Study Protocol

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: 01.00.00000
Date: December 19, 2018
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Confirmatory Study of BK1310 in Healthy Infants

Study Protocol

Sponsor

Mitsubishi Tanabe Pharma Corporation

The Research Foundation for Microbial Diseases of Osaka University

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Confidentiality Notice

This study protocol contains information that is intended only for parties directly involved in the clinical study. Advance written consent must be obtained from Mitsubishi Tanabe Pharma before any of the information contained in this study protocol is published or divulged to any third party.

This study will be conducted in compliance with the Pharmaceutical Affairs Law of Japan, the Ministerial Order on Good Clinical Practice (GCP) and related laws, and this study protocol.

Table of Contents

Attachments

Attachment 1: Classification Criteria for Severity of Adverse Drug Reactions to Drug Products, etc. (PAB/SD Notification No. 80, issued June 29, 1992 by the Safety Division of the Pharmaceutical Affairs Bureau of the Ministry of Health and Welfare)

Attachment 2: Study Procedure Flow Chart

Attachment 3-1: Health Status Report Form -- First Vaccination (Prevaccination Screening Questionnaire 1)

Attachment 3-2: Health Status Report Form -- Second Vaccination (Prevaccination Screening Questionnaire 2)

Attachment 3-3: Health Status Report Form -- Third Vaccination (Prevaccination Screening Questionnaire 3)

Attachment 3-4: Health Status Report Form -- Fourth Vaccination (Prevaccination Screening Questionnaire 4)

Attachment 4: ActHIB® Package Insert

Attachment 5: TETRABIK Syringe for SC Injection Package Insert

Attachment 6: Serious Adverse Event Report Form (Standard Form 12)

Attachment 7: Serious Adverse Event or Issue Information Form (Standard Form 14)

Appendices

Appendix 1: Clinical Study Organizational Structure of The Sponsor

Appendix 2: List of Study Sites

List of Abbreviations

Abbreviation	Unabbreviated expression
CRM197	Cross reacting mutant
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
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
FAS	Full analysis set
FHA	Filamentous Hemagglutinin
GCP	Good clinical practice
GLP	Good laboratory practice
Hib	*Haemophilus Influenzae* type b
IPV	Inactivated polio vaccine
MedDRA/J	Medical dictionary for regulatory activities/Japanese version
PPS	Per protocol set
PRP	polyribosylribitol phosphate
PT	Pertussis Toxin

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 receive the next vaccination 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 receive the next vaccination 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.
Post-vaccination 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 dose
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

Study Protocol Synopsis

1 Study Title

Confirmatory Study of BK1310 in Healthy Infants

2 Study Objectives

To verify the noninferiority in healthy infants of BK1310 to simultaneous vaccination with ActHIB® and TETRABIK for SC Injection Syringe 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.

3 Subjects

3.1 Subjects

Healthy infants with age ≥ 2 months and < 43 months (recommended age in months: ≥ 2 months and < 7 months)

3.2 Inclusion Criteria

Subjects meeting all of the following inclusion criteria at the time of the first vaccination with the investigational product will be eligible for study participation.

(1) Healthy infants aged ≥ 2 months and < 43 months (recommended ≥ 2 months and < 7 months) at the time of the first vaccination with the investigational product. However, although persons meeting the following definition of "persons who should receive a vaccination with care" may participate in the study, whether or not to enroll them in the study should be decided carefully.

(2) Persons from whose legal guardians written consent to study participation has been obtained.

Persons Who Should Receive A Vaccination With Care

1) Subjects who clearly have underlying diseases, such as cardiovascular disease, kidney disease, liver disease, blood disease, respiratory disease, or a developmental disorder

2) Persons who have developed a pyrexia within 2 days after receiving a vaccination in the past

3) Persons with a past history of convulsions

3.3 Exclusion Criteria

Subjects meeting any of the following exclusion criteria at the time of the first vaccination with the investigational product will be excluded from study participation.

(1) Persons who have received diagnoses of immunodeficiencies in the past, or who are currently receiving treatments that cause immunosuppression

(2) Persons with close relatives (up to third degree of kinship) who have a congenital immunodeficiency

(3) Persons who might experience a serious allergy in response to a food, drug product, etc.

(4) Persons who have had Hib infections, pertussis, diphtheria, tetanus, or acute poliomyelitis in the past

(5) Persons who have received a vaccination against Hib, pertussis, diphtheria, tetanus, or polio in the past

(6) Persons who have received live vaccines within 27 days, or inactivated vaccines/toxoids within 6 days, before the first vaccination with the investigational product

(7) Persons who have received blood transfusions, immunosuppressants (except for topical drugs), or immunoglobulin preparations (including HB immunoglobulin preparations and monoclonal antibodies [e.g., Synagis®, palivizumab]) in the past.

(8) Persons who have received corticosteroids (except for topical drugs) at a prednisolone dose level equivalent of 2 mg/kg/day or higher in the past.

