taken for prophylaxis are those intended to prevent the onset of AEs following vaccination. Medications taken for treatment are intended to reduce or eliminate the presence of symptoms that are present.

Assess and record concomitant therapy (prescription medications ONLY) and vaccine history from 1 month prior to Day 1 in the subject's source document.

Prohibited Therapies: Refer to Section 7.2.

These data must be written in the source documents.

Medical history (including corresponding medication) to be obtained will include any significant conditions or diseases that have disappeared or resolved at or prior to signing of informed consent form.

9.1.3 Documentation of Trial Entrance/Randomization

Only subjects who have a signed informed consent form, meet all of the inclusion criteria and none of the exclusion criteria are eligible for entrance/randomization into the vaccination phase. The randomization schedule will be created and processed by the IRT provider. The randomization specification will be approved by the sponsor's trial statistician, or designee.

If the subject is found to be ineligible for randomization/trial phase, the investigator should record the primary reason for failure on the subject enrollment log.

9.1.4 Physical Examination

Physical examinations must be performed by a qualified health professional in accordance with local regulations and licensing requirements designated within the Site Responsibility Delegation Log. Complete physical exam will be performed on Day 1 according to the investigator's standard practice. Additional physical examinations may be performed if indicated by review of the subject's medical history. The findings should be documented in the subject's source document.

Symptom-directed physical examination may be performed if deemed necessary.

9.1.5 Vital Signs

Vital signs to be measured in this study are respiratory and heart rates, and temperature (preferably measured as oral temperature for the adult cohort and rectal temperature for the toddler and infant cohorts).

For the adult lead-in cohort, height and weight are measured at enrollment only; for the toddler lead-in cohort, height and weight are measured at enrollment and at the last study visit. For the infant dose ranging cohort, height and weight are measured at each visit.

9.1.6 Immunogenicity Assessments

Subjects in the toddler lead-in and the infant dose ranging cohorts (all vaccine arms) will undergo blood sampling for serological immunogenicity testing before their first primary

vaccination and 28 days after their second and third primary vaccination in the infant dose ranging cohort, and before and 28 days after booster vaccination in the infant dose ranging and toddler lead-in cohorts. All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood taken at any single visit is approximately 5 mL, and the approximate total volume of blood for the trial is maximum 10 mL for toddlers in the lead-in cohort and 25 mL for infants in the dose ranging cohort. Blood samples will be processed and stored at the trial site in accordance with the Laboratory Guidelines.

9.1.7 Safety Assessments

Safety assessments will include collection and recording of solicited local (injection site) and systemic AEs, and unsolicited AEs (serious and non-serious). Refer to Section 10.1 for safety definitions. Details on collection and reporting of AEs are in Section 10.5.

9.1.8 Contraception and Pregnancy Avoidance Procedure

For female subjects of childbearing potential, pregnancy testing will be performed on Day 1 prior to enrollment. Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy and donation of ova. Women of childbearing potential will receive guidance with respect to the avoidance of pregnancy as part of the trial procedures (Section 2.1).

9.1.9 Pregnancy

Adult lead-in cohort

To ensure subject safety and the safety of the unborn child, each pregnancy in a subject having received a trial vaccine must be reported to the sponsor within 24 hours of the site learning of its occurrence. The pregnancy must be followed to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if the intended duration of safety follow-up for the trial has ended.

Any pregnancy occurring following trial vaccine administration should be reported immediately, using a pregnancy notification form, to the contact listed in the Investigator Site File.

Should a pregnancy occur after the administration of a blinded trial vaccine, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator and procedures must be followed as described in Section 8.5.

9.1.10 Documentation of Subjects who are not Randomized

Investigators must account for all subjects who have a signed informed consent form. If the subject is found to be not eligible at this visit, the investigator should complete the eCRF. The IRT supplier should be contacted as a notification of non-randomization.

The primary reason for non-randomization is recorded in the eCRF using the following categories:

- Screen failure (did not meet one or more inclusion criteria or did meet one or more exclusion criteria),
- Withdrawal by the subject or the subject's LAR,
- Trial terminated by sponsor.

Subject numbers assigned to subjects who fail screening should not be reused.

9.2 Monitoring Subject Treatment Compliance

The investigator records all injections of trial vaccine given to the subject in the eCRF.

9.3 Schedule of Observations and Procedures

The schedule for all trial-related procedures for all evaluations is shown in Section 2.1. Assessments should be completed at the designated visit/time point(s).

9.3.1 Pre-Vaccination Procedures (Day 1)

1. Confirm informed consent and complete signing of informed consent form.
2. Demographics.
3. Prior and concomitant medication. This should include the vaccines that will be concomitantly administered with the trial vaccine at this visit.
4. Medical history.
5. Physical examination.
6. Vital signs.
7. Review of eligibility criteria.
8. Enrollment/randomization.
9. Blood sampling for toddler lead-in and infant dose ranging cohorts. Blood should be taken from the subject in the infant cohort using an aseptic venipuncture technique for serological immunogenicity testing.

