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

SAP Approve Date: 12 June 2018

Certain information within this Statistical Analysis Plan has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable (PPD) information 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.

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: IPV-102

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

PHASE I/II

Version**:** Final 1.0

Date**:** 12 June 2018

Prepared by:

PPD

Based on:

Protocol Version: 2.0
Protocol Date: 11 April 2017

1.1 Approval Signatures

Study 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

Approvals:

PPD

12 JUN 2018
Date

12/June 2018
Date

13/June/2018
Date

13 Jun 2018
Date

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3.0 LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CI	Confidence Interval
eCRF	electronic Case Report Form
CRO	Contract Research Organization
DMC	Data Monitoring Committee
FAS	Full Analysis Set
GMT	Geometric Mean Titer
GSD	Geometric Standard Deviation
IPV	Inactivated Poliomyelitis Vaccine
IQR	Interquartile Range
LLoQ	Lower Limit of Quantitation
LS means	Least Squares means
MedDRA	Medical Dictionary for Regulatory Activities
MLE	Maximum Likelihood Estimate
OPV	Oral Poliomyelitis Vaccine
PPS	Per-Protocol Set
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCR	Seroconversion Rate
SD	Standard Deviation
sIPV	Sabin-based Inactivated Poliomyelitis Vaccine
SOC	System Organ Class
SPR	Seropositivity/Seroprotection Rate
ULoQ	Upper Limit of Quantitation
VRR	Vaccine Response Rate
WHODrug	World Health Organization Drug Dictionary

4.0 OBJECTIVES

4.1 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 Sabin-based IPV (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)

4.2 Secondary Objectives

Safety

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).

4.3 Exploratory Objectives

CCI

[redacted]

4.4 Study 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 **Error! Reference source not found.**. The schedule of study procedures is provided in Appendix A.

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 a licensed, reference IPV. Polio vaccines previously received for primary immunization of these children will be recorded. Routine infant vaccines other than poliovirus vaccine for booster immunization recommended for children at approximately 12 months of age according to national guidelines (eg, measles vaccine) are to be given at least 4 weeks after sIPV / reference IPV booster vaccination. Routine infant vaccines according to the national immunization program 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 a locally-available standard polio vaccine (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.