(9) Persons who have participated in another clinical study and received another investigational product within 12 weeks before obtaining informed consent

(10) Persons who were less than 37 weeks old at birth, or who weighed less than 2500 g at birth

(11) Persons otherwise judged to be unsuitable for participation in this study by the (sub)investigator

3.4 Vaccination Postponement Criteria

(1) If the subject clearly has a pyrexia (if the patient's temperature is ≥ 37.5°C immediately before vaccination)

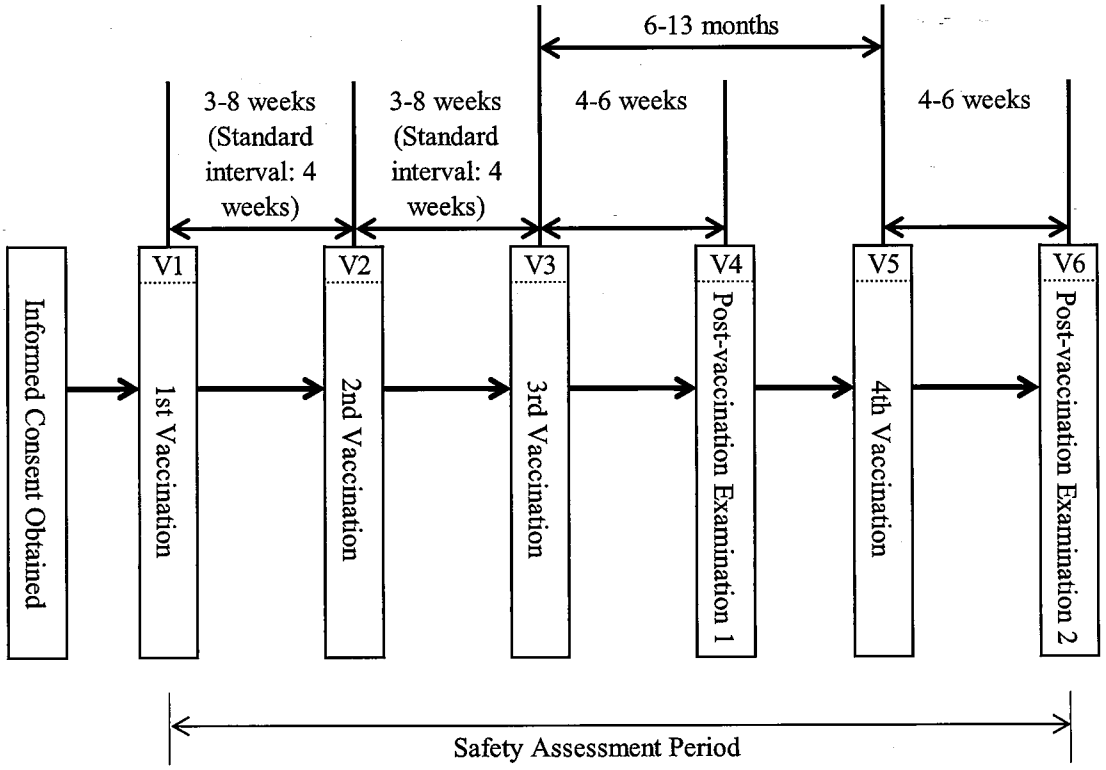
(2) If the subject has clearly developed a severe, acute illness

(3) If the (sub)investigator determines for some other reasons that it would not be appropriate for the subject to receive a vaccination

4 Study Design

4.1 Study Design

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



5 Investigational Product, Dose and Vaccination Method

5.1 Names of the Investigational Products

(1) Investigational Drug

Name: BK1310

Expected nonproprietary name: Adsorbed-purified pertussis/diphtheria/tetanus/inactivated polio (Sabin strain)/Haemophilus b (non-toxic mutant diphtheria toxin conjugate) combination vaccine

BK1310 is a syringe formulation that contains, in 0.5 mL, 10 μg of Hib antigen, in terms of the quantity of oligosaccharide, and that also contains the same antigen levels as those contained in TETRABIK for SC Injection syringe.

(2) Control drugs

Name: ActHIB®

Nonproprietary name: Haemophilus influenzae type b conjugate vaccine (tetanus toxoid conjugate)

A formulation that contains 10 μg of Hib antigen, in terms of the polysaccharide content, when reconstituted in 0.5 mL of the diluent.

Name: TETRABIK for SC Injection Syringe

Nonproprietary name: Adsorbed-purified pertussis/diphtheria/tetanus/inactivated polio (Sabin strain) combination vaccine

A syringe formulation that contains the following antigens: pertussis-preventing antigens, and diphtheria toxoid, tetanus toxoid, and inactivated poliovirus antigens

5.2 Dose and Administration Method

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

BK1310 group: 0.5 mL per dose

Control group: Subjects will receive 0.5 mL of each of ActHIB® and TETRABIK for SC Injection Syringe

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). For the booster immunization, subjects will receive a single subcutaneous (as a rule, administered at the top part of the upper arm extensor) dose at 6 to 13 months after the primary immunization. Subjects in the control group will receive subcutaneous doses of TETRABIK for SC Injection Syringe 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.

5.3 Administration Period

4 doses, 68 weeks maximum

6 Concomitant Drugs/Therapies

6.1 Prohibited Concomitant Medication/Therapy

The concomitant use of the following drugs and therapies will be prohibited during the study periods (Visit 1 through Visit 6).

