Statistical Analysis Plan

Protocol Number: BK1310-J01

Exploratory Study of BK1310 in Healthy Infants

Version Number: 2
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Statistical Analysis Plan

Exploratory Study of BK1310 in Healthy Infants

(Cohort 1)

Mitsubishi Tanabe Pharma Corporation

Date prepared	: April 10, 2018
Protocol Number	: BK1310-J01
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Revision History

Version Number	Details of Revision
Version 1	First Version This SAP was prepared based on the study protocol, version number, "02.00.00000."
Version 2	Added some statistical analysis for anti-diphtheria [redacted]

Statistical Analysis Plan

Exploratory Study of BK1310 in Healthy Infants

(Cohort 1)

Prepared by Statistical analysts	**Date (Month Day, Year)**
Approved by Data Science Department Manager, Ikuyaku. Integrated Value Development Division	**Date (Month Day, Year)**

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List of Abbreviation

Abbreviation	Unabbreviated term
PRP	Polyribosylribitol phosphate
Hib	*Haemophilus Influenzae* type b
PT	Pertussis Toxin
FHA	Filamentous Hemagglutinin
FAS	Full analysis set
MedDRA/J (The following terms are adverse event-related terms.)	Medical dictionary for regulatory activities/Japanese version
PT	Preferred Term
SOC	System Organ Class

Definition of Terms

Term	Definition
Day of vaccination	Day 1
Visit X or VX	Test/observation time point at the Xth visit

1. INTRODUCTION

This document describes the sponsor's plans for the statistical analyses of efficacy and safety in the "P3 study of BK1310 in healthy infants," and covers the information that is included in the study protocol, but in greater detail. Additionally, this document describes the analyses that will be performed for Cohort 1, and does not describe the plans for the statistical analyses being performed for Cohorts 2 and 3.

2. STUDY OBJECTIVE AND STUDY DESIGN

2.1. Objectives

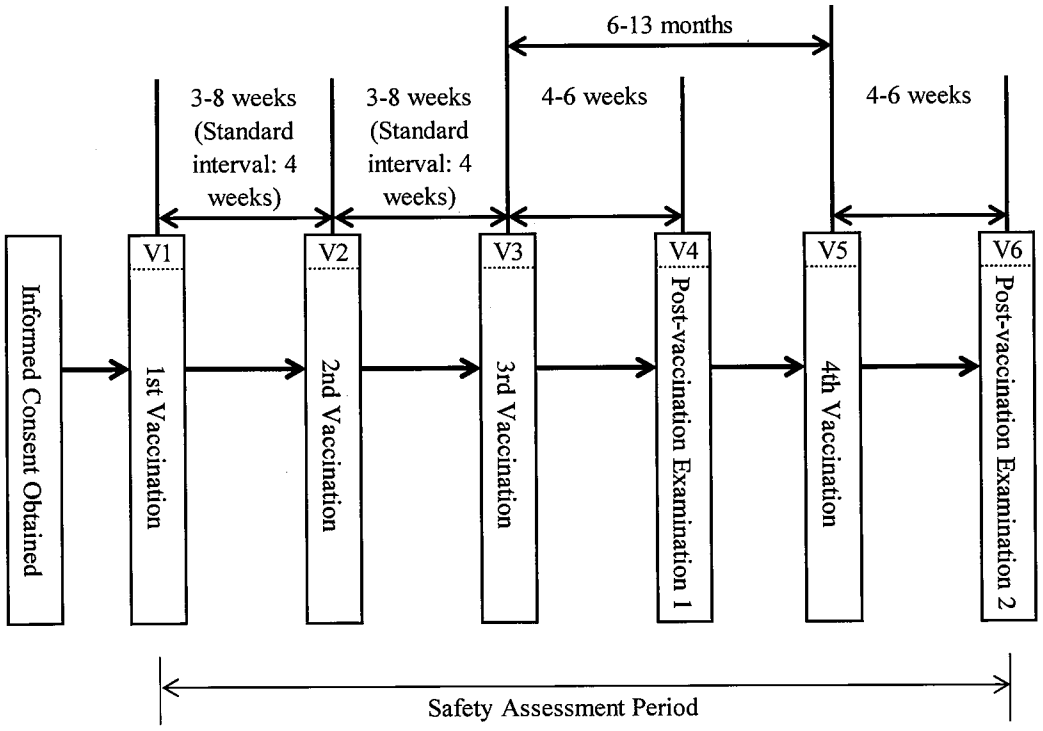
To investigate on an exploratory basis the safety of BK1310 and its immunogenicity against Hib in healthy infants, and to then investigate on an exploratory basis the efficacy and safety of BK1310 using simultaneous vaccination with ActHIB and Tetrabik as the control.

2.2. Study Design

The study population will consist of the 3 cohorts described below (Cohort 1, Cohort 2, and Cohort 3). This statistical analysis plan describes the sponsor's plans for the statistical analyses that will be performed for Cohort 2.

(1) Cohort 1

A randomized, double-blind, parallel-group, multicenter study



Subjects randomized to the following groups will receive the following investigational products.

- BK1310 H group: Formulation H, 0.5 mL per dose

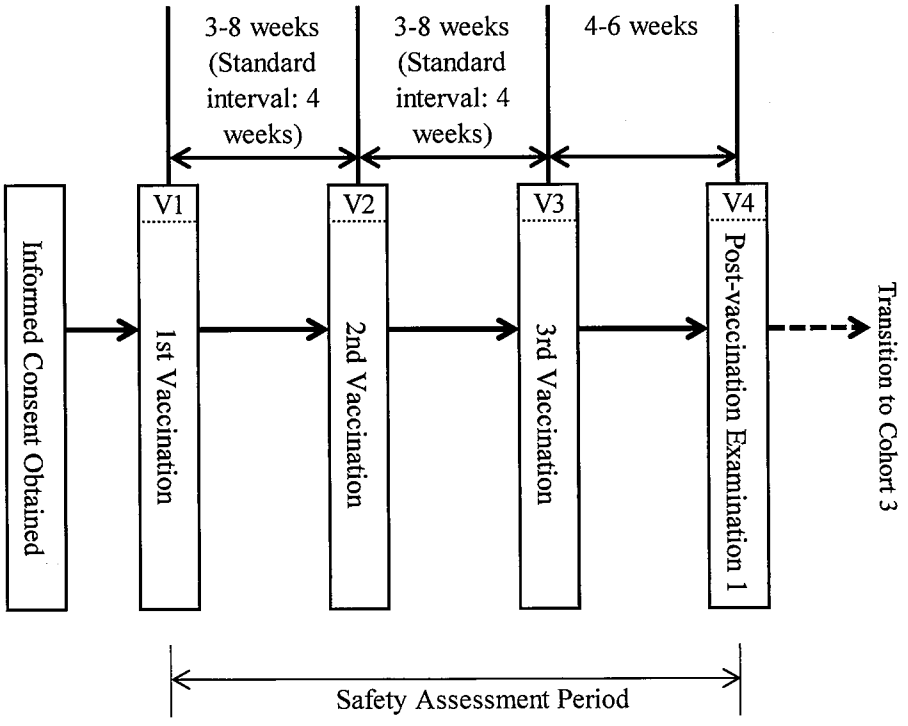
- BK1310 L group: Formulation L, 0.5 mL per dose

Subjects will receive 3 doses of investigational product, 0.5 mL for each dose, for the primary immunization, administered subcutaneously (upper arm extensor) at intervals of 3 to 8 weeks (standard vaccination interval: 4 weeks). For the booster immunization, subjects will receive a single subcutaneous (upper arm extensor) dose at 6 to 13 months after the primary immunization. However, the repeated vaccination of investigational product at the same location as that which was used for the previous dose will be avoided.