9.3.2 Pre-Vaccination Procedures (Days 29, 57 and 365)

Temperature will be taken pre-vaccination and in case of fever a delay of vaccination should be considered (see Section 7.3). Symptom-directed physical examination is to be performed in case of symptoms prior to each vaccination. Concomitant medication, including the vaccines that will be concomitantly administered with the trial vaccine at the visit, should be recorded.

Blood sampling should be taken for subjects in the infant dose ranging cohort; blood sampling will be performed before vaccination on Day 57 and Day 365.

9.3.3 Vaccination Procedures (Days 1, 29, 57 and 365)

After confirming eligibility and enrolling the subject (on Day 1), perform vaccination according to the assigned trial vaccine in all cohorts and according to the procedures described in Section 8.2. At later clinic visits in the infant dose ranging cohort that involve vaccination (Days 29, 57 and 365), confirm that the subject does not meet any criteria for delaying or cancelling additional trial vaccination, as described in Section 7.3.

9.3.4 Post Vaccination procedures (Days 1, 29, 57 and 365)

The following post-vaccination procedures will be performed on Day 1:

- Careful training of the subject (adult cohort) or subject's LAR (toddler and infant cohorts) on how to measure local AEs and body temperature, how to complete the diary card and how often to complete the diary card. Training should be directed at the individual(s) who will perform the measurements of local AEs and those who will enter the information into the diary card. In the toddler and infant cohorts, this individual may or may not be the subject's LAR, but if a person other than the subject's LAR enters information into the diary card, this person's identity must be documented in the trial file and this person must receive training on the diary card. Training of the subject (adult cohort) or subject's LAR (toddler and infant cohorts) on how to measure an injection site AE should be performed while the subject is under observation after vaccination.

Diary card instructions must include the following:

- The subject (adult cohort) or subject's LAR (toddler and infant cohorts) must understand that timely completion of the diary card on a daily basis is a critical component of trial participation. The subject or subject's LAR should also be instructed to write clearly and to complete the diary card in pen. Any corrections to the diary card that are performed by the person completing the diary card should include a single strikethrough line with a brief explanation for any change and be initialed and dated.

Please note:

Diary cards will be the only source document allowed for remote collection of solicited local and systemic AEs (including body temperature measurements). The following additional rules apply to the documentation of safety information collected by diary card:

- The diary card should be reviewed with the subject (adult cohort) or subject's LAR (toddler and infant cohorts).
- No corrections or additions to the diary card will be allowed after it is reviewed with the investigator/designee.
- Any data that is identified as implausible or incorrect, and confirmed by the subject (adult cohort) or subject's LAR (toddler and infant cohorts) to be a transcription error should be corrected by the subject or subject's LAR on the diary card (the correction should include a single strikethrough line and should be initialed and dated by the subject or subject's LAR).

- Any blank or illegible fields on the diary card not otherwise corrected as above will be missing in the eCRF.
- The site must enter all readable entries on the diary card into the eCRF.
- Any newly described solicited safety information should be added to the diary card by the subject (adult cohort) or subject's LAR (toddler and infant cohorts) and initialed and dated. Any new unsolicited safety information would be recorded in the subject source document as a verbally reported event and therefore captured as an AE and recorded in the eCRF.
- Starting on the day of vaccination, the subject (adult cohort) or subject's LAR (toddler and infant cohorts) will check for specific types of events at the injection site (solicited local AEs), any specific generalized symptoms (solicited systemic AEs), body temperature (any method), any other symptoms or change in the subject's health status, and any medications taken (excluding vitamins and minerals). These solicited AEs and body temperature will be recorded in the diary. Assessments should preferably take place in the evening at day's end.
- Temperature measurement (preferrably by the oral route for the adult cohort and by the rectal route for the toddler and infant cohorts) is to be performed using the thermometer provided by the site. If the subject feels unusually hot or cold during the day, the subject or subject's LAR should check their temperature. If the subject has fever, the highest body temperature observed that day should be recorded on the diary card.
- The measurement of solicited local AEs (erythema, swelling, and induration) is to be performed using the ruler provided by the site.
- The collection on the diary card of body temperature, solicited local AEs, and solicited systemic AEs will continue for a total of 7 days following vaccine administration. The collection on the diary card of unsolicited AEs and medications will continue for 28 days following vaccine administration by Diary Card.

After vaccination, the subject will be observed for at least 30 minutes including observation for immediate reactions and body temperature measurement. Information should be recorded in the eCRF as immediate reactions. The investigator or delegate will take the opportunity to remind the subject (adult cohort) or subject's LAR (toddler and infant cohorts) how to measure solicited AEs and body temperature as part of this observation period. All safety data will be collected in the subject's source documents.

The site should schedule the next trial activity with the subject (adult cohort) or subject's LAR (toddler and infant cohorts).

The subject (adult cohort) or subject's LAR (toddler and infant cohorts) will receive a written reminder of the next planned trial activity. The subject or subject's LAR will be reminded to complete the Diary Card daily and to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit. All contact details will be provided to the subject or subject's LAR.