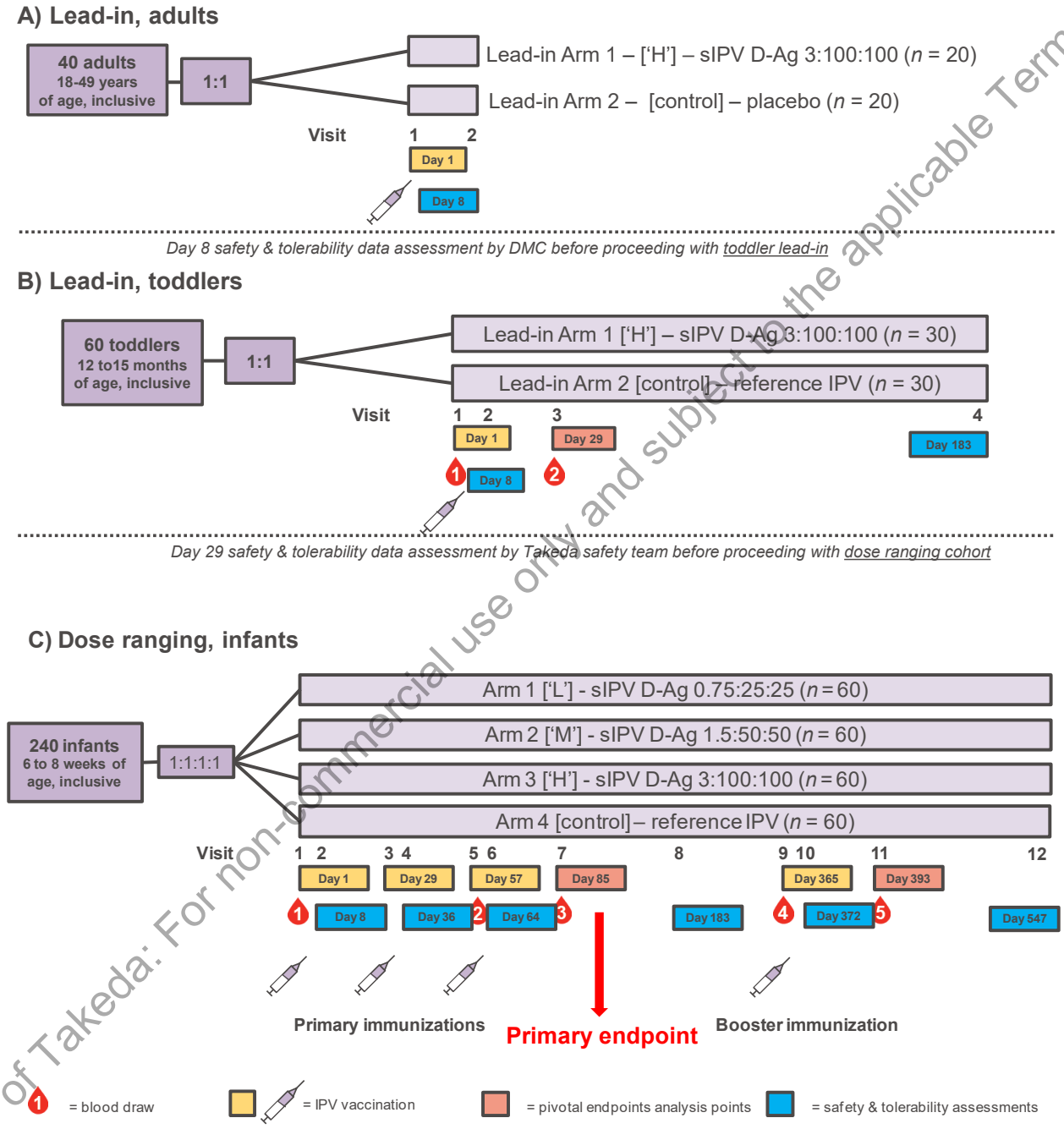
Routine infant vaccines according to the national immunization program other than poliovirus vaccine for primary immunization and for booster vaccination are to be given according to national guidelines outside the trial. Inactivated / oral routine infant vaccines should be given on the same day as sIPV / reference IPV. Injectable live-attenuated vaccines (eg, measles 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 single series of three primary immunizations of a locally-available standard polio vaccine 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 1 Schematic of Trial Design



5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

Infant dose ranging cohort

***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, 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.

5.2 Secondary Endpoints

***Safety**:*

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, and 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 each primary immunization dose of sIPV or IPV, and 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 each primary immunization dose of sIPV or IPV, and after booster vaccination.
- 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, and after booster vaccination.
- Percentage of subjects experiencing SAEs throughout the entire trial duration in the sIPV and IPV study arms.

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.

5.3 Exploratory Endpoints

CCI

[redacted]

6.0 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.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

All statistical analyses will be generated using SAS Version 9.2 or higher.

7.1.1 Data Presentation

In general, descriptive summaries will be provided by study arm for each study cohort. Immunogenicity summaries and analyses will be provided by study arm for the toddler lead-in cohort and the infant dose ranging cohort.

Unless specified otherwise, number of subjects with non-missing observations, mean or geometric mean, standard deviation (SD) or geometric standard deviation (GSD), median, minimum, and maximum will be presented for continuous data; and frequency and percent will be presented for categorical data. In summary tables for categorical data for which categories are defined on the electronic case report form (eCRF), all categories will be presented as specified, even if the subject count within that category is zero. For other categorical data (e.g., AEs and medications), only categories with at least one subject will be presented.

Minimum and maximum values will be presented using the same number of decimal places as the recorded data. Means, geometric means, and medians will be presented to 1 more decimal place than the recorded data. SD and GSD will be presented to 2 more decimal places than the recorded data, with possible exceptions made for derived data. The confidence interval (CI) about a parameter estimate will be presented using the same number of decimal places as the parameter estimate (i.e., 1 more decimal place than the recorded data). Percentages will be presented to 1 decimal place (e.g., 80.3%).

Unless otherwise specified, all data collected during the trial will be presented in the subject listings.

7.1.2 Baseline and Analysis Window Definitions

Study Day 1 is defined as the date of the first vaccination, as recorded on the eCRF vaccination page. Other study days are defined relative to Study Day 1, with Day -1 being the day prior to Day 1.

