Statistical Analysis Plan

Protocol Number: BK1310-J03

Phase 3 Study of BK1310 Compared With ActHIB® and Tetrabik in Healthy Infants: A Randomized, Assessor-blind, Active-controlled

Version Number: 1
Date: September 10, 2020
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Statistical Analysis Plan

Confirmatory Study of BK1310 in Healthy Infants

Mitsubishi Tanabe Pharma Corporation

Date prepared	: September 10, 2020
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Revision History

Version Number	Details of Revision
Version 1	First Version In accordance with the study protocol version number, "01.00.00000."

Statistical Analysis Plan

Confirmatory Study of BK1310 in Healthy Infants

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Prepared by statistical analyst

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Approved by statistical analysis manager

[redacted]

Date (Year/Month/Day)

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List of Abbreviation

Abbreviation	Unabbreviated term
DPT-IPV	Adsorbed Diphtheria - purified Pertussis - Tetanus - Inactivate poliovirus combined vaccine
DPT-IPV-Hib	Adsorbed Diphtheria - purified Pertussis - Tetanus - Inactivate poliovirus - Haemophilus Influenzae type b combined vaccine
ELISA	Enzyme-linked immunosorbent assay
FAS	Full analysis set
FHA	Filamentous Hemagglutinin
Hib	*Haemophilus Influenzae* type b
IPV	Inactivated polio vaccine
PPS	Per protocol set
PRP	Polyribosylribitol phosphate
PT	Pertussis Toxin
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
Age ≥ 2 months and < 43 months	From the day at exactly 2 months after the date of birth until the day before 43 months after the date of birth
Age ≥ 2 months and < 7 months	From the day at exactly 2 months after the date of birth until the day before 7 months after the date of birth
Day of vaccination	Day 1
Vaccination interval: 3-8 weeks	With the day of the previous vaccination being considered Day 1, subjects will be vaccinated again sometime in the period between the same day of the week 3 weeks after Day 1 and the same day of the week 8 weeks after Day 1.
Vaccination interval: 6-13 months	Subjects will be vaccinated again sometime in the period between the same day 6 months after the day of the previous vaccination and the same day 13 months after the day of the previous vaccination. However, if there is no same day for the month in question, then the same day will be considered to be the last day of the month in question.
Postdose examination: 4-6 weeks	Subjects will be examined during the period from the same day of the week 4 weeks after to the same day of the week 6 weeks after the day of the third or fourth vaccination
X months before ○○	The same day X months before.
Within X weeks	Within the same day of the week as that X weeks before
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 "confirmatory study of BK1310 in healthy nursing infants," and covers the information that is included in the study protocol, but in greater detail.