9.3.5 Clinic Visits after Vaccination (Day 8 in the adult lead-in cohort, Day 29 in the toddler lead-in cohort and Days 85 and 393 in the infant dose ranging cohort)

Clinic visits that do NOT include a vaccination will be performed on Day 8 in the adult lead-in cohort, Day 29 in the toddler lead-in cohort, and Days 85 and 393 in the infant dose ranging cohort. At the clinic visit, the Diary Card will be reviewed. The healthcare professional reviewing these data will discuss the AEs (if any) reported by the subject or subject's LAR and will determine if any additional diagnoses and/or AEs are present and/or concomitant medications have been used.

The site should schedule the next trial activity with the subject's LAR for all subjects in the toddler lead-in and infant dose ranging cohorts.

The subject's LAR will receive a written reminder of the next planned trial activity. The subject's LAR will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

9.3.6 Phone Contacts - Reminder Calls (Days 8, 36, 64 and 372)

Post-vaccination reminder phone calls will be performed 7 days after each vaccination (Day 8 in the toddler lead-in cohort, Days 8, 36, 64 and 372 in the infant dose ranging cohort). The purpose is to remind the subject's LAR about completion of the diary card. If the subject's LAR wishes to describe safety information, this information should only be collected by a trained healthcare professional at the site, and the safety data described must be written down in source documents. The subject's LAR should be reminded to write the information down in the diary card and to contact the site via the telephone number provided in the informed consent form to discuss medical questions.

9.3.7 Phone Contacts – Safety Call (Days 183 and 547)

A safety call will be performed on Day 183 in both the toddler lead-in and infant dose ranging cohorts, and additionally on Day 547 in the infant dose ranging cohort. Safety calls are calls made to the subject or subject's LAR by a trained healthcare provider. The subject or subject's LAR will be interviewed according to a script, and information relating to SAEs and/or AEs leading to trial or vaccine withdrawal and concomitant medications or vaccinations associated with those events will be collected. All safety information described by the subject or subject's LAR must be written down in a designated location within the source documents and not written on the script used for the telephone call.

The site should schedule the next clinic visit with the subject's LAR, as appropriate.

The subject's LAR will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

For subjects in the adult lead-in cohort, the investigator should inform and educate the subject that any adverse medical occurrence being perceived as serious up to 6 months after vaccination should be reported (passive follow up for safety).

9.3.8 Final (End of Trial) Visit

Adult lead-in cohort

The Final Study Visit will be on Day 8. For all subjects, the investigator must complete the End of Trial eCRF page.

Toddler lead-in cohort

The Final Site Visit will be on Day 29, but the Final Study Visit is a telephone call on Day 183. If a subject terminates earlier, end of trial visit procedures should be performed if possible. For all subjects, the investigator must complete the End of Trial eCRF page.

Infant dose ranging cohort

The Final Study Visit will be performed on Day 393. If a subject terminates earlier, end of trial visit procedures should be performed if possible. For all subjects, the investigator must complete the End of Trial eCRF page.

9.3.9 Post-Trial Care

No post-trial care will be provided, except to ensure that all subjects in the toddler lead-in and infant dose ranging cohorts receive their complete number of polio vaccine doses as recommended by the NPI, and that toddlers from both the lead-in cohort and the dose ranging cohort (after their booster dose) who received the trial sIPV vaccine are seropositive or have demonstrated a vaccine response which shows seroprotection. Toddlers from the lead-in cohort who do not meet these criteria will be offered a single dose of the reference IPV (note: toddlers that have received bivalent OPV exclusively for primary immunization may not achieve seropositivity to poliovirus type 2. Therefore, subjects with documented primary immunization against serotypes 1 and 3 only who do not respond to serotype 2 post sIPV booster will not be offered re-vaccination). Toddlers in the dose ranging cohort, who received sIPV as infants in their primary series and their toddler booster dose, and who have no neutralizing antibodies to any of the three poliovirus serotypes (titer <8) on Day 393 will be offered re-vaccination with a single series of three immunizations of the reference IPV after the unblinding occurs and serological results become available, and outside of the IPV-102 clinical trial.

9.4 Biological Sample Retention and Destruction

In this trial, specimens for immune response testing will be collected for subjects enrolled in the toddler lead-in and infant dose ranging cohorts as described in Section 9.1.6. After blood draw and serum processing, the serum samples will be preserved and retained at a central laboratory that was contracted by the sponsor for this purpose for up to but not longer than 20 years or as required by applicable law. The sponsor has put into place a system to protect the subjects'

personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

Serum samples will be used for the analyses defined in this protocol, but can also, with permission from the subject's LAR, be used to assess, improve or develop tests related to the disease(s) or the vaccine(s) under trial that will allow more reliable measurement of the response to the vaccine(s).

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Events (AEs)

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a trial vaccine; it does not necessarily have to have a causal relationship with trial vaccine administration.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the administration of a trial vaccine whether or not it is considered related to the trial vaccine.