Baseline is defined as the last non-missing measurement taken before the first dose of vaccination. Where time is available, the time of the collection must be prior to study drug vaccination. Day 1 observations taken after the vaccination are considered post-baseline values.

A windowing convention will be used to determine the analysis value for a given study visit for observed data analyses. As defined in the schedule of study procedures (Appendix A), the "target day" of a visit is relative to either Day 1 or actual day of the previous vaccination. For example, visit "Day 85" is anchored to the third dose, and hence the target day for visit Day 85 is Day 29 relative to Dose 3. Visit "Day 365" is anchored to Day 1, and hence the target day for visit Day 365 is Study Day 365. The analysis windows for immunogenicity are then constructed around these target days, following the window conventions below:

1) A window of +/- 7 days from the target day is applied to Day 29 for the toddler lead-in cohort and Day 57, Day 85, and Day 393 for the infant dose ranging cohort;
2) A window of +/- 28 days from the target day is applied to Day 365 for the infant dose ranging cohort.

In addition, for visits where vaccination is given, e.g. Day 57 and Day 365 in the infant dose ranging cohort, analysis windows for immunogenicity will exclude days after the actual day of the vaccination, as immunogenicity must always be assessed prior to the vaccination scheduled for the same visit. Based on these rules, Table 1 outlines the immunogenicity analysis window for each visit in the toddler lead-in and the infant dose ranging cohorts.

Table 1 Analysis Visit Windows for Immunogenicity

Cohort	Visit	Visit Name	Scheduled Day	Scheduled Vaccination	Visit Window (Study Day / Study Day Relative to Dose) [a]
Toddler Lead-in	1	Baseline[b]	1	Dose 1	≤ Study Day 1
	3	Day 29	29		Study Day 22 – 36
Infant Dose Ranging	1	Baseline[b]	1	Dose 1	≤ Study Day 1
	3	Day 29	29	Dose 2	--
	5	Day 57[b]	57	Dose 3	Day 22 – 36 relative to Dose 2; ≤ Day 1 relative to Dose 3
	7	Day 85	85		Day 22 – 36 relative to Dose 3
	9	Day 365[b]	365	Dose 4 (Booster)	Study Day 337 – 393; ≤ Day 1 relative to Booster
	11	Day 393	393		Day 22 – 36 relative to Booster

(a) Study days are defined relative to Study Day 1. Study days relative to dose are defined relative to the actual date of the specified dose.

(b) CCI [redacted]

One or more results for a particular immunogenicity or vital sign variable may be obtained in the same analysis visit window. In such an event, the result from the date closest to the expected visit date will be used. In the event that two results are equidistant from the expected visit date, the later result will be used.

7.1.3 Handling of Missing Values

Titers Measured Below (or Above) the LLoQ (or ULoQ)

For immunogenicity summaries and analyses, polio neutralizing antibody titer values below and above the limits of the dilution series are assigned a value of 6 or 1448.

When a high proportion of observations post vaccination are above the upper limit of the dilution series, simply substituting these "censored" observations with the value of 1448 may lead to biased parameter estimates. Therefore as a sensitivity analysis, polio neutralizing antibody titers above the ULoQ will also be treated as right-censored data and the censored, log-transformed titers will be analyzed using a censored normal regression model. The sensitivity analysis will be performed for the summaries and analyses of GMTs, where estimates of GMTs will be obtained as the anti-logarithm transformation of the maximum likelihood estimation for censored normal data. The censoring approach will not be used on titers below the LLoQ as it is expected that most pre-vaccination titers will be below LLoQ and the maximum likelihood estimates are not valid if most or all observations are censored.

The titer values will be presented as reported in the listings.

Unsolicited Adverse Events Missing or Partial Dates

Partial dates will be presented as recorded in the listings. Missing and partial AE start dates will be imputed only to determine the relationship between the start date of the event and the dose date of the most appropriate vaccination that the AE should be associated with (e.g., primary Dose 1, 2, 3, or Booster in the infant does ranging cohort).