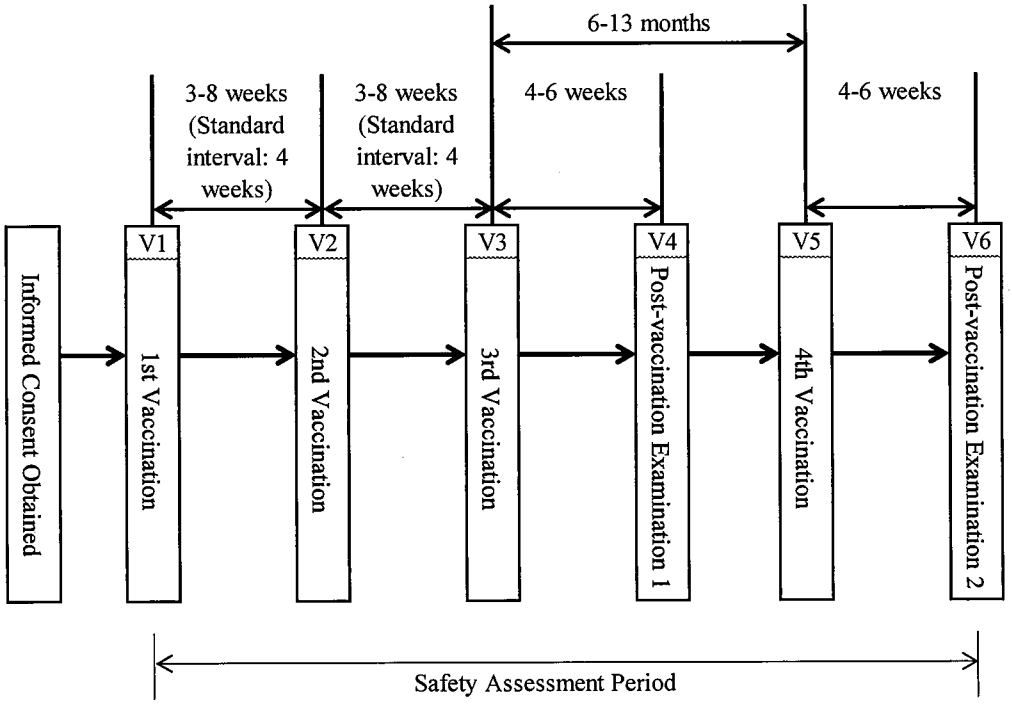
2. STUDY OBJECTIVE AND STUDY DESIGN

2.1. Objectives

To verify the noninferiority in healthy infants of BK1310 to simultaneous vaccination with ActHIB and Tetrabik in terms of the antibody seroprotection rates against each of the antigens contained in BK1310 following the administration of 3 doses of BK1310. Additionally, to investigate the efficacy and safety of BK1310.

2.2. Study Design

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



2.3. Randomization Method

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

2.4. 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 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 health observation 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 pyrexia or 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 health observation diary until the symptoms return to normal.

2.5. Sample Size Justification

○Target sample size

260 (130 in the BK1310 group and 130 in the control group)

Rationale

The objective is to verify noninferiority to the control in each of the anti-PRP antibody seroprotection rate and the antibody seroprotection rates for pertussis, diphtheria toxin, tetanus toxin, and attenuated poliovirus after the administration of 3 doses of BK1310, and the sample size required for this is 119 subjects in each group, 238 subjects in total. To account for dropout rate, the target sample size has been set at 130 subjects in each group, 260 subjects in total. More details are provided below.

The estimated anti-PRP antibody seroprotection rate and antibody seroprotection rates for pertussis, diphtheria toxin, tetanus toxin, and attenuated poliovirus were set as shown below based on the results of study BK1310-J01 (Cohort 2).

Study BK1310-J01 Cohort 2 Results and Estimated Values

	Positive Rate (%)	Estimate
Anti-PRP antibody concentration	100.0	98.0
Anti- pertussis antibody concentration	99.4	99.0
Anti-FHA antibody concentration	97.6	97.0
Anti-diphtheria antibody concentration	97.6	97.0
Anti-tetanus antibody concentration	100.0	99.0
Anti-poliovirus type 1 antibody titer	100.0	99.0
Anti-poliovirus type 2 antibody titer	100.0	99.0
Anti-poliovirus type 3 antibody titer	100.0	99.0

Based on a noninferiority test performed using the Farrington-Manning method, with a lower inferiority margin of 10% and a significance level of 2.5%, one-sided, for the antibody seroprotection rates in the BK1310 and control groups, with a sample size of 119 subjects in each group, the power will be 98.8% for anti-PRP antibodies, 100.0% for PT, 95.7% for FHA, 95.7% for diphtheria, 100.0% for tetanus, 100.0% for poliovirus type 1, 100.0% for poliovirus type 2, and 100.0% for poliovirus type 3. The simultaneous power with a sample size of 119 subjects per group will be 90.3%.

3. ENDPOINTS

3.1. Efficacy Endpoints

(1) Primary endpoint

The anti-PRP antibody seroprotection (antibody titer $\geq$ 1 μg/mL) rate, and the seroprotection rates for pertussis, diphtheria toxin, tetanus toxin, and attenuated polio virus at 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 after the primary immunization
2) 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 after the booster immunization
3) The geometric mean antibody titers for pertussis, diphtheria toxin, tetanus toxin, and attenuated poliovirus after the primary immunization
4) The antibody seroprotection rate and geometric mean antibody titers for pertussis, diphtheria toxin, tetanus toxin, and attenuated poliovirus after the booster immunization

3.2. Safety Endpoints

Adverse events and adverse drug reactions

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

Antibody titer geometric mean ratio 95% confidence interval

= $10^{(\text{lower limit of the 95\% confidence interval of the difference in the means of the log-transformed values (base 10) of the antibody titers})}$ to $10^{(\text{upper limit of the 95\% confidence interval of the difference in the means of the log-transformed values (base 10) of the antibody titers})}$

However, for the anti-poliovirus antibody titers (anti-poliovirus serotypes 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 $2^{(\text{upper limit of the 95\% confidence interval of the mean of the log-transformed value (base 2) of the antibody titer})}$

Antibody titer geometric mean ratio 95% confidence interval

= $2^{(\text{lower limit of the 95\% confidence interval of the difference in the means of the log-transformed values (base 2) of the antibody titers})}$ to $2^{(\text{upper limit of the 95\% confidence interval of the difference in the means of the log-transformed values (base 2) of the antibody titers})}$

(2) The antibody titer measurement methods and antibody seroprotection rate criteria

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

*: Sabin strains

The proportions of subjects with the aforementioned reference antibody titers (the seroprotection rates) 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, a secondary analysis of the primary endpoint will be performed in the per-protocol set (PPS), as well. 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

(1) FAS

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 after the primary immunization

(2) PPS

The PPS is the FAS, minus the following subjects.