(1) Hib, pertussis, diphtheria, tetanus, or polio vaccines other than the investigational products

(2) Immunoglobulin preparations

(3) Corticosteroids at prednisolone equivalent doses of 2 mg/kg/day or higher (except for topical drugs)

(4) Immunosuppressants (except for topical drugs)

(5) Blood transfusions

(6) Immunosuppressant therapies

(7) Investigational products other than BK1310, ActHIB®, and TETRABIK for SC Injection Syringe

The concomitant use of the following drugs will be prohibited from 27 days before until 14 days after the vaccination with investigational product.

(8) Live vaccines (e.g., BCG, measles, rubella, mumps, varicella, rotavirus*)

*: Simultaneous vaccination with the investigational product will be permitted only for a rotavirus vaccine

The concomitant use of the following drugs will be prohibited from 6 days before until 14 days after the vaccination with investigational product.

(9) Inactivated vaccines (e.g., Pneumococcal,** influenza, Japanese encephalitis, hepatitis A, hepatitis B**)

**: Simultaneous vaccination with the investigational product will be permitted only for the pneumococcal and hepatitis B vaccines. The site of vaccination will be the thigh or the arm on the opposite side from that used to administer the investigational product.

7 Endpoints

7.1 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 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

7.2 Safety Endpoints

Adverse events and adverse drug reactions

8 Target Sample Size

260 subjects (130 in each group) as subjects who have received the investigational product

9 Study Period

January 2019 to December 2020 (registration deadline: June 2019)

10 Test/Observation Schedule

	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			◄											►		
Health monitoring 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 monitoring 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 monitoring diary until the symptoms return to normal.

1. Background for the Study Plan and Other Background Information

(1) Target Disease and Therapies Therefor

Hib infections result from infection with *Haemophilus influenzae* type b (Hib), and can develop into invasive infections such as bacteraemia, meningitis, acute epiglottitis, and septic arthritis. Meningitis often has a poor prognosis,[1), 2)] and has a clinical course that is characterized by the emergence of cold-like symptoms followed by pyrexia, vomiting, and irritability, and then progressing to convulsions and disturbed consciousness. In the early stages of pyrexia, diagnosis is difficult, and a confirmed diagnosis is obtained by means of a cerebrospinal fluid test. In Japan, the haemophilus influenzae type b conjugate vaccine (tetanus toxoid conjugate; brand name: ActHIB®) is widely used for infection prevention.

Pertussis is an acute respiratory infection that is caused by infection with *Bordetella pertussis*. *Bordetella pertussis* is transmitted through airborne droplets originating in the upper respiratory secretions of the patient, and grows in tracheal and bronchial mucous membranes. The infection remains localized to the respiratory system throughout its entire course, and the bacterium cannot be isolated from other tissues. The primary symptoms are caused the pertussis toxin (PT), which has a molecular weight of 105,000, that is produced by the bacterium.[3)] PT is the primary causative agent and, along with filamentous hemagglutinin (FHA), is the most important protective antigen,[4)] and PT and FHA that have been weakened by formalin are used to prevent symptomatic infection.

Diphtheria is a respiratory infection that is caused by infection with *Corynebacterium diphtheriae*. The primary symptoms are caused by the diphtheria toxin, which has a molecular weight of 62,000. This toxin spread throughout the body via blood circulation, and causes disorders in the heart, heart conduction system, vasomotor system, and kidneys.[5), 6)] Diphtheria toxoid obtained by detoxifying the diphtheria toxin using formalin is used to prevent symptomatic infection.

Tetanus is a toxemic disease caused by infection with *Clostridium tetani*. The primary symptoms are caused by the tetanus toxin, which has a molecular weight of 150,000, and the infection results in central and peripheral nervous system disorders.[7),8)] Tetanus toxoid, which is obtained by detoxifying the tetanus toxin using formalin, is used to prevent symptomatic infection.

Polio (acute poliomyelitis) is an infection that is caused by the poliovirus. Poliovirus is a serotype of the species Enterovirus C, in the family of Picornaviridae. There are 3 types of poliovirus, 1, 2, and 3, depending on differences in virus particle antigenicity, but all 3 types cause polio. Humans are infected orally, and when the poliovirus proliferates in the central nervous system, it causes degeneration/necrosis in motor nerve cells, resulting in paralysis.[9)] In Japan, inactivated polio vaccine (IPV) from an attenuated strain or inactivated polio vaccine from a virulent strain is used to prevent symptomatic infection.

At the Sixth Health Science Council Immunization/Vaccine Committee's Research and Development and Production/Distribution Subcommittee (held November 28, 2013), it was announced that investigations into the development of a combined vaccine that included DPT-IPV would proceed with an eye towards making the timing of the first vaccination of the vaccine the same as that for the Hib vaccine,[10)] and the "Fundamental Plan for Immunization," which was published in 2014, listed a combined vaccine that includes DPT-IPV as a vaccine whose development needs to be prioritized.[11)] If a DPT-IPV-Hib pentavalent vaccine could be introduced to the clinical setting to simultaneously, in one product, confer basic immunity against pertussis, diphtheria, tetanus, polio, and Hib, this would be advantageous from the standpoint of alleviating the burden placed on infants by injections as well as reducing the burden associated with drug management.