An adverse event should be temporally associated with the correct vaccination dose as far as possible using the following guidelines:

- If the available start date information indicates that the start of an event is between two consecutive vaccination dates, then the AE start date will be imputed such that the AE will be associated with the earlier dose. For example, for the infant dose ranging cohort, if Dose 1 is on 30 January 2017 and Dose 2 is on 02 March 2017 and the event has an incomplete start date of February 2017, then the event will be associated with Dose 1 and have an imputed date of 01 February 2017.
- If the available start date information is insufficient to distinguish between 1 or more vaccination dates, the event end date will be assessed. If possible, the AE will be assigned to the dose after which the event ends, assuming transient nature of the events. In the above example if an event is known to start in 2017 (day and month missing) and the end date is known as 20 March 2017, then an imputed start date of 02 March 2017 (date of Dose 2) will be used and the event will be associated with Dose 2.
- If the available date information indicates possible association of the AE with multiple doses, then the AE start date will be imputed such that the AE is assigned to the first possible dose. In the above example if Dose 3 is on 02 April 2017 and Booster is on 20 January 2018, and an event is known to start in 2017 (day and month missing) and the end date is missing, then the event will be associated with Dose 1 and have an imputed start date of 25 January 2017 (date of Dose 1).
- If both start and end dates are completely missing, then the AE will be associated with Dose 1 and the first dose date will be used as the imputed start date.

Adverse Events Missing Intensity and Relationship

Missing intensity or relationship will be presented as reported in the listings. Missing information regarding 'relationship to study vaccine' (related, not related) for solicited and unsolicited AEs, and 'severity' (mild, moderate, severe) for unsolicited AEs, will be handled using the worst case approach. That is, unsolicited AEs with missing severity/intensity will be considered as 'severe' and solicited and unsolicited AEs with missing relationship will be considered as 'related'.

Prior/Concomitant Medication Missing or Partial Dates

Partial dates will be presented as recorded in the listings. Missing and partial medication dates will be imputed only to determine the relationship between the end date of the medication and the first dose of study vaccine (to determine if a medication is a prior or a concomitant medication). The medication end date will be imputed using the latest date possible, e.g., the earlier of the database lock date or the last day of the year (when year available and month/day missing).

7.2 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. Subjects with major protocol violations will be identified as part of the blinded data review prior to unblinding and clinical judgment from Takeda will be necessary to classify each violation as "major" or not. These violations and the judgment regarding their use will be listed and summarized in the final clinical study report. The major protocol violation criteria will be finalized as part of the blinded data review and may include:

1) Not meeting selected entry criteria defined in protocol sections 7.1 and 7.2 [1]:

   Toddler lead-in cohort: exclusion criteria #1, #2, #3:

   - 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: exclusion criteria #2, #3, #4:

   - 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: exclusion criteria #4, #7:

- Subjects who received any vaccine within 28 days prior to enrollment in this trial;
- 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;
  d) Receipt of immunostimulants within 60 days prior to Day 1;
  e) Genetic immunodeficiency.

2) Receiving a wrong trial vaccine or an incorrect regimen;
3) Receiving prohibited therapies in the following categories:
   - Any vaccination with polio vaccines outside the trial;
   - Known or suspected impairment/alteration of immune function any time during the trial, 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; 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);
     c) Administration of immunoglobulins and/or any blood or blood products;
     d) Receipt of immunostimulants;
4) Other major violations that may be identified during blinded data reviews.

As there is no immunogenicity assessment for the adult lead-in cohort, the FAS and PPS are only applicable to the toddler lead-in cohort and the infant dose ranging cohort. Analyses using the

FAS will be based on the randomized treatment. Analyses using the Safety Set will be based on the actual treatment.

7.3 Disposition of Subjects

Disposition of all screened subjects will be summarized descriptively by study cohort, including a summary of the number of screened subjects, the number of randomized subjects and the primary reason for ineligibility for randomization. The number of screen failures and their characteristics will also be summarized by cohort.

Disposition for all randomized subjects will be summarized by study arm for each study cohort as applicable. Disposition categories include:

- Number of randomized subjects by country and site;
- Number of randomized subjects and number of randomized subjects but not dosed;
- Number of subjects completing the vaccine regimen/study visits;
- Number of subjects who prematurely discontinued the vaccine regimen/study visits;
- Primary reason for premature discontinuation of the vaccine regimen/study visits;

Major protocol violations leading to exclusion from PPS will be summarized by study arm for the toddler lead-in cohort and the infant dose ranging cohort, based on the FAS.