Once the assessments have been performed following the first vaccination with the investigational product to the last subject in Cohort 1 (after the primary immunization), and after the measurement of the antibody titer against Hib antigen (the anti-PRP antibody concentration) has been completed (at the time point shown in the figure above (*)), the blind will be broken, and the BK1310 safety information will be assessed, and once it has been confirmed that the subject has been afforded adequate immunity against Hib antigen, a decision about whether or not to initiate Cohort 2 will be made based on the criteria described in "5.2.2 Cohort 2 Initiation Criteria." Additionally, except for the study sponsor, for whom the study will not be blinded after unblinding (except for the monitors, as described in "25.1.6 Monitors"), the study will continue with the double blind maintained even after unblinding.

(2) Cohort 2

A randomized, observer -blinded, active-controlled, parallel-group, multicenter study



Subjects randomized to the following groups will receive the following investigational products.

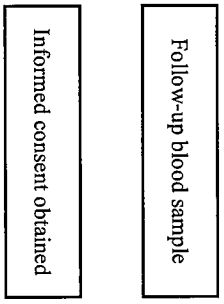
Furthermore, for BK1310 H and L groups, to which group each subject will be assigned will be decided after the completion of Cohort 1 and before the start of Cohort 2.

- BK1310 H and L groups: Subjects will receive 0.5 mL per dose of formulation H or L
- Control group: Subjects will receive 0.5 mL of each of ActHIB and Tetrabik

For the primary immunization,* subjects will receive 3 subcutaneous doses (as a rule, administered at the top part of the upper arm extensor) at intervals of 3 to 8 weeks (standard vaccination interval: 4 weeks). Subjects in the control group will receive subcutaneous doses of Tetrabik and ActHIB (as a rule, administered at the top and bottom, respectively, of the upper arm extensor on the same side). However, the repeated vaccination with investigational product at the same location as that which was used for the previous dose will be avoided.

*: The completion of the primary immunization series with the investigational product. For the booster immunization, a dose will be administered as part of, for example, routine immunization.

(3) Cohort 3



Only for subjects from whom written informed consent has been obtained, after the end of Cohort 2, and generally after 4 weeks have passed since the administration of the booster immunization received as part of, for example, routine immunization, the investigator will perform antibody titer measurements as a follow-up investigation, depending on the results that have been obtained after the primary immunization in Cohort 2, or in accordance with the wishes of the subject (subject's legal guardian).

2.3. Randomization Method

In this study, subjects will be randomly assigned to either the BK1310:H group or the BK1310:L group using a variable block method.

2.4. Assessment Time Point

The Cohort 1 assessment time points are shown below.

	Day of consent	Visit 1			Visit 2			Visit 3			Visit 4	Visit 5			Visit 6	At discontinuation
		1st vaccination			2nd vaccination			3rd vaccination			Post-vaccination Examination 1	4th vaccination			Post-vaccination Examination 2	
		Before	Vaccination	After	Before	Vaccination	After	Before	Vaccination	After		Before	Vaccination	After		
Allowable window		D1			Visit 1 + 3 - 8 weeks			Visit 2 + 3 - 8 weeks			Visit 3 + 4 - 6 weeks	Visit 3 + 6 - 13 months			Visit 5 + 4 - 6 weeks	
Written informed consent	●															
Investigation of subject background		●										●				
Examination		●		●*1	●		●*1	●		●*1	●	●		●*1	●	●
Body temperature measurement (axillary)		●			●			●				●				
Investigational product vaccination			●			●			●				●			
Blood sampling (antibody titer)		●									●	●			●	●*2
Adverse events*3			◄													►
e-Diary*4				●			●			●				●		

*1: Subjects will be asked to wait in the hospital for 30 minutes after receiving the investigational product, and will be examined 30 minutes after vaccination.

*2: Blood samples will be collected for antibody titer measurement only at discontinuation after the third or fourth dose of the investigational product has been administered.

*3: An investigation will be performed to confirm whether or not the subject experienced any adverse events during the period from Visit 1 to Visit 4, and during the period from Visit 5 to Visit 6, based on examination of the subject at the study visits and based on the subject's e-Diary. Only serious adverse events will be investigated during the period from Visit 4 to Visit 5.

4: Every day until 14 days after each dose, if the subject's symptoms have not returned to normal by Day 14, then the subject will be asked to, as a rule, fill out the e-Diary until the symptoms return to normal.

2.5. Sample Size Justification

○ Target sample size

Cohort 1: 30 subjects (BK1310 L group: 15 subjects; BK1310 H group: 15 subjects)

Rationale

In Cohort 1, the sample size was set at 15 subjects per group, 30 subjects in total, as the number of subjects that will make it possible to confirm that the anti-PRP antibody concentrations and antibody

seroprotection rate have not decreased appreciably, in order to confirm that combining the vaccines does not result in a reduction in Hib antigen immunogenicity.

3. ENDPOINTS

3.1. Efficacy Endpoints

(1) Primary endpoint

The anti-PRP antibody seroprotection (antibody titer ≥ 1 μg/mL) rate, and the seroprotection rates for pertussis, diphtheria toxin, tetanus toxin, and attenuated polio virus at 4 weeks after the primary immunization.

(2) Secondary Endpoints

(a) The anti-PRP antibody seroprotection (antibody titer ≥ 0.15 μg/mL) rate and the geometric mean antibody titer for anti-PRP antibodies at 4 weeks after the primary immunization

(b) The geometric mean antibody titers for pertussis, diphtheria toxin, tetanus toxin, and attenuated poliovirus at 4 weeks after the primary immunization

(c) The anti-PRP antibody seroprotection (antibody titer ≥ 1 μg/mL) rate, the anti-PRP antibody seroprotection (antibody titer ≥ 0.15 μg/mL) rate and the geometric mean antibody titer for anti-PRP antibodies at 4 weeks after the booster immunization.

(d) The antibody seroprotection rates and geometric mean antibody titers for pertussis, diphtheria toxin, tetanus toxin, and attenuated polio virus at 4 weeks after the booster immunization.

3.2. Safety Endpoints

Adverse events and adverse drug reactions

3.3. Other Endpoints

None

4. DEFINITIONS OF DERIVED VARIABLES AND TABULATION METHODS

4.1. Methods of Derivation

(1) Age in months

The age in months will be calculated based on the date of the first vaccine dose and the date of birth. The difference between the date in question (YYYY1/MM1/DD1) and the date of birth (YYYY2/MM2/DD2) will be defined as A.

$A = (YYYY1 - YYYY2) \times 12 + (MM1 - MM2)$

If DD1 < DD2, then the age in full months will be A – 1.

If DD1 ≥ DD2, then the age in full months will be A.

(2) Age in months at adverse event onset

The age in months at adverse event onset will be calculated from the date of onset of the adverse event and the date of birth. Additionally, the date in question in "4.1. (1) Age in Months" in this document will be reclassified as the date of adverse event onset in the calculation formula.

(3) Number of days from the immediately preceding dose of investigational product to adverse event onset

The "number of days from the immediately preceding dose of investigational product to adverse event onset" will be calculated as the day of adverse event onset minus the day of the immediately preceding dose. Furthermore, the day of adverse event onset will be the "day on which symptoms were observed or the day of the test that yielded abnormal findings."

(4) Adverse event duration

Adverse event duration = Date of outcome – Date of onset + 1 (in days)

4.2. Methods of Tabulation

(1) Antibody titer geometric mean and geometric standard deviation

Antibody titer geometric mean = $10^{(\text{mean of the log-transformed value (base 10) of the antibody titer})}$

Antibody titer geometric standard deviation = $10^{(\text{standard deviation of the log-transformed value (base 10) of the antibody titer})}$

Antibody titer geometric mean 95% confidence interval

= $10^{(\text{lower limit of the 95\% confidence interval of the mean of the log-transformed value (base 10) of the antibody titer})}$ to $10^{(\text{upper limit of the 95\% confidence interval of the mean of the log-transformed value (base 10) of the antibody titer})}$

However, for the anti-polio antibody titers (anti-poliovirus antibody titers [type 1, type 2, type 3]), because the data obtained are base 2 log-transformed values, they will be calculated as shown below. In this case, the data obtained will be calculated as "the log-transformed values (base 2) of the antibody titers."