AEs will be graded by the investigator in the following manner:

Mild	Grade 1	• Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities. Relieved with or without symptomatic treatment.
Moderate	Grade 2	• Sufficient discomfort is present to cause interference with normal activity. Only partially relieved with symptomatic treatment.
Severe	Grade 3	• Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities. Not relieved with symptomatic treatment

10.1.2 Solicited Adverse Events

The occurrence of selected indicators of safety (Table 10.a) will be measured/collected for the 7 days after vaccination (including the day of vaccination) and will be recorded on the "Local and Systemic AEs" eCRF as applicable. These will be summarized in the final report under the category "solicited adverse events" to differentiate them from other AEs which were not solicited. Any solicited local or systemic AE observed as continuing on Trial Day 8 will be recorded as an AE on the Adverse Event eCRF.

Table 10.a Local and Systemic AEs

Local AEs (injection site):	Pain
	Erythema
	Induration
	Swelling
Systemic AEs (adult lead-in cohort):	Fever[(a)]
	Headache
	Asthenia
	Malaise
	Arthralgia
	Myalgia
Systemic AEs (toddler lead-in and infant dose ranging cohorts):	Drowsiness
	Irritability/fussiness
	Loss of appetite
	Fever[(a)]

(a) Body temperature will be collected and recorded. Fever is defined as greater than or equal to 38°C (100.4°F) regardless of method used [10].

The intensity of solicited safety parameters will be assessed as described in Table 10.b (adult cohort) and Table 10.c (toddler and infant cohorts).

Table 10.b Solicited Safety Parameters - Adult Lead-In Cohort

Adverse Event	Intensity grade	Severity/Intensity
Pain at injection site	0	None
	1	Mild: No interference with daily activity
	2	Moderate: Interference with daily activity with or without treatment
	3	Severe: Prevents daily activity with or without treatment
Erythema at injection site [(a)]	0	<25 mm
	1	Mild: ≥25 – ≤ 50 mm
	2	Moderate: > 50 – ≤ 100 mm
	3	Severe: > 100 mm
Induration at injection site [(a)]	0	<25 mm
	1	Mild: ≥25 – ≤ 50 mm
	2	Moderate: > 50 – ≤ 100 mm
	3	Severe: > 100 mm
Swelling at injection site [(a)]	0	<25 mm
	1	Mild: ≥25 – ≤ 50 mm
	2	Moderate: > 50 – ≤ 100 mm
	3	Severe: > 100 mm
Headache	0	None
	1	Mild: No interference with daily activity
	2	Moderate: Interference with daily activity with or without treatment
	3	Severe: Prevents normal activity with or without treatment
Asthenia	0	None
	1	Mild: No interference with daily activity
	2	Moderate: Interference with daily activity
	3	Severe: Prevents daily activity
Malaise	0	None
	1	Mild: No interference with daily activity
	2	Moderate: Interference with daily activity
	3	Severe: Prevents daily activity
Arthralgia	1	None
	2	Mild: No interference with daily activity
	3	Moderate: Interference with daily activity
	4	Severe: Prevents daily activity
Myalgia	0	None
	1	Mild: No interference with daily activity
	2	Moderate: Interference with daily activity
	3	Severe: Prevents daily activity
Fever[(b)]	Record body temperature in °C/°F	

(a) Subjects are to record greatest surface diameter in mm in the Diary.
(b) Fever is defined as greater than or equal to 38°C (100.4°F) regardless of method taken.

Table 10.c Solicited Safety Parameters - Toddler Lead-In Cohort and Infant Dose Ranging Cohort

Adverse Event	Intensity grade	Severity/Intensity
Pain at injection site	0	None
	1	Mild: Minor reaction to touch
	2	Moderate: Cries/protests on touch
	3	Severe: Cries when limb is moved/spontaneously painful
Erythema at injection site [(a)]	0	<10 mm
	1	Mild: ≥10 – ≤ 20 mm
	2	Moderate: > 20 – ≤ 40 mm
	3	Severe: > 40 mm
Induration at injection site [(a)]	0	<10 mm
	1	Mild: ≥10 – ≤ 20 mm
	2	Moderate: > 20 – ≤ 40 mm
	3	Severe: > 40 mm
Swelling at injection site [(a)]	0	<10 mm
	1	Mild: ≥10 – ≤ 20 mm
	2	Moderate: > 20 – ≤ 40 mm
	3	Severe: > 40 mm
Drowsiness	0	Behavior as usual
	1	Mild: Drowsiness easily tolerated
	2	Moderate: Drowsiness that interferes with normal activity
	3	Severe: Drowsiness that prevents normal activity
Irritability/fussiness	0	Behavior as usual
	1	Mild: Crying more than usual/no effect on normal activity
	2	Moderate: Crying more than usual/interferes with normal activity
	3	Severe: Crying that cannot be comforted/prevents normal activity
Loss of appetite	0	Appetite as usual
	1	Mild: Eating less than usual/no effect on normal activity
	2	Moderate: Eating less than usual/interferes with normal activity
	3	Severe: Not eating at all
Fever[(b)]	Record body temperature in °C/°F	

(a) Subject's LARs are to record greatest surface diameter in mm in the Diary.
(b) Fever is defined as greater than or equal to 38°C (100.4°F) regardless of method taken.