7.4 Demographic and Other Baseline Characteristics

Age, gender, race, and other baseline characteristics will be summarized descriptively based on the randomized set and the PPS. Baseline characteristics for the toddler lead-in cohort and the infant dose ranging cohort will also include the baseline seropositivity status for each poliovirus type (poliovirus types 1, 2, and 3, Sabin and Salk). Seropositivity at Baseline is defined as a reciprocal neutralizing titer ≥ 8 for each poliovirus type.

7.5 Medical History and Concurrent Medical Conditions

Medical history and concurrent medical conditions will be coded using the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA) coding system.

A medical history is defined as any significant condition/disease that stopped at or prior to first dose of study vaccine and a concurrent medical condition is defined as any significant condition/disease that started on/after or is ongoing at first dose of study vaccine.

Summary tables will be provided by system organ class (SOC) and preferred term (PT) based on the safety set.

7.6 Medication History and Concomitant Medications

Medication history, vaccination history, concomitant medications, and concomitant vaccinations will be coded using the current version of World Health Organization Drug Dictionary (WHODrug).

A prior medication/vaccination (history) is any medication/vaccination taken before first dose of study vaccine. A concomitant medication/vaccination is any medication/vaccination ongoing at first dose of study vaccine or taken on/after first dose of study vaccine.

Summary tables will be provided for medication history and concomitant medications by preferred medication name based on the safety set. Summary tables will be provided for vaccination history and concomitant vaccinations by vaccination name based on the safety set.

7.7 Investigational Product Exposure and Compliance

The duration of follow-up will be summarized for the safety set as a continuous variable, and also as frequency and percentage of subjects in the following categories:

- Adult lead-in cohort: (1) 1 – 7 days, (2) ≥ 8 days;
- Toddler lead-in cohort: (1) 1 – 28 days, (2) 29 – 182 days, (3) ≥ 183 days;
- Infant dose ranging cohort: (1) 1 – 28 days, (2) 29 – 56 days, (3) 57 – 84 days, (4) 85 – 182 days, (5) 183 – 364 days, (6) 365 – 392 days, (7) 393 – 546 days, (8) ≥ 547 days.

The duration of follow-up is defined as the number of days from the first vaccination to the end of study visit.

For the infant dose ranging cohort, study vaccine compliance will be also summarized by presenting the numbers and percentages of subjects receiving:

1) First dose only;
2) First and second dose only;
3) Three doses of the primary immunization only;
4) Three doses of the primary immunization and the booster dose.

7.8 Immunogenicity Analysis

Summaries and analyses of immunogenicity endpoints will be provided for the toddler lead-in cohort and the infant dose ranging cohort separately.

The primary population for all immunogenicity summaries and analyses will be the PPS. Supportive immunogenicity summaries will be provided based on the FAS as specified in Table 2.

The primary, secondary, and exploratory immunogenicity endpoints are listed in **Error! Reference source not found.**, as well as the analyses (descriptive summaries, graphical presentations, or pairwise comparisons) planned for each endpoint/population. Whenever applicable, Baseline (i.e. Day 1) results will also be included in the summary tables and graphs.

Table 2 Planned Analyses and Populations for Immunogenicity Endpoints

Cohort	Endpoint		Endpoint Type	Planned Analyses and Populations		
	Variable	Time Point		Descriptive Summaries	Graphical Presentations	Pairwise Comparisons
Toddler Lead-in	CCI	CCI	Exploratory	CCI		
			Exploratory			
			Exploratory			
Infant Dose Ranging	SCR		Exploratory	PPS, FAS	PPS	PPS
		Day 85	Primary			PPS
	VRR	Day 393	Secondary	PPS	PPS	PPS
	SPR	CCI	Exploratory	PPS	PPS	PPS
		Day 85	Secondary			PPS
		Day 365	Secondary			
		Day 393	Secondary			
	GMT	CCI	Exploratory	PPS	PPS	PPS
		Day 85	Secondary			PPS
		Day 365	Secondary			
		Day 393	Secondary			

In addition to the overall summaries and analyses specified in Table 2, for the infant dose ranging cohort, descriptive summaries of SCR and GMT at Day 85 will also be provided by subjects' seropositivity status at Baseline.