Antibody titer geometric mean = $2^{(\text{mean of the log-transformed value (base 2) of the antibody titer})}$

Antibody titer geometric standard deviation = $2^{(\text{standard deviation of the log-transformed value (base 2) of the antibody titer})}$

Antibody titer geometric mean 95% confidence interval

= $2^{(\text{lower limit of the 95\% confidence interval of the mean of the log-transformed value (base 2) of the antibody titer})}$ to $2^{(\text{upper limit of the 95\% confidence interval of the mean of the log-transformed value (base 2) of the antibody titer})}$

(2) Seroprotection rates

Table 4.2

Measurement Parameter		Measurement Method	Reference Value
Hib	Anti-PRP antibody concentrations	Enzyme-linked	≥ 1 μg/mL

		immunosorbent assay (ELISA)	≥ 0.15 μg/mL
Diphtheria	Anti-diphtheria antibody concentrations (Both [redacted]	Neutralization method	≥ 0.1 IU/mL
Pertussis	Anti-pertussis antibody concentrations	Enzyme-linked immunosorbent assay (ELISA)	≥ 10.0 EU/mL
	Anti-FHA antibody concentrations		≥ 10.0 EU/mL
Tetanus	Anti-tetanus antibody concentrations	Indirect agglutination (KPA)	≥ 0.01 IU/mL
Polio	Anti-poliovirus antibody titers* (types 1, 2, and 3)	Neutralization method	≥ 8-fold

The proportions of subjects with the aforementioned reference antibody titers following vaccination with the investigational product will be calculated.

Seroprotection rate (%) =
[(Number of subjects with antibodies)/(Number of subjects evaluated for efficacy)] x 100

The number of subjects assessed for efficacy will be the number of subjects for whom antibody titer results have been obtained.

(3) Adverse drug reactions

Adverse events for which it is thought there is a reasonable possibility of there being a causal relationship with the investigational product are considered adverse drug reactions.

5. ANALYSIS SETS

The analysis of efficacy is performed in the full analysis set (FAS). In addition, safety analysis is performed in the safety analysis set.

The analysis sets are defined below. Detailed rules about subject handling will be decided by the study sponsor before the database lock

5.1. Efficacy Analysis Sets

The FAS will consist of all randomized subjects except for the following subjects.

- Subjects who did not take the investigational product at all
- Subjects for whom no antibody titer results at all could be obtained at 4 weeks after the primary immunization

5.2. Safety Analysis Sets

The SAF will consist of all randomized subjects except for the following subjects.

- Subjects who did not take the investigational product at all

- Subjects for whom absolutely no safety data are available following vaccination with the investigational product

6. HANDLING OF DATA

6.1. Handling of Missing Values

If a value cannot be measured or is the reference value because of, for example, the assessment was not performed, the test value was missing, or there was a problem with the test sample, this parameter will be handled as a missing value.

6.2. Allowable Assessment Time Point Deviation Window

For the tabulation at each time point of test and observation parameters, data meeting the allowable time window in days specified in "9.1 Test/Observation Schedule" of the study protocol will be used, and data will not be replaced using data from outside the allowable windows.

6.3. Handling of Antibody Titer Data Below the Limit of Quantitation

For the calculation of the descriptive statistics, if the measured antibody titer is below the limit of quantitation, then it will be treated as being the lower limit of quantitation divided by 2.

6.4. Handling of Adverse Event Data

6.4.1. Handling of Adverse Event Data When There Are Multiple Events In the Same Period

If the same PT occurs in the same subject occurs multiple times in the period in question (e.g., the safety assessment period or the specified period for each number of doses), then these will only be counted as a single event.

6.4.2. Handling Period of Adverse Event Data by Number of Injections

Adverse events to be summarized as the number of applicable vaccinations are those that occur after the vaccination on the day of the vaccination in question and before the vaccination on the day of the next vaccination. For the fourth vaccination, adverse events that occurred from the day of the fourth vaccination to the last day of the safety assessment period will be summarized.

7. STATISTICAL METHODS

7.1. General Methods

7.1.1. Significance Level and Confidence Coefficient

Since this study is an exploratory study, no significance levels have been established. The confidence intervals will be two-sided confidence intervals, and the confidence coefficient will be 95%.

7.1.2. Descriptive Statistics

Unless otherwise specified, the descriptive statistics shown in the following table will be calculated, depending on the type of the data.

Table 7.1.2: Descriptive Statistics

Data Category	Descriptive Statistics
Categorization/Sequential	Numbers and proportions of subjects
Continuous	Numbers of subjects, mean values, SDs, minimums, maximums, medians

7.1.3. Confidence Intervals (e.g., Seroprotection rate, Incidence)

When calculating the confidence intervals for the incidences of adverse events, etc., or the antibody seroprotection rates, Clopper & Pearson method will be used.

7.1.4. Number of Display Digits

The number of digits displayed will be as follows. Additionally, the digits after the number of display digits will be rounded off (or up), except for the minimum and maximum values.

Table 7.1.3: Number of Display Digits

Descriptive Statistics	Number of Display Digits
Number of subjects	Integers
Proportions	Values rounded off to 1 decimal place
Minimum and maximum values	Same as the number of digits of the original variable
Means, standard deviations, and medians	Number of digits of the original variable + 1

7.1.5. Display of Treatment Groups

The display of the treatment groups will be handled as shown in the following table.

Table 7.1.4: Treatment Groups

Treatment Groups	Display
BK1310 H group: Formulation H, 0.5 mL per dose	H group
BK1310 L group: Formulation L, 0.5 mL per dose	L group

7.1.6. Tabulation Time Points and Baselines

The tabulation time points will be displayed as shown in the table below. The baseline will be "Before

the first dose at Visit 1."

Table 7.1.5: Tabulation Time Points

Notation for Tabulation		Assessment Time Points in the Protocol
Assessment Time Point	Abbreviation	
Before the first vaccination	V1	Before the first dose at Visit 1
4 weeks after the primary immunization	V4	Post-vaccination examination at Visit 4
Before the booster immunization	V5	Before the fourth dose at Visit 5
4 weeks after the booster immunization	V6	Postdose examination 2 at Visit 6 and at discontinuation

7.2. Subject Disposition

7.2.1. Analysis Population Eligibility

Analysis population(s): Randomized subjects

Analysis parameter: Eligibility for the FAS/safety analysis set (included, not included)

Analysis method: For each analysis parameter, the numbers and proportions of subjects will be calculated by group.

7.2.2. Disposition of Discontinued Subjects

Analysis population(s): Randomized subjects

Analysis parameter: Discontinued or completion after the vaccination of the investigational product, reason for discontinuation

Analysis method: For each group, the number and proportion of subjects discontinuing or completing will be calculated. Additionally, for subjects discontinuing, the numbers of subjects for each reason for discontinuation will be output.

Listings

Listing 7.2.2: Listing of Discontinuations

7.3. Demographic and Other Baseline Characteristics

Analysis population(s): FAS, safety analysis set

Analysis parameter: See Table 7.3

Analysis method: For each parameter, the number and proportion of subjects will be calculated, by group, for discrete data, and descriptive statistics will be calculated for continuous data. Additionally, if the FAS and the safety analysis set are the same, only the figures for the FAS will be output.

