Statistical Analysis Plan

Protocol Number: BK1310-J02

Phase 3 Study of BK1310 Intramuscular Injection in Healthy Infants

Version Number: 2
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Statistical Analysis Plan

Safety and Efficacy of BK1310 Intramuscular Injection in Healthy Infants

Mitsubishi Tanabe Pharma Corporation

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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 "01.00.00000."
Version 2	"11. Output Listings" was partially changed.

Statistical Analysis Plan

Safety and Efficacy of BK1310 Intramuscular Injection in Healthy Infants

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 "Safety and Efficacy of BK1310 Intramuscular Injection in Healthy Infants," and covers the information that is included in the study protocol, but in greater detail.

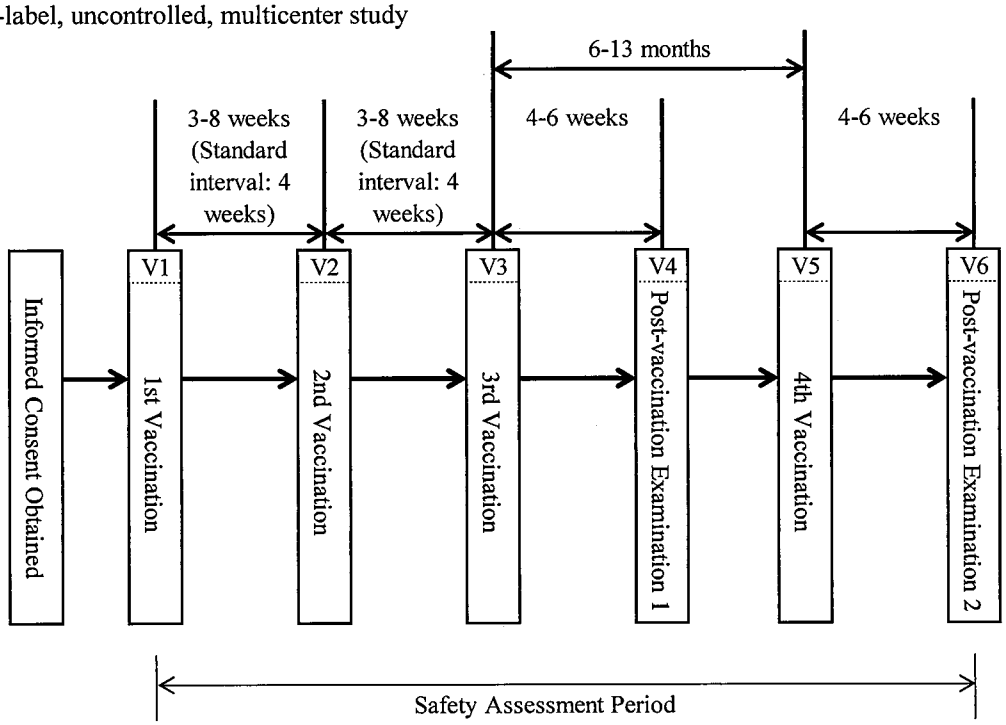
2. STUDY OBJECTIVE AND STUDY DESIGN

2.1. Objectives

To investigate the efficacy and safety of the intramuscular administration of BK1310 in healthy nursing infants.

2.2. Study Design

Open-label, uncontrolled, multicenter study



The following investigational products will be administered.

- BK1310: A single dose of 0.5 mL (that contains 10 μg of Hib antigen as the oligosaccharide)

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

2.3. Assessment Time Point

	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 immunization.

*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 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.

2.4. Sample Size Justification

30 subjects as investigational product vaccinated subjects

Rationale

The sample size was set at 30 subjects who are eligible for inclusion in a stratified analysis for exploring the causes of any differences that may be found in efficacy or safety between intramuscular

administration (this study) and subcutaneous administration (study BK1310-J01), based on the sample size that was used in the intramuscular administration study that was conducted for the vaccine that has already been approved (VaxemHIB aqueous suspension for injection).
Additionally, a simulation found that the probability of a solicited adverse event that has an incidence of 5.8% occurring in a single subject if the sample size is 30 would be 83%. The figure of 5.8% was chosen because this was the incidence of the least frequently reported solicited adverse drug reaction in the BK1310 group in the Japanese phase 2 study of MT-2301 (study MT-2301-J01).

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

1) 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
2) The anti-PRP antibody seroprotection (antibody titer ≥ 1 μg/mL) rate, at a concentration of 1 μg/mL or above, and the anti-PRP antibody seroprotection (antibody titer ≥ 0.15 μg/mL) rate and the geometric mean anti-PRP antibody titer for anti-PRP antibodies at 4 weeks after the booster immunization
3) The geometric mean antibody titers for pertussis, diphtheria toxin, tetanus toxin, and attenuated poliovirus at 4 weeks after the primary immunization
4) The antibody seroprotection rates and geometric mean antibody titers for pertussis, diphtheria toxin, tetanus toxin, and attenuated poliovirus 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) 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-poliovirus antibody titers (anti-poliovirus serotype 1, 2, and 3 antibody titers), 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) Antibody 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 seroprotection rates for the aforementioned reference antibodiess following immunization with the investigational product will be calculated.

Antibody 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 enrolled 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 enrolled 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 immunization 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 7.1.4: 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 7.1.5: Treatment Groups

Treatment Groups	Display
BK1310 0.5 mL per dose	BK1310

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	Postdose examination 1 at Visit 4
Before the boosterimmunization	V5	Before the fourth dose at Visit 5
4 weeks after the booster immunization	V6	Postdose examination 2 at Visit 6

7.2. Subject Disposition

7.2.1. Analysis Population Eligibility

Analysis population(s): Enrolled 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.

7.2.2. Disposition of Discontinued Subjects

Analysis population(s): Enrolled subjects

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

Analysis method: 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.

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 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

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).

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 rates for other antibodies (anti-diphtheria [redacted] anti-diphtheria [redacted], anti-PT, anti-FHA, anti-tetanus, anti-poliovirus serotype 1, anti-poliovirus serotype 2, anti-poliovirus serotype 3)

Analysis method: For each analysis parameter, the number of subjects for each time point (4 weeks after the primary immunization, 4 weeks after the booster immunization), 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.

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 (titer ≥ 0.15 μg/mL) rate

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

7.5.2.2 Antibody Titer Profiles

Analysis population(s): FAS

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

Analysis method: For each analysis parameter, the number of subjects by time point, 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.

7.5.3. 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

Not planned

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

Not planned

7.6. Safety Analyses

7.6.1. Adverse Events

The adverse event terms will be reclassified based on MedDRA/J Version 20.0.

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: 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: 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. 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.

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, 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).

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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