10.1.3 Serious Adverse Events (SAEs)

An SAE is defined as any untoward medical occurrence that:

1. Results in DEATH.
2. Is LIFE THREATENING.
   - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 4 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

10.2 Causality of AEs

Relatedness (causality) to vaccine will also be assessed by the investigator. The relationship of each AE, including solicited systemic AEs (solicited local AEs are considered as related) to trial vaccine(s) will be assessed using the following categories:

Related:	There is suspicion that there is a relationship between the trial vaccine and the AE (without determining the extent of probability); there is a reasonable possibility that the trial vaccine contributed to the AE.
Not Related:	There is no suspicion that there is a relationship between the trial vaccine and the AE; there are other more likely causes and administration of the trial vaccine is not suspected to have contributed to the AE.

10.2.1 Relationship to Trial Procedures

Relationship (causality) to trial procedures should be determined for all AEs.

The relationship should be assessed as "Yes" if the investigator considers that there is reasonable possibility that an event is due to a trial procedure. Otherwise, the relationship should be assessed as "No".

10.2.2 Outcome of AEs

Resolved:	The subject has fully recovered from the event or the condition has returned to the level observed at baseline
Resolving:	The event is improving but the subject is still not fully recovered
Not resolved:	The event is ongoing at the time of reporting and the subject has still not recovered
Resolved with *sequelae*:	As a result of the AE, the subject suffered persistent and significant disability/incapacity (eg, became blind, deaf or paralysed)
Fatal:	The subject died due to the event. If the subject died due to other circumstances than the event, the outcome of the event per se should be stated otherwise (eg, Not Resolved or Resolving)
Unknown:	If outcome is not known or not reported.

10.3 Additional Points to Consider for AEs

An untoward occurrence generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. Intermittent events for pre-existing conditions or underlying disease should not be considered as AEs.
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require vaccine discontinuation or a change in concomitant medication.
- Be considered unfavorable by the investigator for any reason.

Diagnoses *vs.* signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, signs or symptoms should be recorded appropriately as AEs.

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after starting administration of the trial vaccine, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in trial vaccine, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs:

- If the subject experiences changes in severity of an AE, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent form are not considered AEs. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

10.4 Procedures

10.4.1 Collection and Reporting of AEs

All AEs, whether considered related with the use of the trial vaccine or not, must be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report should be supplied, if possible. All findings must be reported on an AE eCRF and on the SAE form, if necessary (see Section 10.4.2). All findings in subjects experiencing AEs must also be reported in the subject's source documents. Any unsolicited AEs will be collected for 7 days (adult lead-in cohort) or 28 days (toddler lead-in and infant dose ranging cohorts) after each vaccination via diary cards.

The following information will be documented for each event:

- Reported term for the Adverse Event,
- Start and end date,
- Serious (Y/N),
- Severity,
- Investigator's opinion of the causality (relationship) between the event and administration of trial vaccine(s) ("related" or "not related"),
- Investigator's opinion of the causality (relationship) to trial procedure(s), including the details of the suspected procedure,
- Action taken with the trial treatment (trial vaccine),
- Outcome of event.

10.4.2 Collection and Reporting of Solicited AEs

The occurrence of selected indicators of safety will be collected on diary cards by the subject (adult cohort) or the subject's LAR (toddler and infant cohorts) for 7 days post-vaccination and will be recorded on the "Local and Systemic AEs" eCRF, as appropriate.

In the toddler lead-in and in the infant dose ranging cohorts, any solicited local or systemic AE observed as continuing on trial Day 8 will be recorded as an unsolicited AE on the Adverse Event eCRF. Any solicited local or systemic AE that resolved before Day 7 but recurs at a later time (ie, if discontinues), will be recorded as an unsolicited AE on the Adverse Event eCRF.

Any solicited AE that meets any of the following criteria must be entered as an AE on the Adverse Event eCRF.

- Solicited local or systemic AEs that lead the subject's withdrawal from the trial.
- Solicited local or systemic AEs that lead to the subject being withdrawn from the trial by the Investigator.
- Solicited local and systemic AEs that otherwise meet the definition of an SAE (see Section 10.1.2).

10.4.3 Collection and Reporting of SAEs

Collection of SAEs will commence from the time that the subject is first administered the trial vaccine (Day 1). Routine collection of SAEs will continue until the end of the trial (Day 8 in the adult lead-in cohort, Day 183 in the toddler lead-in cohort and Day 547 in the infant dose ranging cohort).

SAEs should be reported according to the following procedure:

A sponsor SAE form must be completed, in English, and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the trial vaccine(s) – if no unblinding is necessary, in a blinded way.
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact(s) in the list provided to each site.

10.5 Follow-up Procedures

10.5.1 AEs

All AEs will be monitored until resolution or a stable status is reached or until a formal diagnosis can be made or until the end of the trial, whichever occurs first.

10.5.2 SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, laboratory tests, discharge summary, postmortem results) should be sent to the sponsor.