Table 7.3: Demographic and Other Baseline Characteristics/Analysis Parameters

Analysis Parameter		Data Category
Sex	Male, Female	Discrete
Age in months		Continuous
	≥ 2 and < 3 months, ≥ 3 months	Discrete
Concurrent illnesses	Yes, No	Discrete

Listings

Listing 7.3.1: Listing of Subject Backgrounds

Listing 7.3.2: Listing of Concomitant Medications

7.4. Status of Treatment Compliance

Analysis population(s): Safety analysis set

Analysis parameter: Presence or absence of receipt of a study drug injection

Analysis method: The number of subjects will be calculated for each number of injections (1, 2, 3, 4), by group.

Listings

Listing 7.3: Listing of Doses of Investigational Product

7.5. Efficacy Analyses

7.5.1. Primary endpoints

Analysis population(s): FAS

Analysis parameter: The anti-PRP antibody seroprotection (antibody titer ≥ 1 μg/mL) rate , and also the seroprotection rate for other antibodies (anti-diphtheria antibodies [redacted], anti-PT antibodies, anti-FHA antibodies, anti-tetanus antibodies, anti-poliovirus serotype 1 antibodies, anti-poliovirus serotype 2 antibodies, anti-poliovirus serotype 3 antibodies).

Analysis method: For each analysis parameter, the number of subjects, the number of subjects assessed for efficacy based on each antibody, the number of seroprotections, the seroprotection rate (%), and the two-sided, 95% confidence intervals will be calculated by group and time point (at 4 weeks after the primary immunization and at 4 weeks after the booster immunization).

7.5.2. Secondary endpoints

7.5.2.1 Anti-PRP Antibody Seroprotection (titer ≥ 0.15 μg/mL) Rate

Analysis population(s): FAS

Analysis method: Anti-PRP antibody seroprotection at (titer ≥ 0.15 μg/mL) rate

Analysis method: For each group, for each analysis parameter, the number of subjects, the number of subjects assessed for efficacy, the number of seroprotections, the seroprotection rate (%), and the two-sided 95% confidence intervals will be calculated by time point (at 4 weeks after the primary

immunization and at 4 weeks after the booster immunization).

7.5.2.2 Antibody Titer Profiles

Analysis population(s): FAS

Analysis parameter: Titers of each type of antibody (anti-PRP antibodies, anti-diphtheria antibodies[, anti-PT antibodies, anti-FHA antibodies, anti-tetanus antibodies, anti-poliovirus serotype 1 antibodies, anti-poliovirus serotype 2 antibodies, anti-poliovirus serotype 3 antibodies)

Analysis method: For each group, for each analysis parameter, the number of subjects, the number of subjects assessed for efficacy, the geometric mean, the geometric standard deviation, the two-sided 95% confidence interval of the geometric mean, and the minimum, median, and maximum values will be calculated.

Listings

Listing 7.5.2.2: Antibody Titer Listing

7.5.3. Other (post-hoc analysis)

After the start of this study, it was decided that the measurement of diphtheria toxin antibody titer using would be performed. Therefore, section 7.5.3 was added to clarify doing additional analysis for it.

7.5.3.1. Anti- diphtheria Antibody Seroprotection Rate [

Analysis population(s): FAS

Analysis parameter: The anti-diphtheria antibody [ ] seroprotection rate

Analysis method: The number of subjects, the number of subjects assessed for efficacy based on each antibody, the number of seroprotections, the seroprotection rate (%), and the two-sided, 95% confidence intervals will be calculated by group and time point (at 4 weeks after the primary immunization and at 4 weeks after the booster immunization).

7.5.3.2. Anti- diphtheria Antibody Titer Time Profiles [ ]

Analysis population(s): FAS

Analysis parameter: Anti- diphtheria antibody [f] titer

Analysis method: For each group, the number of subjects, the number of subjects assessed for efficacy, the geometric mean, the geometric standard deviation, the two-sided 95% confidence interval of the geometric mean, and the minimum, median, and maximum values will be calculated.

Listings

Listing 7.5.3.2: Titers of anti-diphtheria antibody [ ] Listing

7.5.4. Issues in Statistical Analyses

7.5.4.1. Adjustments for Covariates

Not planned

7.5.4.2. Handling of Dropouts or Missing Data

Described in "5.1 Handling of Missing Values" of this document.

7.5.4.3. Interim Analyses and Data Monitoring

Not implemented

7.5.4.4. Multicenter Studies

Not implemented due to small sample size in cohort 1.

7.6. Safety Analyses

7.6.1. Adverse Events

The adverse event terms will be reclassified based on MedDRA/J Version 19.0.

7.6.1.1. Adverse Event Incidences

Analysis population(s): Safety analysis set

Analysis parameter: Adverse events (solicited adverse events, immediate reactions, other), adverse drug reactions (solicited adverse events, immediate reactions, other), serious adverse events, serious adverse drug reactions, adverse events leading to discontinuation, adverse drug reactions leading to discontinuation

Analysis method: For each group, the number and proportion (and 95% confidence interval thereof) of subjects experiencing each type of event will be calculated.

7.6.1.2. Individual Adverse Events

Analysis population(s): Safety analysis set

Analysis parameter: Adverse events, adverse drug reactions, serious adverse events and reactions, adverse events and reactions leading to discontinuation

Analysis method: For each group, the numbers and proportions of subjects experiencing each type of event will be calculated by event category (solicited adverse events, immediate reactions, other) and by MedDRA/J SOC and PT. Group totals will be shown, as well. Additionally, adverse events and adverse drug reactions will be tabulated by event category (solicited adverse events, immediate reactions, other) and severity (mild, moderate, severe). If the same subject experiences the same event multiple times at different levels of severity, the event will be tabulated using the highest reported level of severity.

Listings

Listing 7.6.1.2.1: Listing of Adverse Events

Listing 7.6.1.2.2: Listing of Adverse Drug Reactions

7.6.1.3. Incidence of Solicited Adverse Events by Number of Doses

Analysis population(s): Safety analysis set

Analysis parameter: Adverse events and reactions that are considered solicited adverse events

Analysis method: For each number of doses, for each group, and for each MedDRA/J SOC and PT, the numbers and proportions of subjects experiencing each type of event will be tabulated by event category (solicited adverse events, immediate reactions).

7.6.1.4. Adverse Events by Subgroup

Not implemented due to small sample size in cohort 1.

8. SOFTWARE USED

The SAS Windows version (release 9.4) will be used for statistical analysis.

9. CHANGES TO STATISTICAL ANALYSIS PLAN FROM THE PROTOCOL

Nothing particular

10. REFERENCES

None

11. OUTPUT LISTINGS

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Statistical Analysis Plan

Exploratory Study of BK1310 in Healthy Infants

(Cohort 2)

Mitsubishi Tanabe Pharma Corporation

Date prepared	: January 16, 2018
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Revision History

Version Number	Details of Revision
Version 1	First Version This SAP was prepared based on the study protocol, version number, "02.00.00000."
Version 2	The revisions made to this version reflect the results of the blind review.

Statistical Analysis Plan

Exploratory Study of BK1310 in Healthy Infants

(Cohort 2)

Prepared by Statistical analysts	**Date (Month Day, Year)**
Approved by Data Science Department Manager, Ikuyaku. Integrated Value Development Division	**Date (Month Day, Year)**

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List of Abbreviation

Abbreviation	Unabbreviated term
PRP	Polyribosylribitol phosphate
Hib	*Haemophilus Influenzae* type b
PT	Pertussis Toxin
FHA	Filamentous Hemagglutinin
FAS	Full analysis set
MedDRA/J (The following terms are adverse event-related terms.)	Medical dictionary for regulatory activities/Japanese version
PT	Preferred Term
SOC	System Organ Class

Definition of Terms

Term	Definition
Day of vaccination	Day 1
Visit X or VX	Test/observation time point at the Xth visit

1. INTRODUCTION

This document describes the sponsor's plans for the statistical analyses of efficacy and safety in the "P3 study of BK1310 in healthy infants," and covers the information that is included in the study protocol, but in greater detail. Additionally, this document describes the analyses that will be performed on the assessments conducted up through the assessments after the vaccination of the third dose of the investigational product to Cohort 2 (after the primary immunization), and does not describe the plans for the statistical analyses being performed for Cohorts 1 and 3.