(2) Name and Description of the Investigational Product

BK1310 is a pentavalent vaccine that was developed by Mitsubishi Tanabe Pharma Corporation and the Research Foundation for Microbial Diseases of Osaka University and that combines MT-2301, TETRABIK for SC Injection Syringe (adsorbed-purified pertussis/diphtheria/tetanus/inactivated polio [Sabin strain] combined vaccine; "TETRABIK" hereafter). MT-2301 is an influenza b conjugated vaccine that Mitsubishi Tanabe Pharma Corporation is developing in Japan. MT-2301 contains a *Haemophilus influenzae* type b-derived oligosaccharide--non-toxic mutant diphtheria toxin CRM_{197} conjugate made by binding a non-toxic mutant diphtheria toxin (CRM_{197}) as a carrier protein to an

oligosaccharide produced by polyribosylribitol phosphate (PRP), which is a capsular polysaccharide of Hib. MT-2301 does not contain any immune adjuvants such as aluminum. In the US, a phase 2 clinical study has been completed. Mitsubishi Tanabe Pharma Corporation has conducted a phase 2 study in Japan. Both of these studies have confirmed the efficacy and safety of BK1310.

TETRABIK contains as its active ingredients the protective antigens for pertussis (PT and FHA), diphtheria toxoid, tetanus toxoid, and inactivated poliovirus (IPV antigen). Since its approval in 2012, TETRABIK has been widely used in Japan, and its safety and efficacy confirmed.

The physical-chemical properties and drug product stability of BK1310 have been confirmed, and it is expected that BK1310 will be safe and effective in the clinical setting on the basis of the results of toxicity studies, pharmacology studies supporting efficacy, and the 2 clinical studies that have been conducted to date.

(3) Nonclinical Study Results and Clinical Study Results

1) Nonclinical Study Results

(a) Pharmacology Studies

Two non-GLP immunogenicity studies in rabbits were conducted as studies supporting the efficacy of BK1310. In Immunogenicity Study 1, the animals received BK1310 (the 10 μg formulation) by subcutaneous injection 3 times (doses of 5, 10, or 20 μg) at 2-week intervals. In Immunogenicity Study 2, the animals received BK1310 (the 5 μg and 10 μg formulations) by subcutaneous injection 3 times (doses of 5 or 10 μg PRP) at 2-week intervals. In addition, for each of the active ingredients of DPT-IPV, which is contained in BK1310, studies were conducted in accordance with the criteria stipulated in the Japanese Biological Drug Product Standards, "Adsorbed-Purified Pertussis/Diphtheria/Tetanus/Inactivated Polio (Sabin strain) Combined Vaccine," Small Lot Product Tests, Potency Tests.

The results showed that, in rabbits, the administration of BK1310 resulted in an increase in the level of anti-PRP antibodies, and that combination did not result in an interference effects in the anti-PRP antibody concentration obtained.

In addition, the active ingredients contained in the DPT-IPV vaccine in BK1310 conform to the specifications listed in the Japanese Biological Drug Product Standards, and combination was not found to result in any interference effects.

(b) Safety Pharmacology Studies

The effects on the central nervous system, cardiovascular system, and respiratory system were evaluated in BK1310 safety pharmacology studies. Rats were used to assess the effects on the central nervous system, and monkeys were used to assess the effects on the cardiovascular and respiratory systems. The 10 μg formulation of BK1310 was used in all of these studies. The rats received doses of 0.5 mL (10 μg PRP, the same as the dose used in clinical studies), and the monkeys received 5 mL (100 μg PRP, a dose 10-fold that used in clinical studies). The animals in all of the studies received single subcutaneous doses.

It was found as a result of these studies that BK1310 (the 10 μg formulation) did not affect the animals' general symptoms or behavior observations, or any of the respiratory system parameters (respiration rate, tidal volume, respiratory minute volume) or the cardiovascular system parameters (blood pressure, heart rate, ECG) that were measured using a telemetry system.

It was therefore concluded that BK1310 does not have any effects on the central nervous system, cardiovascular system, or respiratory system.

(c) Toxicity Studies

Single subcutaneous dose and repeated subcutaneous dose toxicity studies were conducted in rats as BK1310 toxicity studies. In each of these studies, the 10 μg formulation of BK1310 was used, the dose was 0.5 mL/body (10 μg PRP, the same as the dose used in the clinical studies), and the animals received either single subcutaneous doses or 5 (repeated) doses at 1-week intervals at the same administration site.

No systemic or administration site toxicities attributed to BK1310 were observed in the single subcutaneous dose toxicity studies, and it was therefore determined that the approximate lethal dose of

BK1310 under these test conditions is greater than 0.5 mL/body.

Although administration site induration and changes in some of the white blood cell fractions and some of the globulin fractions were observed in the repeated subcutaneous dose toxicity studies, all of these were immune reactions to BK1310, which contains aluminum, and none were toxicologically significant. The aforementioned changes were seen to around the same extent in both the BK1310 group and the group that received the control substance (DPT-IPV), and no clear differences were found in the recoverability of these changes, either. The NOAEL of BK1310 under these test conditions exceeded 0.5 mL/body, and it was concluded that the local irritation with BK1310 was comparable to that with DPT-IPV.