All SAEs should be followed up until resolution or permanent outcome of the event or is otherwise explained. Ongoing SAEs could potentially be followed outside of this trial or in a planned extension trial. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.5.3 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor or designee will be responsible for the reporting of all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the trial is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted within 7 days for fatal and life-threatening events and 15 days for other SUSARs, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the trial vaccine administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to their IRB or IEC in accordance with national regulations.

10.5.4 Post-Trial Events

Adult lead-in cohort

The investigator should inform and educate the subjects that any adverse medical occurrence being perceived as serious up to 6 months after vaccination should be reported (passive follow up for safety). The investigator must report these SAEs to the sponsor.

Toddler lead-in and infant dose ranging cohorts

Any AE that occurs outside of the protocol-specified observation period or after the end of the trial must be reported to the sponsor. These AEs will be processed by the sponsor's Pharmacovigilance Department. Instructions for how to submit these AEs will be provided in a handout in the Investigator Site File.

11.0 TRIAL-SPECIFIC REQUIREMENT(S)

No trial-specific committee is planned for this trial.

11.1 Halting Rules

No specific halting rules have been defined for this trial.

11.2 Trial-Specific Committees

11.2.1 Data Monitoring Committee

The DMC will have study-specific responsibilities to review IPV-102 data and decide on the enrollment of the toddler and infant cohorts after reviewing 7 days of safety and tolerability follow-up post vaccination in adults in the lead-in cohort. In addition, the DMC will evaluate the overall tolerability and safety of Takeda's sIPV on an ongoing basis. The DMC will be entitled to stop enrollment of additional subjects or to stop administration of additional sIPV doses. The composition, role and responsibilities of the DMC are presented in a separate DMC Charter.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA [SOC, HLGT, HLT, LL, PT, and their corresponding descriptive terms]). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 Electronic CRFs (eCRF)

Completed eCRFs are required for each subject who provides a signed informed consent form.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this trial to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are entered directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by sponsor personnel (or designees) and will be answered by the site.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal investigator or designee must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the trial site during periodic visits by trial monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the trial to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.0 and those documents that include (but are not limited to) the trial-specific documents, the identification log of all participating subjects, medical records. Temporary media such as thermal sensitive paper should be copied and certified, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of vaccine disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Furthermore, International Council on Harmonization (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at

least 2 years after the last approval of a marketing application for a specified vaccine indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the trial records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of subject's treatment assignment. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all trial objectives.

A blinded data review will be conducted prior to unblinding of subject's vaccination assignment. This review will assess the accuracy and completeness of the trial database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

Safety Set: The Safety Set will consist of all subjects who received at least one dose of the trial vaccines.

Full Analysis Set (FAS): The FAS will include all subjects who were randomized and received at least one dose of the trial vaccines.

Per–Protocol Set (PPS): The PPS will include all subjects in the FAS who have no major protocol violations. The major protocol violation criteria will be defined in the Statistical Analysis Plan (SAP). Subjects with major protocol violations will be identified as part of the blinded data review prior to the unblinding of subject's investigational trial vaccine assignment. The categories of major protocol violations include: (1) not meeting selected entry criteria, (2) receiving a wrong trial vaccine or an incorrect regimen, (3) receiving prohibited therapies, and (4) other major protocol violations that may be identified during blinded data reviews.

All summaries and analyses of safety data will be based on subjects in the Safety Set. The primary immunogenicity analyses will be based on the PPS, and additional sensitivity analyses will be based on the FAS.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Descriptive summaries of age, gender, race, and other baseline characteristics will be presented by formulation arm. Unless specified otherwise, number of subjects with non-missing observations, mean, standard deviation (SD), median, minimum and maximum will be presented for continuous data; and frequency and percent will be presented for categorical data.

13.1.3 Immunogenicity Analysis

Descriptive statistics for the primary, secondary, and exploratory immunogenicity endpoints, including estimates and 95% confidence intervals for SCR, SPR, VRR, and GMT will be provided by study arm and by poliovirus type. For the dose ranging cohort only, estimates and 95% confidence intervals for differences in SCR, SPR, and VRR, as well as ratios in GMT, will be provided for each pair of study arms by poliovirus type.

More specific details about the immunogenicity analyses will be provided in the SAP.

13.1.4 Safety Analysis

Reactogenicity will be assessed for 7 days following each vaccination (including day of vaccination) via collection of solicited AEs, including local reactions (injection site: pain, erythema, induration, and swelling) and systemic AEs of irritability/fussiness, drowsiness, loss of appetite, for children in both cohorts daily. In addition, body temperature as indicator of reactogenicity will be collected (with fever defined as body temperature ≥38°C).

For each solicited AE and fever, the percentage of subjects will be summarized by event severity for each day for the 7 days after each vaccination and overall. For subjects with more than one episode of the same event, the maximum severity will be used for tabulations.

Unsolicited AEs, and SAEs, will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT) for each formulation arm.

In general, unsolicited AEs will be tabulated at each of the following levels: overall summary (subject with at least 1 AE), and by SOC and PT. Unsolicited AEs will be summarized as follows: by PT; by SOC and PT; by SOC, PT, and severity; by SOC, PT, and relationship (causality) to the investigational trial vaccine; and by SOC and PT, including events with frequency greater than a pre-defined frequency (the percentage will be specified in the SAP).