2. STUDY OBJECTIVE AND STUDY DESIGN

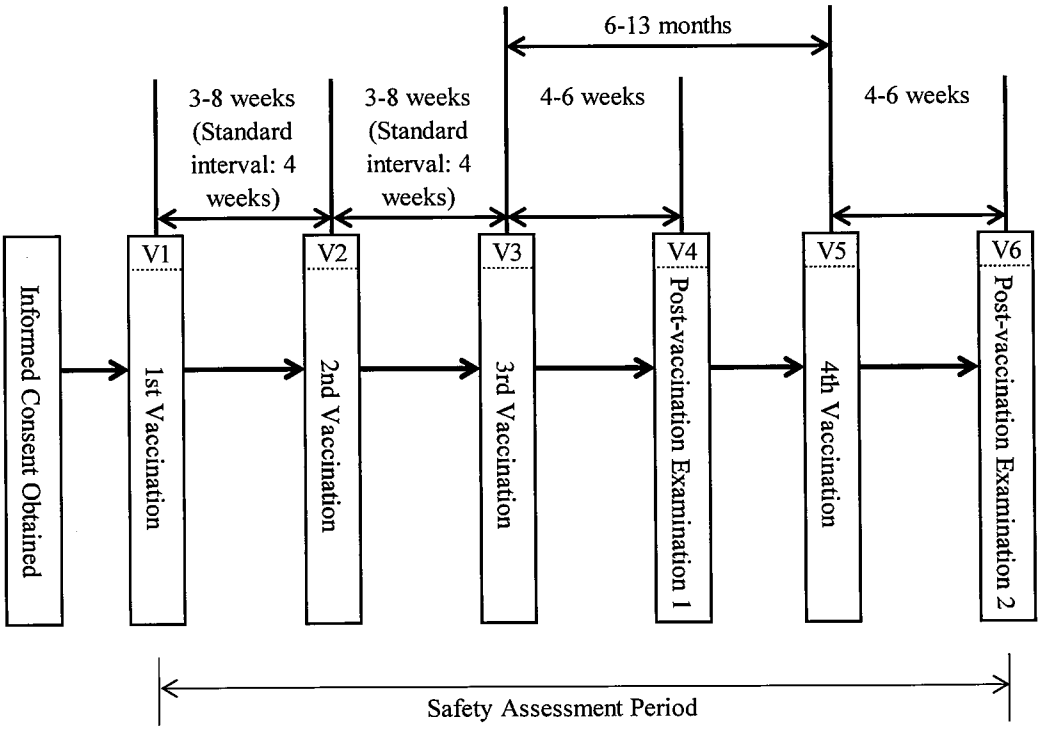
2.1. Objectives

To investigate on an exploratory basis the safety of BK1310 and its immunogenicity against Hib in healthy infants, and to then investigate on an exploratory basis the efficacy and safety of BK1310 using simultaneous vaccination with ActHIB and Tetrabik as the control.

2.2. Study Design

The study population will consist of the 3 cohorts described below (Cohort 1, Cohort 2, and Cohort 3). This statistical analysis plan describes the sponsor's plans for the statistical analyses that will be performed for Cohort 2.

(1) Cohort 1
A randomized, double-blind, parallel-group, multicenter study



Subjects randomized to the following groups will receive the following investigational products.

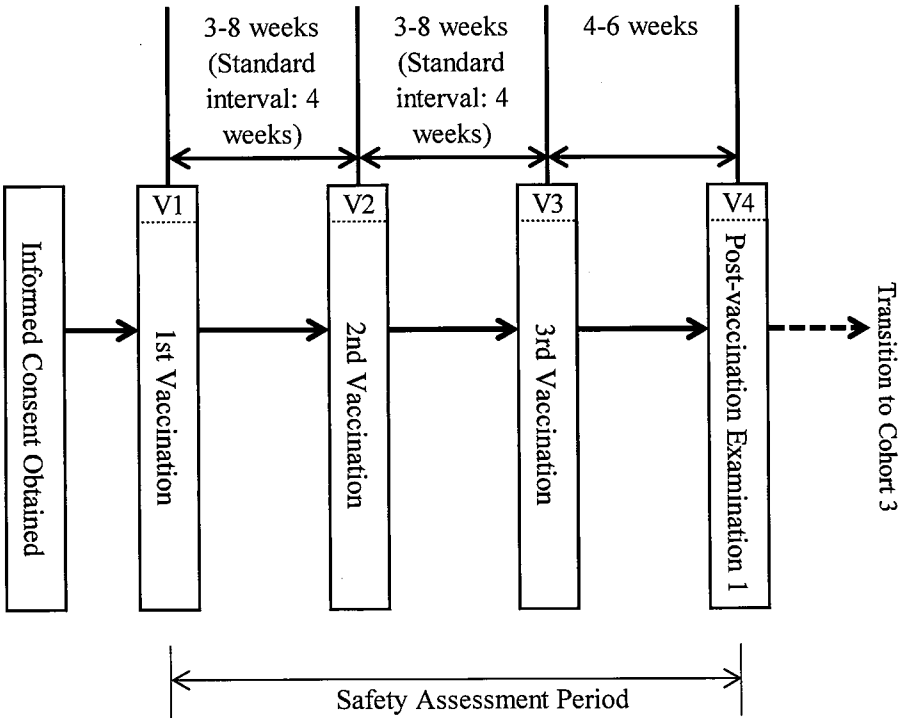
- BK1310 H group: Formulation H, 0.5 mL per dose
- BK1310 L group: Formulation L, 0.5 mL per dose

Subjects will receive 3 doses of investigational product, 0.5 mL for each dose, for the primary immunization, administered subcutaneously (upper arm extensor) at intervals of 3 to 8 weeks (standard vaccination interval: 4 weeks). For the booster immunization, subjects will receive a single subcutaneous (upper arm extensor) dose at 6 to 13 months after the primary immunization. However, the repeated vaccination of investigational product at the same location as that which was used for the previous dose will be avoided.

Once the assessments have been performed following the first vaccination with the investigational product to the last subject in Cohort 1 (after the primary immunization), and after the measurement of the antibody titer against Hib antigen (the anti-PRP antibody concentration) has been completed (at the time point shown in the figure above (*)), the blind will be broken, and the BK1310 safety information will be assessed, and once it has been confirmed that the subject has been afforded adequate immunity against Hib antigen, a decision about whether or not to initiate Cohort 2 will be made based on the criteria described in "5.2.2 Cohort 2 Initiation Criteria." Additionally, except for the study sponsor, for whom the study will not be blinded after unblinding (except for the monitors, as described in "25.1.6 Monitors"), the study will continue with the double blind maintained even after unblinding.

(2) Cohort 2

A randomized, observer -blinded, active-controlled, parallel-group, multicenter study



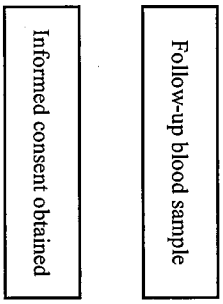
Subjects randomized to the following groups will receive the following investigational products. Furthermore, for BK1310 H and L groups, to which group each subject will be assigned will be decided after the completion of Cohort 1 and before the start of Cohort 2.