- Subjects with inclusion criteria violations
- Subjects who met any of the exclusion criteria
- Subjects who violated any of the prohibited concomitant drug rules during the primary immunization
- Subjects from whom the blood samples for the antibody titer measurements after the primary immunization had not been collected within the specified time window for the post-immunization tests after the third dose (Visit 3 plus 4-6 weeks)

- Subjects who, during the primary immunization, received investigational products other than the investigational products they were assigned
- Subjects for whom the immunization dose levels, numbers of doses, or dosing intervals were not as specified during 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 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

The data from the scheduled assessment time points listed in "9.1 Test/Observation Schedule" of the study protocol will be used for the tabulations at each time point of, for example, the test and observation parameters.

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

The test will be one-sided, with a significance level of 2.5%. 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, the Clopper & Pearson method will be used. Additionally, the 95% confidence interval of the difference between the BK1310 group and the control group in the antibody seroprotection rate will be calculated using the Farrington-Manning method with a lower inferiority margin of 10%.

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 group: 0.5 mL per dose	BK1310

Subjects will receive 0.5 mL of each of ActHIB and Tetrabik	Control

7.1.6. Tabulation Time Points and Baselines

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

Table 7.1.6: 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, and at discontinuation*
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**

* Only at discontinuation after the vaccination of the third dose of the investigational product and before the vaccination of the additional dose

** Only at discontinuation after the vaccination of the additional dose

7.2. Subject Disposition

7.2.1. Analysis Population Eligibility

Analysis population(s): Randomized subjects

Analysis parameter: Eligibility for the FAS, the PPS, and the 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. Additionally, a listing of discontinuations will be prepared.

7.3. Demographic and Other Baseline Characteristics

Analysis population(s): FAS, PPS, 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. In addition, if the FAS is the same as the PPS, then only the FAS will be output. Listings of background information and concomitant medications will also be prepared for all randomized subjects.

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), by group. Listings will also be prepared.

7.5. Efficacy Analyses

7.5.1. Primary endpoints

Analysis population(s): FAS, PPS

Analysis parameter: The anti-PRP antibody seroprotection (titer ≥ 1 μg/mL) rate, and the anti-Bordetella pertussis antibody, anti-diphtheria antibody, anti-tetanus antibody, and anti-poliovirus antibody seroprotection rates 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 antibody seroprotection rate (%), and the two-sided, 95% confidence intervals will be calculated by group. In addition, the differences between the BK1310 group and the control group in the seroprotection rates (%) for each type of antibody, as well as the two-sided, 95% confidence intervals thereof, will be calculated, and noninferiority tests will be applied using the Farrington-Manning method, with a significance level of 2.5%, one-sided, and a lower noninferiority limit of 10%. Moreover, if the antibody seroprotection rate is 100% in both groups, then the test will not be performed, and it will be concluded that noninferiority has been verified.

If the FAS and the PPS are the same, then only the FAS will be output.

Rationale for the Lower Noninferiority Limit

In the phase 3 confirmatory studies that have been conducted to assess Hib vaccines and precipitated-purified pertussis/diphtheria/tetanus combined vaccine, 10% has been used as the lower noninferiority

limit for the difference in antibody seroprotection rates. The lower noninferiority limit was therefore set at 10% for this study, as well.

7.5.2. Secondary endpoints

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

Analysis population(s): FAS

Analysis method: Anti-PRP antibody seroprotection (titer ≥ 0.15 μg/mL) rate 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 antibody seroprotection rate (%), and the two-sided 95% confidence intervals will be calculated. Additionally, the 95% confidence intervals of the differences between the BK1310 group and the control group in the antibody seroprotection rates will be calculated.