13.2 Interim Analysis and Criteria for Early Termination

An interim analysis will be performed after the primary safety and immunogenicity data (28 days after the last dose of the primary immunization series in the infant dose ranging cohort) are available on Day 85. The interim analyses will be performed by a separate set of unblinded statisticians and programmers who will have access to individual treatment assignments but will not be involved in subsequent study conduct. The results of the interim analysis will be used, following the appropriate Takeda Vaccines guidance, to inform the choice of dose to be used in subsequent phase 3 studies of the sIPV. The rest of the personnel involved in the conduct of the study, including those at Takeda, the contract research organization (CRO) and the study sites, will remain blinded to the individual subject data (including treatment assignments) until unblinding after database lock (Day 547).

More details on the analyses will be provided in the SAP.

13.3 Determination of Sample Size

This trial is designed to be descriptive and is not based on testing formal null hypotheses, and therefore the sample size was not determined based on formal statistical power calculations.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Trial-Site Monitoring Visits

Monitoring visits to the trial site will be made periodically during the trial to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the trial and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, trial vaccine, subject medical records, informed consent form documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), and review of eCRFs and associated source documents. It is important that the investigator and other trial personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to trial subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the medical monitor (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospective approved deviation) from the inclusion or exclusion criteria.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The trial site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the vaccine is stored and prepared, and any other facility used during the trial. In addition, there is the possibility that this trial may be inspected by regulatory agencies, including those of foreign governments (eg, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the trial site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all trial documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE TRIAL

This trial will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonized Guideline for GCP. Each investigator will conduct the trial according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix A. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable national and local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this trial, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent form must be obtained and submitted to the sponsor or designee before commencement of the trial (ie, before shipment of the sponsor-supplied Vaccine or trial specific screening activity). The IRB or IEC approval must refer to the trial by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will notify the site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from the competent authority to begin the trial. Until the site receives [notification] no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the trial at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent (ICF), and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all

applicable laws and regulations. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the trial.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and if applicable, the subject authorization form. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject's LAR. It is the responsibility of the investigator to explain the detailed elements of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject's LAR. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC.

The subject (adult cohort) or the subject's LAR (toddler and infant cohorts) must be given ample opportunity to: (1) inquire about details of the trial and (2) decide whether or not to allow their child to participate in the trial. If the subject determines that he/she will participate or if the subject's LAR determines their child will participate in the trial, then the ICF and subject authorization must be signed and dated by the subject or subject's LAR at the time of consent and prior to the subject entering into the trial. The subject or subject's LAR should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the ICF and subject authorization at the time of consent and prior to subject entering into the trial; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, subject authorization form, and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject or subject's LAR signs the ICF in the subject's medical record and eCRF. Copies of the signed ICF, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject or subject's LAR.

All revised ICFs must be reviewed and signed by the subject or relevant subject's LAR in the same manner as the original ICF. The date the revised consent was obtained should be recorded in the subject's medical record and eCRF, and the subject or subject's LAR should receive a copy of the revised ICF.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this trial, a subject's source data will only be linked to the sponsor's clinical trial database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's trial participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject's LAR as part of the ICF process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The results of this trial are expected to be published in a scientific journal. It is anticipated that clinical and laboratory co-investigators will participate in authorship. The order of authorship and choice of journal will be proposed by the sponsor to the PIs, to be eventually agreed upon by all authors. The data analysis center for this trial will provide the analyses needed for publication. Information regarding this trial will be posted on ClinicalTrials.gov.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable law, regulation and guidance, the sponsor will, at a minimum register all clinical trials conducted in subjects that it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before trial initiation. The sponsor contact information, along with investigator's city, country, and recruiting status will be registered and available for public viewing.

15.4.3 Clinical Trial Results Disclosure

The sponsor will post the results of this clinical trial, regardless of outcome, on ClinicalTrials.gov or other publicly accessible websites, as required by applicable laws and/or regulations.

Trial completion corresponds to the date on which the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.

In line with EC Regulation N° 1901/2006 [11], the sponsor will submit a pediatric trial within six months of their completion and irrespective of whether it is part of a completed or not yet completed Pediatric Investigation Plan (PIP) or not, or whether it is intended for submission later

on as part of a variation, extension or new stand-alone marketing-authorization application or not.