- BK1310 H and L groups: Subjects will receive 0.5 mL per dose of formulation H or L
- Control group: Subjects will receive 0.5 mL of each of ActHIB and Tetrabik

For the primary immunization,* subjects will receive 3 subcutaneous doses (as a rule, administered at the top part of the upper arm extensor) at intervals of 3 to 8 weeks (standard vaccination interval: 4 weeks). Subjects in the control group will receive subcutaneous doses of Tetrabik and ActHIB (as a rule, administered at the top and bottom, respectively, of the upper arm extensor on the same side). However, the repeated vaccination with investigational product at the same location as that which was used for the previous dose will be avoided.

*: The completion of the primary immunization series with the investigational product. For the booster immunization, a dose will be administered as part of, for example, routine immunization.

(3) Cohort 3



Only for subjects from whom written informed consent has been obtained, after the end of Cohort 2, and generally after 4 weeks have passed since the administration of the booster immunization received as part of, for example, routine immunization, the investigator will perform antibody titer measurements as a follow-up investigation, depending on the results that have been obtained after the primary immunization in Cohort 2, or in accordance with the wishes of the subject (subject's legal guardian).

2.3. Randomization Method

In this study, subjects will be randomly assigned to either the BK1301:H group or the control group using a variable block method.

2.4. Assessment Time Point

The Cohort 2 assessment time points are shown below.

	Day of consent	Visit 1			Visit 2			Visit 3			Visit 4	At discontinuation
		1st vaccination			2nd vaccination			3rd vaccination			Post-vaccination Examination 1	
		Before	Vaccination	After	Before	Vaccination	After	Before	Vaccination	After		
Allowable window		D1			Visit 1 + 3 - 8 weeks			Visit 2 + 3 - 8 weeks			Visit 3 + 4 - 6 weeks	
Written informed consent	●											
Investigation of subject background		●										
Examination		●		●*1	●		●*1	●		●*1	●	●
Body temperature measurement (axillary)		●			●			●				
Investigational product vaccination			●			●			●			
Blood sampling (antibody titer)		●									●	●*2
Adverse events*3			←							→		
e-Diary*4				●			●			●		

*1:Subjects will be asked to wait in the hospital for 30 minutes after receiving the investigational product, and will be examined 30 minutes after vaccination.

*2: Blood samples will be collected for antibody titer measurement only at discontinuation after the third dose of the investigational product has been administered.

*3: An investigation will be performed to confirm whether or not the subject experienced any adverse events during the period from Visit 1 to Visit 4 based on examination of the subject at the study visits and based on the subject's e-Diary.

*4: Every day until 14 days after each dose, if the subject's symptoms have not returned to normal by Day 14 after receiving the investigational product, then the subject will be asked to, as a rule, fill out the e-Diary until the symptoms return to normal.

2.5. Sample Size Justification

o Target sample size

Cohort 2: 340 subjects (BK1310 L group or H group: 170 subjects; control group: 170 subjects)

Rationale

Cohort 2 is positioned as a cohort for exploring the seroprotection rate in a phase 3 confirmatory study, and it was therefore decided that a sample size of 340 subjects (170 subjects per group) would allow for a proper assessment, taking into account the precision of estimating anti-PRP antibodies, etc.

3. ENDPOINTS

3.1. Efficacy Endpoints

(1) Primary endpoint

The anti-PRP antibody seroprotection (antibody titer ≥ 1 μg/mL) rate, and the seroprotection rates for pertussis, diphtheria toxin, tetanus toxin, and attenuated polio virus at 4 weeks after the primary immunization.

(2) Secondary Endpoints

(a) The anti-PRP antibody seroprotection (antibody titer ≥ 0.15 μg/mL) rate and the geometric mean antibody titer for anti-PRP antibodies at 4 weeks after the primary immunization

(b) The geometric mean antibody titers for pertussis, diphtheria toxin, tetanus toxin, and attenuated poliovirus at 4 weeks after the primary immunization

3.2. Safety Endpoints

Adverse events and adverse drug reactions

3.3. Other Endpoints

None

4. DEFINITIONS OF DERIVED VARIABLES AND TABULATION METHODS

4.1. Methods of Derivation

(1) Age in months

The age in months will be calculated based on the date of the first vaccine dose and the date of birth. The difference between the date in question (YYYY1/MM1/DD1) and the date of birth (YYYY2/MM2/DD2) will be defined as A.

A = (YYYY1 – YYYY2) x 12 + (MM1 – MM2)

If DD1 < DD2, then the age in full months will be A – 1.

If DD1 ≥ DD2, then the age in full months will be A.

(2) Age in months at adverse event onset

The age in months at adverse event onset will be calculated from the date of onset of the adverse event and the date of birth. Additionally, the date in question in "4.1. (1) Age in Months" in this document will be reclassified as the date of adverse event onset in the calculation formula.

(3) Number of days from the immediately preceding dose of investigational product to adverse event onset

The "number of days from the immediately preceding dose of investigational product to adverse event onset" will be calculated as the day of adverse event onset minus the day of the immediately

preceding dose. Furthermore, the day of adverse event onset will be the "day on which symptoms were observed or the day of the test that yielded abnormal findings."

(4) Adverse event duration

Adverse event duration = Date of outcome – Date of onset + 1 (in days)

4.2. Methods of Tabulation

(1) Antibody titer geometric mean and geometric standard deviation

Antibody titer geometric mean = $10^{(\text{mean of the log-transformed value (base 10) of the antibody titer})}$

Antibody titer geometric standard deviation = $10^{(\text{standard deviation of the log-transformed value (base 10) of the antibody titer})}$

Antibody titer geometric mean 95% confidence interval

= $10^{(\text{lower limit of the 95\% confidence interval of the mean of the log-transformed value (base 10) of the antibody titer})}$ to $10^{(\text{upper limit of the 95\% confidence interval of the mean of the log-transformed value (base 10) of the antibody titer})}$

However, for the anti-polio antibody titers (anti-poliovirus antibody titers [type 1, type 2, type 3]), because the data obtained are base 2 log-transformed values, they will be calculated as shown below. In this case, the data obtained will be calculated as "the log-transformed values (base 2) of the antibody titers."

Antibody titer geometric mean = $2^{(\text{mean of the log-transformed value (base 2) of the antibody titer})}$

Antibody titer geometric standard deviation = $2^{(\text{standard deviation of the log-transformed value (base 2) of the antibody titer})}$

Antibody titer geometric mean 95% confidence interval

= $2^{(\text{lower limit of the 95\% confidence interval of the mean of the log-transformed value (base 2) of the antibody titer})}$ to $2^{(\text{upper limit of the 95\% confidence interval of the mean of the log-transformed value (base 2) of the antibody titer})}$

(2) Seroprotection rates

Table 4.2

Measurement Parameter		Measurement Method	Reference Value
Hib	Anti-PRP antibody concentrations	Enzyme-linked immunosorbent assay (ELISA)	≥ 1 μg/mL
			≥ 0.15 μg/mL
Diphtheria	Anti-diphtheria antibody concentrations	Neutralization method	≥ 0.1 IU/mL
Pertussis	Anti-pertussis antibody concentrations	Enzyme-linked immunosorbent assay (ELISA)	≥ 10.0 EU/mL
	Anti-FHA antibody concentrations		≥ 10.0 EU/mL
Tetanus	Anti-tetanus antibody concentrations	Indirect agglutination (KPA)	≥ 0.01 IU/mL

Polio	Anti-poliovirus antibody titers* (types 1, 2, and 3)	Neutralization method	≥ 8-fold

The proportions of subjects with the aforementioned reference antibody titers following vaccination with the investigational product will be calculated.

Seroprotection rate (%) =
[(Number of subjects with antibodies)/(Number of subjects evaluated for efficacy)] x 100

The number of subjects assessed for efficacy will be the number of subjects for whom antibody titer results have been obtained.