2) Clinical Study Results

In Japan, 2 studies of BK1310 have been conducted, an exploratory study in healthy infants (study BK1310-J01), and an intramuscular dosing study in healthy infants (study BK1310-J02). In study BK1310-J01, the safety and immunogenicity against the Hib antigen were confirmed in Cohort 1 and, in Cohort 2, the efficacy and safety of BK1310 were investigated using as a control simultaneous vaccination with ActHIB®and TETRABIK. In Cohort 1, safety up until after the booster immunization was confirmed, and it was also confirmed that there was adequate immunogenicity against each of the antigens, including the Hib antigen. In Cohort 2, it was confirmed that the efficacy and safety of BK1310 up until after the primary immunization were similar to those of simultaneous vaccination with ActHIB® and TETRABIK.

In study BK1310-J02, the efficacy and safety of the intramuscular administration of BK1310 were investigated. Although the study has ended, the analysis is ongoing.

For further details, refer to the most recent version of the BK1310 investigator's brochure.

(4) Plans for This Study

The introduction of a DPT-IPV-Hib pentavalent vaccine would make it possible to simultaneously, in one product, confer basic immunity against pertussis, diphtheria, tetanus, polio, and Hib. This would be advantageous from the standpoint of alleviating the burden placed on infants by injections as well as reducing the burden associated with drug management. The purpose of this study is to develop BK1310, which is a pentavalent vaccine that combines MT-2301, which is an influenza b conjugate vaccine that is being developed in Japan, with TETRABIK, which is a DPT-IPV combined vaccine. With the results of study BK1310-J01 in mind, this study was designed to verify the noninferiority of BK1310 to simultaneous immunization with ActHIB® and TETRABIK.

2. Study 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.

3. Subjects

3.1 Subjects

Healthy infants with age ≥ 2 months and < 43 months (recommended age in months: ≥ 2 months and < 7 months)

3.2 Inclusion Criteria

Subjects meeting all of the following inclusion criteria at the time of the first vaccination of the investigational product will be eligible for study participation.

(1) Healthy infants aged ≥ 2 months and < 43 months (recommended ≥ 2 months and < 7 months) at the time of the first vaccination with the investigational product. However, although persons meeting the following definition of "persons who should receive a vaccination with care" may participate in the study, whether or not to enroll them in the study should be decided carefully.

(2) Persons from whose legal guardians written consent to study participation has been obtained.

Persons Who Should Receive A Vaccination With Care

1) Persons who clearly have underlying diseases, such as cardiovascular disease, kidney disease, liver disease, blood disease, respiratory disease, or a developmental disorder

2) Persons who have developed a pyrexia within 2 days after receiving a vaccination in the past

3) Persons with a past history of convulsions

Rationale

(1) This inclusion criterion was established in accordance with the "Routine Immunization for Hib Infection" section in the Routine Immunization Guidelines. The timing of the start of immunization with DPT-IPV was established taking into account the fact that, at the Sixth Health Science Council Immunization/Vaccine Committee's Research and Development and Production/Distribution Subcommittee (held November 28, 2013),[10] it was announced that investigations into the development of a combined vaccine that included DPT-IPV would proceed with an eye towards making the timing of the first vaccination of the vaccine the same as that for the Hib vaccine. In addition, as far as the upper limit of vaccination age in months is concerned, if the vaccination interval is maximized (the second dose is administered 8 weeks after the first dose, the third dose is administered 8 weeks after the second dose, and the fourth dose is administered 13 months after the third dose, for a total period of 17 months), then in order to complete the administration of the fourth dose of the investigational product while the subjects are still younger than 60 months of age, the target age for routine Hib immunization, the subjects who can be enrolled into the study must be younger than 43 months of age. Furthermore, the recommended age for study entry was set as ≥ 2 months and < 7 months, because this is the target population for the fourth dose of the Hib vaccine in routine immunization.

Persons Who Should Receive A Vaccination With Care

The persons who should receive a vaccination with care, as defined in (1) through (3) above, were established in accordance with the Immunization Act Enforcement Regulations and the Immunization Guidelines.

(2) The legal guardians are defined as the parents, in accordance with the "Guidance on Clinical Studies of Drug Products in Pediatric Populations"[12] (PFSB/ELD Notification No. 1334, dated December 15, 2000).

3.3 Exclusion Criteria

Subjects meeting any of the following exclusion criteria at the time of the first vaccination with the investigational product will be excluded from study participation.

(1) Persons who have received diagnoses of immunodeficiencies in the past, or who are currently receiving treatments that cause immunosuppression

(2) Persons with close relatives (up to third degree of kinship) who have a congenital immunodeficiency

(3) Persons who might experience a serious allergy in response to a food, drug product, etc.