Descriptive Summaries

Descriptive statistics for the primary, secondary, CCI CCI endpoints will be provided by study arm and for each poliovirus type, and will include the following:

- SCR, SPR, VRR: number and percentage of subjects with seroconversion/seropositivity /vaccine response, and corresponding 95% CIs calculated with the exact (Clopper-Pearson) method;
- Titer values: geometric mean, GSD, 95% CIs, minimum, and maximum. The geometric mean, GSD, and the 95% CIs of the geometric mean will be calculated as the anti-logarithm transformation of the mean, standard deviation, and 95% CIs of the log-transformed titers;
- Titer values (sensitivity analysis): maximum likelihood estimate (MLE) of the geometric mean, GSD, and 95% CIs, allowing for censored antibody titers. The MLE geometric

mean, GSD, and 95% CIs will be calculated as the anti-logarithm transformation of the MLE mean, standard deviation, and 95% CIs of the log-transformed titers based on a censored normal regression model.

Graphical Presentations

For the infant dose ranging cohort only, graphical presentations for selected immunogenicity endpoints will be provided by study arm and for each poliovirus type, and will include the following:

- SCR, SPR, VRR: bar graphs presenting the percentage of subjects with seroconversion/ seropositivity/vaccine response, including error bars for the 95% CIs, plotted over time;
- Titer values: reverse cumulative distribution curves of antibody titers at Day 57 and Day 85 (infant dose ranging cohort);
- Titer values: line plots of GMTs, including error bars for the 95% CIs, plotted over time;
- Titer values (sensitivity analysis): line plots of maximum likelihood estimate of the GMTs, including error bars for the 95% CIs, plotted over time;

Pairwise Comparisons

For the infant dose ranging cohort only, pairwise comparisons of study arms (with the lower level as a reference group) will be performed for selected immunogenicity endpoints, without multiplicity adjustment. The pre-specified comparisons of interest are the following:

- Arm 2 vs Arm 1; Arm 3 vs Arm 1; Arm 3 vs Arm 2;
- Arm 1 vs Arm 4; Arm 2 vs Arm 4; Arm 3 vs Arm 4.

The following statistics will be provided for each comparison:

- SCR, SPR, VRR: risk difference and corresponding 95% CIs based on the Newcombe score method; risk ratio, corresponding 95% CIs and p-values based on Fisher's exact test;
- Titer values: geometric mean ratio, 95% CI, and p-values based on an analysis of covariance (ANCOVA) model which includes the log-transformed value of titer as the dependent variable, the corresponding log-transformed baseline titer value as a covariate and study arm as a factor. The geometric mean, geometric mean ratio and 95% CI are presented in anti-log values of least squares means (LS means) estimated from the ANCOVA model;
- Titer values (sensitivity analysis): maximum likelihood estimate of the geometric mean ratio, 95% CI, and p-values based on a censored normal regression model which includes the log-transformed value of titer (with censoring) as the dependent variable, the corresponding log-transformed baseline titer value as a covariate and study arm as a factor. The geometric mean, geometric mean ratio and 95% CI are presented in anti-log values of the maximum likelihood estimates.

7.8.1 Primary Immunogenicity Endpoints

The primary immunogenicity endpoints of this trial are in the infant dose ranging cohort, seroconversion rate at Day 85 for each of the poliovirus types (types 1, 2, and 3 for both Sabin and Salk strains). Seroconversion is defined as:

i. initially seronegative infants (titer < 8 at Baseline) having a titer ≥ 8 at Day 85, or
ii. initially seropositive infants (titer ≥ 8 at Baseline) 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.

As specified in Table 2, descriptive summaries based on PPS and FAS, as well as graphical presentations and pairwise comparisons based on the PPS, will be provided for the primary immunogenicity endpoints.

7.8.2 Secondary Immunogenicity Endpoints

The secondary immunogenicity endpoints of this trial are in the 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.

As specified in Table 2, descriptive summaries and graphical presentations based on the PPS will be provided for the secondary immunogenicity endpoints. Pairwise comparisons based on the PPS will also be provided for selected secondary immunogenicity endpoints.

7.8.3 Exploratory Immunogenicity Endpoints

CCI

[redacted]

CCI

[redacted]

7.9 Pharmacokinetic/Pharmacodynamic Analysis

Not applicable.

7.10 Other Outcomes

Not applicable.

7.11 Safety Analysis

All summaries and analyses of safety data will be based on subjects in the safety set. Unless otherwise specified, safety data will be summarized by study arm and for each cohort separately.