(3) Adverse drug reactions

Adverse events for which it is thought there is a reasonable possibility of there being a causal relationship with the investigational product are considered adverse drug reactions.

5. ANALYSIS SETS

The analysis of efficacy is performed in the full analysis set (FAS). In addition, safety analysis is performed in the safety analysis set.

The analysis sets are defined below. Detailed rules about subject handling will be decided by the study sponsor before the database lock

5.1. Efficacy Analysis Sets

The FAS will consist of all randomized subjects except for the following subjects.

- Subjects who did not take the investigational product at all
- Subjects for whom no antibody titer results at all could be obtained at 4 weeks after the primary immunization

5.2. Safety Analysis Sets

The SAF will consist of all randomized subjects except for the following subjects.

- Subjects who did not take the investigational product at all
- Subjects for whom absolutely no safety data are available following vaccination with the investigational product

6. HANDLING OF DATA

6.1. Handling of Missing Values

If a value cannot be measured or is the reference value because of, for example, the assessment was not performed, the test value was missing, or there was a problem with the test sample, this parameter will be handled as a missing value.

6.2. Allowable Assessment Time Point Deviation Window

For the tabulation at each time point of test and observation parameters, data meeting the allowable time window in days specified in "9.1 Test/Observation Schedule" of the study protocol will be used, and data will not be replaced using data from outside the allowable windows.

6.3. Handling of Antibody Titer Data Below the Limit of Quantitation

For the calculation of the descriptive statistics, if the measured antibody titer is below the limit of quantitation, then it will be treated as being the lower limit of quantitation divided by 2.

6.4. Handling of Adverse Event Data When There Are Multiple Events In the Same Period

If the same PT occurs in the same subject occurs multiple times in the period in question (e.g., the safety assessment period or the specified period for each number of doses), then these will only be counted as a single event.

7. STATISTICAL METHODS

7.1. General Methods

7.1.1. Significance Level and Confidence Coefficient

Since this study is an exploratory study, no significance levels have been established. The confidence intervals will be two-sided confidence intervals, and the confidence coefficient will be 95%.

7.1.2. Descriptive Statistics

Unless otherwise specified, the descriptive statistics shown in the following table will be calculated, depending on the type of the data.

Table 7.1.2: Descriptive Statistics

Data Category	Descriptive Statistics
Categorization/Sequential	Numbers and proportions of subjects
Continuous	Numbers of subjects, mean values, SDs, minimums, maximums, medians

7.1.3. Confidence Intervals (e.g., Seroprotection rate, Incidence)

When calculating the confidence intervals for the incidences of adverse events, etc., or the antibody seroprotection rates, Clopper & Pearson method will be used.

7.1.4. Number of Display Digits

The number of digits displayed will be as follows. Additionally, the digits after the number of display digits will be rounded off (or up), except for the minimum and maximum values.

Table 7.1.3: Number of Display Digits

Descriptive Statistics	Number of Display Digits
Number of subjects	Integers
Proportions	Values rounded off to 1 decimal place
Minimum and maximum values	Same as the number of digits of the original variable
Means, standard deviations, and medians	Number of digits of the original variable + 1

7.1.5. Display of Treatment Groups

The display of the treatment groups will be handled as shown in the following table.

Table 7.1.4: Treatment Groups

Treatment Groups	Display
BK1310 H group: Formulation H, 0.5 mL per dose	H group
Subjects will receive 0.5 mL of each of ActHIB and Tetrabik	Control group

7.1.6. Tabulation Time Points and Baselines

The tabulation time points will be displayed as shown in the table below. The baseline will be "Before the first dose at Visit 1."

Table 7.1.5: Tabulation Time Points

Notation for Tabulation		Assessment Time Points in the Protocol
Assessment Time Point	Abbreviation	
Before the first vaccination	V1	Before the first dose at Visit 1
4 weeks after the primary immunization	V4	Post-vaccination examination at Visit 4, and at discontinuation

7.2. Subject Disposition

7.2.1. Analysis Population Eligibility

Analysis population(s): Randomized subjects

Analysis parameter: Eligibility for the FAS/safety analysis set (included, not included)

Analysis method: For each analysis parameter, the numbers and proportions of subjects will be calculated by group.

7.2.2. Disposition of Discontinued Subjects

Analysis population(s): Randomized subjects

Analysis parameter: Discontinued or completion after the vaccination of the investigational product, reason for discontinuation

Analysis method: For each group, the number and proportion of subjects discontinuing or completing will be calculated. Additionally, for subjects discontinuing, the numbers of subjects for each reason for discontinuation will be output.

Listings

Listing 7.2.2: Listing of Discontinuations

7.3. Demographic and Other Baseline Characteristics

Analysis population(s): FAS, safety analysis set

Analysis parameter: See Table 7.3

Analysis method: For each parameter, the number and proportion of subjects will be calculated, by group, for discrete data, and descriptive statistics will be calculated for continuous data. Additionally, if the FAS and the safety analysis set are the same, only the figures for the FAS will be output.

Table 7.3: Demographic and Other Baseline Characteristics/Analysis Parameters

Analysis Parameter		Data Category
Sex	Male, Female	Discrete
Age in months		Continuous
	≥ 2 and < 3 months, ≥ 3 months	Discrete
Concurrent illnesses	Yes, No	Discrete

Listings

Listing 7.3.1: Listing of Subject Backgrounds

Listing 7.3.2: Listing of Concomitant Medications

7.4. Status of Treatment Compliance

Analysis population(s): Safety analysis set

Analysis parameter: Presence or absence of receipt of a study drug injection

Analysis method: The number of subjects will be calculated for each number of injections (1, 2, 3), by group.

Listings

Listing 7.3: Listing of Doses of Investigational Product

7.5. Efficacy Analyses

7.5.1. Primary endpoints

Analysis population(s): FAS

Analysis parameter: The anti-PRP antibody seroprotection (antibody titer ≥ 1 μg/mL) rate , and also the seroprotection rate for other antibodies (anti-diphtheria antibodies, anti-PT antibodies, anti-FHA antibodies, anti-tetanus antibodies, anti-poliovirus serotype 1 antibodies, anti-poliovirus serotype 2 antibodies, anti-poliovirus serotype 3 antibodies), at 4 weeks after the primary immunization

Analysis method: For each analysis parameter, the number of subjects, the number of subjects assessed for efficacy based on each antibody, the number of seroprotections, the seroprotection rate (%), and the two-sided, 95% confidence intervals will be calculated by group. Additionally, the 95% confidence interval of the difference between Group H and the control group in the seroprotection rate (%) for each type of antibody will be calculated using the Farrington-Manning method.

7.5.2. Secondary endpoints

7.5.2.1 Anti-PRP Antibody Seroprotection (titer ≥ 0.15 μg/mL) Rate at 4 Weeks After the Primary Immunization

Analysis population(s): FAS

Analysis method: Anti-PRP antibody seroprotection at (titer ≥ 0.15 μg/mL) rate at 4 weeks after the primary immunization

Analysis method: For each group, for each analysis parameter, the number of subjects, the number of subjects assessed for efficacy, the number of seroprotections, the seroprotection rate (%), and the two-sided 95% confidence intervals will be calculated. Additionally, the 95% confidence interval of the difference between Group H and the control group in the seroprotection rate (%) will be calculated using the Farrington-Manning method.

7.5.2.2 Antibody Titer Profiles

Analysis population(s): FAS

Analysis parameter: Titers of each type of antibody (anti-PRP antibodies, anti-diphtheria antibodies, anti-PT antibodies, anti-FHA antibodies, anti-tetanus antibodies, anti-poliovirus serotype 1 antibodies, anti-poliovirus serotype 2 antibodies, anti-poliovirus serotype 3 antibodies)

Analysis method: For each group, for each analysis parameter, the number of subjects, the number of subjects assessed for efficacy, the geometric mean, the geometric standard deviation, the two-sided 95% confidence interval of the geometric mean, and the minimum, median, and maximum values will be calculated. Additionally, the 95% confidence interval of the ratio of the geometric mean in Group H relative to that of the control group will be calculated at 4 weeks after the primary immunization.