(4) Persons who have had Hib infections, pertussis, diphtheria, tetanus, or acute poliomyelitis in the past

(5) Persons who have received a vaccination against Hib, pertussis, diphtheria, tetanus, or polio in the past

(6) Persons who have received live vaccines within 27 days, or inactivated vaccines/toxoids within 6 days, before the first vaccination with the investigational product

(7) Persons who have received blood transfusions, immunosuppressants (except for topical drugs), or immunoglobulin preparations (including HB immunoglobulin preparations and monoclonal antibodies [e.g., Synagis, palivizumab])

(8) Persons who have received corticosteroids (except for topical drugs) at a prednisolone dose level equivalent of 2 mg/kg/day or higher

(9) Persons who have participated in another clinical study and received another investigational product within 12 weeks before obtaining informed consent

(10) Persons who were less than 37 weeks old at birth, or who weighed less than 2500 g at birth

(11) Persons otherwise judged to be unsuitable for participation in this study by the (sub)investigator

Rationale

(1)(2)(4)(5)(7)(8)(10) These criteria were established because these conditions could affect efficacy and safety.

(3)This criterion was established with safety in mind, and in accordance with the Immunization Act Enforcement Regulations and the Routine Immunization Guidelines.

(6)This criterion was established in accordance with the vaccination interval in the Routine Immunization Guidelines.

(9)This criterion was established to ensure that this study is conducted ethically, and also because the effects on efficacy and safety of drugs that have not been properly evaluated are unpredictable.

(11) This criterion was established to ensure that this study is conducted safely and ethically.

3.4 Vaccination Postponement Criteria

(1) If the subject clearly has a pyrexia (if the patient's temperature is $\geq$ 37.5°C immediately before vaccination)

(2) If the subject has clearly developed a severe, acute illness

(3) If the (sub)investigator determines for some other reasons that it would not be appropriate for the subject to receive a vaccination

Rationale

These criteria were established in accordance with the Immunization Act Enforcement Regulations and the Routine Immunization Guidelines.

4. Explanation and Consent

4.1 Preparation of Subject Explanation Sheet and Informed Consent Form

The principal investigator will prepare an explanation sheet for legal guardians and informed consent form (explanation sheet/informed consent form). The explanation sheet/informed consent form will be prepared as a single, unified document, and will be revised as needed.

The prepared or revised explanation sheet/informed consent form will be submitted to the study sponsor and approved by the institutional review board prior to the start of the study.

4.2 Information That Should be Included in the Explanation Sheet

The explanation sheet must include the following information at a minimum.

(1) The fact that the study has an experimental aspect

(2) The objectives of the study

(3) The names, job titles, and contact information for the principal investigators and subinvestigators

(4) Study method (including the experimental aspects of the study, the subject inclusion criteria and, if randomization is being performed, the probabilities of the patient being assigned to each treatment)

(5) The expected clinical risks and benefits (If there are no expected benefits to the subject, then this must be explained to the legal guardians.)

(6) Whether or not there are other preventive therapies that are available to the subjects

(7) The planned term of participation in the study

(8) The fact that participation in the study is entirely up to the legal guardian, and that the legal guardian may refuse to participate in the study or withdraw from the study at any time, and that the subject will not be subject to any discriminatory treatment because of the legal guardian's refusal to participate in or withdrawal from the study, nor will not participating in the study cause the subject to lose any benefits that the subject would have been expected to receive.

(9) The fact that the monitors, auditors, institutional review board, and regulatory authorities will be able to access the subject's medical records (source documents), and that in the case of said access the subject's privacy will be protected Also, the fact that by affixing his or her sign or sealing on the informed consent form the legal guardian consents to said access

(10) The fact that the subject's privacy will be protected even if the results of the study are published

(11) Whom the legal guardian should contact at the study site if the legal guardian wants to obtain information about the study or the subject's rights or to report any health injury that is related to the study

(12) The compensation and treatment that the subject will be able to receive if the subject suffers any health injury related to the study

(13) Information about the types of institutional review boards that will review, for example, the appropriateness of this study, what issues will be reviewed by each institutional review board, and other information about the institutional review boards that are involved in this study

(14) The planned sample size for the study

(15) The fact that the legal guardian will be notified promptly if any information that could affect the legal guardian's willingness to continue participating in the study

(16) The conditions or reasons that would cause the subject's participation in the study to be discontinued

(17) If participating in the study will impose any financial burden on the legal guardian, the exact nature thereof

(18) If the legal guardian will receive any financial compensation for participating in the study, the exact nature thereof (e.g., agreement on how the payments will be calculated)

(19) The rules the legal guardian will be expected to follow

4.3 Method of Obtaining Consent

Because the subjects of this study are infants, written consent will be obtained not from the subjects themselves but from the subjects' legal guardians. A legal guardian is defined as the person with parental rights for the subject in question (i.e., the father or mother).

(1) Before initiating the study, the (sub)investigator will provide the legal guardian with an explanation sheet/informed consent form that has been approved by the institutional review board and explain its contents thoroughly to the legal guardian. A clinical research coordinator may also provide a supplemental explanation. The (sub)investigator will provide the explanation based on the explanation sheet using as simple language as possible to make sure that the legal guardian understands, and must provide adequate responses to the legal guardian's questions. The (sub)investigator will confirm that the legal guardian has thoroughly understood the explanation before obtaining the legal guardian's written consent to have the subject participate voluntarily in the study.