For all summaries by each vaccination, summaries after any vaccination will also be included.

7.11.1 Adverse Events

Subjects in the adult lead-in cohort will be evaluated for solicited local and systemic AEs and unsolicited AEs (including SAEs and AEs leading to early termination) for 7 days after dosing (including day of vaccination).

Subjects in the toddler lead-in cohort and the infant dose ranging cohort will be evaluated for solicited local and systemic AEs for 7 days, and unsolicited AEs for 28 days, after each primary or booster vaccination (including day of vaccination). SAEs and AEs leading to early termination will be assessed throughout the entire trial duration.

Biologically implausible measurements of body temperature and solicited local symptoms (i.e., body temperature < 35°C or > 42°C, and erythema, induration, and swelling > 50.0 cm) will be excluded from the summaries and analyses, but included in the data listings.

Reactogenicity (Solicited AEs)

For subjects in all cohorts reactogenicity will be assessed daily for 7 days after each vaccination (day of vaccination + 6 days) via diary collection of solicited AEs. These solicited AEs and their intensity grades are defined in Section 10.1.2 of the protocol [1].

For local solicited AEs erythema, induration and swelling, the subject/legal guardian will record the length of the greatest surface diameter. For the systemic solicited AE fever, the subject/legal guardian will record the body temperature in either degrees Fahrenheit (°F) or degrees Celsius

(°C). Fever data will be displayed in °C in summaries and listings. Intensity grades for erythema, induration and swelling will be derived from the recorded diameters, and fever will be derived from the recorded temperature measurements and presented in categories as defined in **Error! Reference source not found.**.

Table 3 Temperature Categories

Fever Present?	Temperatures °C
No	< 38.0°C
Yes	38.0°C – 38.4°C
	38.5°C – 38.9°C
	39.0°C – 39.4°C
	39.5°C – 39.9°C
	40.0°C or higher

For each solicited AE, the number and percentage of subjects reporting an event will be summarized by event severity at the following time intervals:

- Days 1 – 7 following each vaccination;
- Days 1 – 7 (daily) following each vaccination;
- Days 1 – 3 and Days 4 – 7 following each vaccination.

For subjects with more than 1 episode of the same event, the maximum severity will be used for tabulations.

For solicited systemic AEs, the number and percentage of subjects reporting an event will also be summarized by relationship to trial vaccine(s) for Days 1 – 7 following each vaccination. If a subject reported more than one episode of the same event, then the strongest relationship will be included in the summaries.

A summary of the day of first onset of each event and the number of days subjects reported experiencing each event will be presented following each vaccination. The number of days a subject reported experiencing an event is calculated as the total of all days the subject reported the event, regardless of whether the symptom was reported on consecutive days.

Prolonged solicited AEs that continued beyond Day 7 will be captured in the Adverse Event eCRF page, indicated by the checkbox "Is this event a continuation of a Solicited event". These prolonged solicited AEs will be presented in a separate data listing.

Unsolicited AEs

Any event captured in the Adverse Event eCRF page that is a continuation of a solicited event will not be included in any unsolicited AE summaries or listings.

For subjects in the adult lead-in cohort, unsolicited AEs including SAEs and AEs leading to early termination will be assessed for 7 days after vaccination (day of vaccination + 6 days). The

number and percentage of subjects with an unsolicited AE will be tabulated up to 7 days after vaccination at the following levels:

- Overview (Unsolicited AEs, SAEs, Deaths);
- By SOC, PT, and relationship (not related, related) to vaccine;
- By SOC, PT, and intensity (mild, moderate, severe);
- Non-serious unsolicited AEs by SOC and PT including events with frequency greater than 5% in any study arm.

For subjects in the toddler lead-in and infant dose ranging cohorts, unsolicited AEs will be assessed for 28 days following administration of each study dose (day of vaccination + 27 days). SAEs and AEs leading to early termination will be assessed throughout the trial duration.