7.5.2.2. Antibody Seroprotection Rates After the Booster Immunization

Analysis population(s): FAS

Analysis parameter: The anti-PRP antibody seroprotection (titer ≥ 1 μg/mL) rate, the anti-PRP antibody seroprotection (titer ≥ 0.15 μg/mL) rate after the booster immunization, and the seroprotection rates for other antibodies (anti-diphtheria, anti-PT, anti-FHA, anti-tetanus, anti-poliovirus serotype 1, anti-poliovirus serotype 2, and 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 number of seroprotections, the antibody seroprotection rate (%), and the two-sided 95% confidence intervals will be calculated. Additionally, the 95% confidence intervals of the differences between the BK1310 group and the control group in the antibody seroprotection rates will be calculated.

7.5.2.3. Antibody Titer Time Profiles

Analysis population(s): FAS

Analysis parameter: Titers of each type of antibody (anti-PRP, anti-diphtheria, anti-PT, anti-FHA, anti-tetanus, anti-poliovirus serotype 1, anti-poliovirus serotype 2, and 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 BK1310 group relative to that of the control group will be calculated after the primary immunization or the booster immunization. Listings will also be prepared for all randomized subjects.

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 "6.1 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 and seroprotection rates for each type of antibody (anti-PRP, anti-diphtheria, anti-PT, anti-FHA, anti-tetanus, anti-poliovirus serotype 1, anti-poliovirus serotype 2, and anti-poliovirus serotype 3 antibodies)

Analysis method: For each site, for each group, for each antibody titer, 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. In addition, the number of subjects, the number of subjects assessed for efficacy, the number of seroprotections, and the antibody seroprotection rates (%) will be calculated by site, group, antibody titer, and time point. The time profiles of the mean values of the antibody titers, by site, will also be presented.

7.5.3.5. Multiple Comparison/Multiplicity

Multiplicity adjustment will not be performed, because the objective of this study is to verify the noninferiority of BK1310 to the control in terms of all of the anti-PRP antibody seroprotection rate and the antibody seroprotection rates for pertussis, diphtheria toxin, tetanus toxin, and attenuated poliovirus.

7.5.3.6. Use of an "Efficacy Subset" of Patients

The analysis of the primary endpoint will be performed using the PPS.

7.5.3.7. Active-Control Studies Intended to Show Equivalence

The objective of this study is to confirm the inferiority of BK1310 to a placebo in terms of the antibody seroprotection rates, and this study is therefore being conducted as a noninferiority confirmatory study with an active control. Detailed information about the analyses is presented in 7.5.1 and 7.5.2.

7.5.3.8. Analyses of Subgroups

7.5.3.8.1. Seroprotection Rates for Each Type of Antibody, by Subgroup

Analysis population(s): FAS

Analysis parameter: The anti-PRP antibody seroprotection (titer ≥ 1 μg/mL) rate, and also the seroprotection rates for other antibodies (anti-diphtheria, anti-PT, anti-FHA, anti-tetanus, anti-poliovirus serotype 1, anti-poliovirus serotype 2, and anti-poliovirus serotype 3 antibodies) after the primary immunization or the booster 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 the BK1310 group and the control group in the seroprotection rates will be calculated.

Table 7.5.3.8: Subgroups

Subgroup	
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, anti-diphtheria, anti-PT, anti-FHA, anti-tetanus, anti-poliovirus serotype 1, anti-poliovirus serotype 2, and 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 21.1.

7.6.1.1. Incidences of Adverse Events And Adverse Drug Reactions

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 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, 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 stratification factors 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: Stratification factors

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

7.6.1.4.2. Pyrexia (Solicited Adverse Drug Reaction)

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).

7.6.1.5. Vaccination Site Reactions

In the following sections, information about the vaccination site reactions (redness, swelling, induration, pain) that occur in the BK1310 group and in the "Tetrabik" control group will be tabulated.

7.6.1.5.1. Injection Sites Reaction by Severity

Analysis population(s): Safety analysis set

Analysis parameter: Vaccination site reactions (redness, swelling, induration, pain) (adverse drug reactions)

Analysis method: The number and proportion of subjects experiencing such reactions will be tabulated by severity (mild, moderate, severe), group, and MedDRA/J SOC and PT. 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.

7.6.1.5.2. Injection Sites Reaction(Adverse Drug Reactions) by Number of Injections

Analysis population(s): Safety analysis set

Analysis parameter: Vaccination site reactions (redness, swelling, induration, pain) (adverse drug reactions)

Analysis method: The numbers and proportions of subjects experiencing such reactions will be tabulated by dose number, group, and MedDRA/J SOC and PT. If any administration site reaction data are missing, then the subjects will be excluded from the tabulation of administration site reactions for the dose number (e.g., first, second, third, or fourth) for which said data are missing for that subject.

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