15.5 Insurance and Compensation for Injury

Each subject in the trial must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical trial insurance against the risk of injury to clinical trial subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

1. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH Harmonised Guideline. Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2) 9 November 2016.
2. World Health Organization (WHO). Polio vaccines WHO Position paper. Wkly Epidemiol Rec 2016; 12: 145-168.
3. Sutter RW, Pallansch MA, Sawyer LA, Cochi SL, Hadler SC. Defining surrogate serologic tests with respect to predicting protective vaccine efficacy: Poliovirus vaccination. Ann NY Acad Sci 1995; 754: 289–299.
4. World Health Organization (WHO) Expert Committee on Biological Standardization. 65th Report. Annex 3. Recommendations to assure the quality, safety and efficacy of poliomyelitis vaccines (inactivated). WHO Technical Report Series 993. 2015
5. World Health Organization (WHO). Government of Nigeria reports 2 wild polio cases, first since July 2014. Available at: http://www.who.int/mediacentre/news/releases/2016/nigeria-polio/en/
6. Polio Eradication and Endgame Strategic Plan 2013–2018. Available at: http://polioeradication.org/wp-content/uploads/2016/07/PEESP_EN_A4.pdf
7. Shimizu H. Development and introduction of inactivated poliovirus vaccines derived from Sabin strains in Japan. Vaccine 2016; 34:1975-1985.
8. Verdijk P, Rots NY, Bakker WA. Clinical development of a novel inactivated poliomyelitis vaccine based on attenuated Sabin poliovirus strains. Exp Rev Vacc 2011; 10:635–644.
9. World Health Organization (WHO). Reducing pain at the time of vaccination: WHO position paper – September 2015. Wkly Epidemiol Rec 2015; 90:505–510.
10. Marcy SM, Kohl KS, Dagan R, et al. Fever as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. Vaccine 2004; 22:551-556.
11. EC Regulation N° 1901/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 12 December 2006 on medicinal products for pediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004.

Appendix A Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The investigator agrees to assume the following responsibilities:

1. Conduct the trial in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that trial related procedures, including trial specific (non-routine/non-standard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the trial are informed of these obligations.
5. Secure prior approval of the trial and any changes by an appropriate IRB/IEC that conform to ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the trial to the IRB/IEC, and issue a final report within 3 months of trial completion.
7. Ensure that requirements for informed consent, as outlined in ICH and local regulations, are met.
8. Obtain valid informed consent from the LAR of each subject who participates in the trial, and document the date of consent in the subject's medical chart. Valid ICF is the most current version approved by the IRB/IEC. Each ICF should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the trial. If an ICF does not include such a subject authorization, then the investigator must obtain a separate subject authorization form for each subject from the subject's LAR.
9. Prepare and maintain adequate case histories of all persons entered into the trial, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied vaccines, and return all unused sponsor-supplied vaccines to the sponsor.

12. Report AEs to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.
13. Review and provide a signature as approval of the content of the clinical study report.

Appendix B Elements of the Subject Informed Consent

In seeking the subject's (adult cohort) or the LAR's (toddler and infant cohorts) consent, the following information shall be provided to each subject or subject's LAR:

1. A statement that the trial involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the trial.
7. A description of the subject or subject's LAR's responsibilities.
8. A description of the conduct of the trial.
9. A statement describing the vaccination(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects following vaccine administration that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject or the subject's LAR should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing an ICF, the subject or subject's LAR is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the trial.
17. The anticipated expenses, if any, to the subject for participating in the trial.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.

19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may discontinue participation or the subject's LAR may discontinue participation of their child at any time without penalty or loss of benefits to which the subject is otherwise entitled.
20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or subject's LAR will be informed in a timely manner if information becomes available that may be relevant to their willingness to continue participation in the trial.
22. A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the trial may be terminated.
24. A written subject authorization (either contained within the ICF or provided as a separate document) describing to the subject or subject's LAR the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the trial. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your or your child's personal information confidential, and your or your child's name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the investigational vaccine(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that the subject or subject's LAR agrees not to restrict the use and disclosure of their or their child's personal information (including personal health information) upon withdrawal from the trial to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and

e) that the subject's identity will remain confidential in the event that trial results are published.

25. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix C Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the trial and/or other clinical studies.
- Management, monitoring, inspection, and audit of the trial.
- Analysis, review, and verification of the trial results.
- Safety reporting and pharmacovigilance relating to the trial.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the trial.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other vaccines used in other clinical studies that may contain the same chemical compound present in the investigational vaccine.
- Inspections and investigations by regulatory authorities relating to the trial.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of trial records.
- Posting investigator site contact information, trial details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country. Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix D Serology Plan

Assay	Validation status required for the assay[b]	Sample type	Analytical readout of assay data	Sample volume/ time point/ assay[c]	Sample volume reserved as backup (min.)[c]	Subset of Subjects	Time points[d]	Total # of time points	Total # of tests/ assays/ study	Study Objective: (Primary, Secondary or Exploratory)	Contract Testing Lab	Comments
CCI												

CCI [redacted]

(a) CCI [redacted]
(b)
(c)
(d)

Primary sample required per time point (e.g. blood draw):

Time point	Primary sample type → secondary sample type	Primary sample volume or amount per time point	Expected secondary sample volume or amount
D1, 29 (Toddler lead-in cohort)	Blood → Serum	5 mL	2000 µL
D1, 57, 85, 365, 393 (Infant dose ranging cohort)	Blood → Serum	5 mL	2000 µL
	Total blood drawn in study for Serology	**10 mL/ 25 mL**	

In this table primary sample means e.g. blood, corresponding secondary sample means e.g. serum