(2) The (sub)investigator who provides the explanation and the legal guardian will affix their own names and seals or signatures on the consent form, and also date it. If a clinical research coordinator provides a supplementary explanation, that clinical research coordinator will also affix his or her sign or seal on the document and date it.

(3) The (sub)investigator will, before the subject starts participating in the study, provide the explanation sheet/informed consent form with the names, seals or signatures, and dates to the legal guardian and store the original informed consent form properly, in accordance with the rules of the study site.

(4) The date of the first informed consent obtainment will be recorded on the case report form.

4.4 Informed Consent Form/Subject Explanation Sheet Revision

(1) If new, important information is obtained that could pertain to the legal guardian's consent, the (sub)investigator will promptly convey this information orally to the legal guardian and check whether or not the subject will continue participating in the study, and will record the results in the subjects' medical records.

(2) The principal investigator will promptly determine based on this information whether or not the informed consent form/explanation sheet needs to be revised.

(3) If the principal investigator determines that the informed consent form/explanation sheet needs to be revised, the principal investigator will do so promptly, and must then once again have it approved by the institutional review board.

(4) The (sub)investigator will provide the legal guardian with an explanation using the explanation sheet/informed consent form that has been newly approved by the institutional review board, and will obtain the legal guardian's written consent to voluntarily continue having the subject participate in the study.

(5) Similar to when consent is initially obtained, the (sub)investigator who provided the explanation and the legal guardian will affix their signs or seals on the revised explanation sheet/informed consent form, and date it. If a clinical research coordinator provides a supplementary explanation, that clinical research coordinator will also affix his or her sign or seal on the document and date it.

(6) The (sub)investigator will provide the legal guardian the explanation sheet/informed consent form with the names, seals or signatures, and dates, and will retain the original of the informed consent form properly, in accordance with the rules of the study site.

5. Study Design

5.1 Study Phase and Type

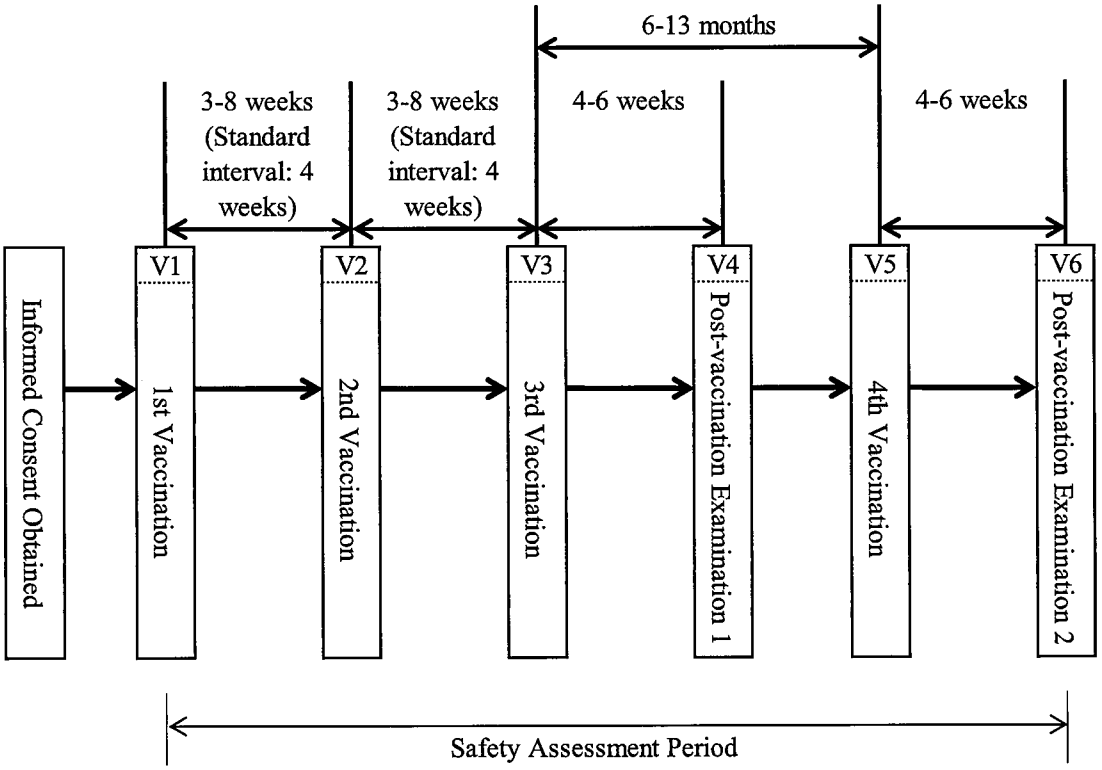
Phase of the study: 3

Type of study: Confirmatory

5.2 Study Design

5.2.1 Study Design

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



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

- BK1310 group: 0.5 mL per dose
- Control group: Subjects will receive 0.5 mL of each of ActHIB® and TETRABIK

For the primary immunization, subjects will receive 3 doses of investigational product subcutaneously (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). For the booster immunization, subjects will receive a single dose of investigational product subcutaneously (as a rule, administered at the top part of the upper arm extensor) at 6 to 13 months after the primary immunization. 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.