Listings

Listing 7.5.2.2: Antibody Titer Listing

7.5.3. Issues in Statistical Analyses

7.5.3.1. Adjustments for Covariates

Not planned

7.5.3.2. Handling of Dropouts or Missing Data

Described in "5.1 Handling of Missing Values" of this document.

7.5.3.3. Interim Analyses and Data Monitoring

Not implemented

7.5.3.4. Multicenter Studies

Analysis population(s): FAS

Analysis parameter: Titers of each type of antibody (anti-PRP antibodies, anti-diphtheria antibodies, anti-PT antibodies, anti-FHA antibodies, anti-tetanus antibodies, anti-poliovirus serotype 1 antibodies, anti-poliovirus serotype 2 antibodies, anti-poliovirus serotype 3 antibodies)

Analysis method: For each site, for each group, for each analysis parameter, and for each time point, the number of subjects, the number of subjects assessed for efficacy, the geometric mean, the geometric standard deviation, and the minimum, median, and maximum values will be calculated.

7.5.3.5. Multiple Comparison/Multiplicity

Not applicable

7.5.3.6. Use of an "Efficacy Subset" of Patients

Not implemented

7.5.3.7. Active-Control Studies Intended to Show Equivalence

Not applicable

7.5.3.8. Analyses of Subgroups

7.5.3.8.1 Seroprotection Rates for Each Type of Antibody for Each Subgroup

Analysis population(s): FAS

Analysis parameter: The anti-PRP antibody seroprotection (titer $\geq$ 1 μg/mL) rate, and also the antibody seroprotection rates for other antibodies (anti-diphtheria antibodies, anti-PT antibodies, anti-FHA antibodies, anti-tetanus antibodies, anti-poliovirus serotype 1 antibodies, anti-poliovirus serotype 2 antibodies, anti-poliovirus serotype 3 antibodies) at 4 weeks after the primary immunization

Analysis method: For the stratification factors shown in Table 7.5.3.8, for each group, the number of subjects, the number of subjects assessed for efficacy for each antibody, the number of seroprotections, the seroprotection rate (%), and the two-sided 95% confidence interval, will be calculated. Additionally, the 95% confidence intervals of the differences between Group H and the control group in the seroprotection rates will be calculated.

Table 7.5.3.8: Subgroups

Subgroups	
Sex	Male, Female
Age in months	≥ 2 and < 3 months, ≥ 3 months
Antibody titer before the first dose in the population in question	For each antibody titer: < reference value, ≥ reference value

7.5.3.8.2 Time Profiles of Each Type of Antibody, by Subgroup

Analysis population(s): FAS

Analysis parameter: Titers of each type of antibody (anti-PRP antibodies, anti-diphtheria antibodies, anti-PT antibodies, anti-FHA antibodies, anti-tetanus antibodies, anti-poliovirus serotype 1 antibodies, anti-poliovirus serotype 2 antibodies, anti-poliovirus serotype 3 antibodies)

Analysis method: For the subgroups shown in Table 7.5.3.8, for each group, for each analysis parameter, and for each time point, the number of subjects, the number of subjects assessed for efficacy, the geometric mean, the geometric standard deviation, the two-sided 95% confidence interval of the geometric mean, and the minimum, median, and maximum values will be calculated.

7.6. Safety Analyses

7.6.1. Adverse Events

The adverse event terms will be reclassified based on MedDRA/J Version 19.0.

7.6.1.1. Adverse Event Incidences

Analysis population(s): Safety analysis set

Analysis parameter: Adverse events (solicited adverse events, immediate reactions, other), adverse drug reactions (solicited adverse events, immediate reactions, other), serious adverse events, serious adverse drug reactions, adverse events leading to discontinuation, adverse drug reactions leading to discontinuation

Analysis method: For each group, the number and proportion (and 95% confidence interval thereof) of subjects experiencing each type of event will be calculated.

7.6.1.2. Individual Adverse Events

Analysis population(s): Safety analysis set

Analysis parameter: Adverse events, adverse drug reactions, serious adverse events and reactions, adverse events and reactions leading to discontinuation

Analysis method: For each group, the numbers and proportions of subjects experiencing each type of event will be calculated by event category (solicited adverse events, immediate reactions, other) and by MedDRA/J SOC and PT. Group totals will be shown, as well. Additionally, adverse events and adverse drug reactions will be tabulated by event category (solicited adverse events, immediate reactions, other)

and severity (mild, moderate, severe). If the same subject experiences the same event multiple times at different levels of severity, the event will be tabulated using the highest reported level of severity.

Listings

Listing 7.6.1.2.1: Listing of Adverse Events

Listing 7.6.1.2.2: Listing of Adverse Drug Reactions

7.6.1.3. Incidence of Solicited Adverse Events by Number of Doses

Analysis population(s): Safety analysis set

Analysis parameter: Adverse events and reactions that are considered solicited adverse events

Analysis method: For each number of doses, for each group, and for each MedDRA/J SOC and PT, the numbers and proportions of subjects experiencing each type of event will be tabulated by event category (solicited adverse events, immediate reactions).

7.6.1.4. Adverse Events by Subgroup

7.6.1.4.1 Solicited Adverse Events by Subgroup (Adverse Drug Reactions)

Analysis population(s): Safety analysis set

Analysis parameter: Adverse drug reactions classified as solicited adverse events

Analysis method: For the subgroups shown in Table 7.6.1.4, for each group, the numbers and proportions of subjects experiencing each type of event will be calculated by MedDRA/J SOC and PT.

Table 7.6.1.4: Subgroups

Subgroups	
Sex	Male, Female
Age in months	≥ 2 and < 3 months, ≥ 3 months

7.6.1.4.2 Pyrexia (Solicited Adverse Drug Reactions)

Analysis population(s): Safety analysis set

Analysis parameter: Pyrexia (solicited adverse event) (adverse drug reaction)

Analysis method: For each number of doses, and both overall and by the presence or absence of simultaneous immunization with a pneumococcal vaccine, the number and proportion of subjects experiencing each type of event will be calculated (using the total number of administrated doses as the denominator). The number and proportion of subjects experiencing each type of event will also be calculated by number of injections (1, 2, or 3) and also both overall and by the presence and absence of simultaneous immunization with a pneumococcal vaccine.

8. SOFTWARE USED

The SAS Windows version (release 9.4) will be used for statistical analysis.

9. CHANGES TO STATISTICAL ANALYSIS PLAN FROM THE PROTOCOL

Nothing particular

10. REFERENCES

None

11. OUTPUT LISTINGS

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Table 7.6.1.4.1	Solicited Adverse Events by Subgroup (Adverse Drug Reactions) (Safety Analysis Set)
Table 7.6.1.4.2	Emergence of Pyrexia by Subgroup (Adverse Drug Reactions) (Safety Analysis Set)

Listing 7.2.2	Listing of Discontinuations (Discontinued Subjects)
Listing 7.3.1	Listing of Subject Backgrounds (Randomized Subjects)
Listing 7.3.2	Listing of Concomitant Medications (Randomized Subjects)
Listing 7.4	Listing of Doses of Investigational Product (Safety Analysis Set)
Listing 7.5.2.2	Antibody Titer Listing (FAS)
Listing 7.6.1.2.1	Listing of Adverse Events (Safety Analysis Set)
Listing 7.6.1.2.2	Listing of Adverse Drug Reactions (Safety Analysis Set)