In these two cohorts, unsolicited AEs will be summarized up to 28 days after each vaccination. The number and percentage of subjects with an unsolicited AE will be tabulated at each of the following levels:

- Overview (Unsolicited AEs, SAEs, Deaths);
- By SOC and PT;
- By SOC (in decreasing frequency);
- By PT (in decreasing frequency);
- Non-serious unsolicited AEs by SOC and PT including events with frequency greater than 5% in any study arm, up to 28 days after any vaccination;
- By SOC, PT, and relationship (not related, related) to vaccine;
- Vaccine-related unsolicited AEs by SOC and PT;
- by SOC, PT, and intensity (mild, moderate, severe);
- Vaccine-related unsolicited AEs by SOC, PT, and intensity.

Subjects reporting more than 1 occurrence for the term (level) being summarized will be counted only once. When relationship or intensity is concerned, the AE with the most closely related occurrence or the highest known intensity will be counted.

SAEs after each vaccination will be summarized by SOC and PT. AEs leading to early termination after each vaccination will be summarized by SOC and PT.

7.11.2 Clinical Laboratory Evaluations

Not applicable.

7.11.3 Vital Signs

Vital sign variables will be summarized descriptively at each scheduled visit. The change from baseline to each scheduled post-baseline visit will be presented as applicable.

7.11.4 12-Lead ECGs

Not applicable.

7.11.5 Other Observations Related to Safety

Not applicable.

7.12 Interim Analysis

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).

7.13 Changes in the Statistical Analysis Plan

The SAP contains no changes to the planned analyses described in the protocol.

8.0 REFERENCES

1. 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, Takeda Vaccines, Inc., Protocol No. IPV-102, Version 2.0, dated 11 April 2017.

Appendix A Schedule of Trial Procedures

Table 4 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		
Assessment of Eligibility Criteria (a)		X		
Demographics		X		
Medical History		X		
Prior Medications		X		
Concomitant Medications		X	X	(X)
Physical Examination	**Complete** (b)	X		
	Symptom Directed (b)		(X)	(X)
Vital Signs (c)		X	(X)	(X)
Randomization		X		
IPV/placebo administration		X		
Diary Card	**Distribution** (d)	X		
	Collection (d)		X	(X)
Adverse Events (e)		X	X	(X)(f)
Serious Adverse Events (g)		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.
Footnotes:
(a) Eligibility by review of relevant inclusion/exclusion criteria will be documented before enrollment.
(b) 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) Vital signs: as defined in section 9.1.5.
(d) Diary cards will be distributed on the day of vaccination, and will be collected at the return visit 7 days later.
(e) 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 vaccination.
(f) AEs leading to Early Termination will be recorded by the investigator.
(g) 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 5 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	(X)
Physical Examination	**Complete** (b)	X				
	Symptom Directed (b)			(X)		(X)
Vital Signs (c)		X		X		(X)
Randomization		X				
IPV administration (d)		X				
Diary Card	**Distribution** (e)	X				
	Collection (e)			X		(X)
Adverse Events (f)		X	X	X		(X)(g)
Serious Adverse Events (h)		X	X	X	X	(X)
Blood Draw (5 mL)		X(i)		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.

Footnotes:

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

(b) 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) Vital signs: as defined in section 9.1.5.

(d) sIPV or reference IPV.

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

(f) 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) AEs leading to Early Termination will be recorded by the investigator.

(h) 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) Blood should be drawn prior to vaccination

Table 6 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 Visit 1		-/-	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								X				
Medical History		X												
Prior Medications		X												
Concomitant Medications		X	X	X	X	X	X	X						(X)
Physical Exam	**Complete** (b)	X												
	Symptom Directed (b)			(X)		(X)		(X)		X		(X)		(X)
Vital Signs (c)		X		X		X				X				(X)
Randomization		X												
IPV administration (d)		X		X		X				X				
Diary Card	**Distribution** (e)	X		X		X				X				
	Review/Collection			X		X		X				X		
Adverse Events (f)		X	X	X		X		X		X				(X)(g)
Serious Adverse Events (h)		X	X	X	X	X	X	X	X	X	X	X	X	(X)
Blood Draw (5 mL)		X(i)				X(i)		X		X(i)		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.

Footnotes:
(a) Eligibility by review of relevant inclusion/exclusion criteria will be documented before enrollment.
(b) 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) Vital signs: as defined in section 9.1.5.
(d) sIPV or reference IPV.
(e) Diary cards will be distributed on the day of each vaccination, and will be collected at the return visit 28 days later.
(f) 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) AEs leading to Early Termination will be recorded by the investigator.
(h) 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) Blood should be drawn prior to vaccination