Rationale

In order to verify noninferiority with respect to simultaneous immunization with ActHIB® and TETRABIK for in the antibody seroprotection rate following vaccination with 3 doses of BK1310 against each of the antigens contained in BK1310, the study was positioned as an active-controlled, parallel-group, multicenter study.

It was decided that randomization will be performed to ensure the comparability of the subject populations of each of the groups, and that observer blinding method will be used in order to minimize biases that could arise in, for example, subject selection, management, and assessment.

5.3 Methods of Blinding and Randomization

5.3.1 Method of Blinding

5.3.1.1 Confirmation of Indistinguishability

The study sponsor will provide the investigational product randomization manager with investigational products that are externally indistinguishable, including their packaging, in order to maintain the blind. The investigational product randomization manager will confirm the external indistinguishability of the packaging of the investigational products (investigational drug and control drug) before allocating subjects to the investigational products. The indistinguishability of the investigational products when they are packaged in their outer cartons will be confirmed.

5.3.1.2 Materials List Preparation and Handling

The investigational product randomization manager will prepare a materials list in accordance with the "Materials List Preparation and Storage Procedures," and will retain and control it carefully, in accordance with separately prepared procedures, until the opening of the key code. Additionally, the investigational product randomization manager will prepare an emergency key for use in response to emergencies. The emergency key will be retained and controlled until the time of the final analysis (until the opening of the key code) under the control of the emergency call center manager.

5.3.1.3 Observer Blinding Method

In this study, in order to minimize biases, a observer blind will be applied, as described below, to the legal guardians, study sponsor, and various study site staff members, except for the vaccinators (the persons administering the investigational products). More detailed information is provided in "7.4 Investigational Product Handling and Storage" and in separate written procedures.

- At each study site, unblinded staff members (vaccinators, unblinded CRCs) will be designated using, for example, a "co-investigator/clinical research coordinator list."
- The investigational product controller will distribute the investigational product to the vaccinator with the packaging of the investigational product still sealed and intact, and the vaccinator will prepare a record of investigational product package opening.
- The vaccinator will administer the investigational product to the subject, taking care to not reveal what investigational product is being administered (the key code) to the subject's legal guardian or to study site staff members other than unblinded staff members (vaccinators, unblinded CRCs). The vaccinators will not reveal the assigned key code to any third party, including any staff members involved in this study.

- The vaccinator will return only the empty outer cartons to the investigational product controller. Additionally, the vaccinator will pay careful attention to maintaining the blind, so that the drugs cannot be identified from products/packaging that has been disposed of and, after administering the investigational product, the vaccinator will dispose of all syringes, vials, vial caps, injectors with injection needles, blister packs (blisters and blister films), trays, individual cartons, etc.
- The investigational product controller will retain the empty outer cartons of the investigational products until they are collected by the study sponsor.

5.3.2 Randomization and Allocation Methods

The investigational product randomization manager will assign drug numbers to the investigational products based on the materials list, in accordance with written procedures that have been specified in advance. The assignment of subjects to vaccination groups will be performed randomly, using a variable block method. Additionally, more detailed information about the allocation method and the randomization method will be provided in separate written procedures.

5.4 Endpoints

5.4.1 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 poliovirusat 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 occupancy and geometric mean antibody titers for pertussis, diphtheria toxin, tetanus toxin, and attenuated poliovirus after the additional immunity

Rationale

(1) The assessment was planned to be performed based on an immunological endpoint, in accordance with the "Guidelines for Clinical Studies of Vaccines to Prevent Infectious Diseases" (PFSB/ELD Notification No. 0527-5, issued May 27, 2010).[13] With Hib, it is generally held that an anti-PRP antibody concentration of 1 μg/mL is needed for long-term infection prevention,[14] and the anti-PRP antibody seroprotection rate at an Hib level of at least 1 μg/mL in the primary immunization was therefore established as the primary endpoint. The assessment was planned to be performed based on immunological endpoints for pertussis, diphtheria toxin, tetanus toxin, and attenuated poliovirus, as well, in order to confirm the effects of the addition of the Hib antigen on the efficacy of DTP-IPV.

(2) 1) The anti-PRP antibody seroprotection rate at an Hib level of at least 0.5 μg/mL, the level that is considered necessary for preventing Hib infection in the primary immunization, and the geometric mean antibody titer at an Hib antigen level of at least 0.15 μg/mL, were established as secondary endpoints.

2) Long-term infection prevention through the booster immunization, and the anti-PRP antibody seroprotection rate and geometric mean antibody titer required to prevent infection, were established as secondary endpoints.

3) and 4): The antibody seroprotection rates and geometric mean antibody titers required to prevent pertussis, diphtheria, tetanus, and polio in the primary immunization and secondary immunization were established as secondary endpoints.

5.4.2 Safety Endpoints

Adverse events and adverse drug reactions

6. Target Sample Size and Term of the Study

6.1 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%.

6.2 Study Period

January 2019 to December 2020 (registration deadline: June 2019)

7. Investigational Product

7.1 Names of the Investigational Products

(1) Investigational Drug

Name: BK1310

Expected nonproprietary name: Adsorbed-purified pertussis/diphtheria/tetanus/inactivated polio (Sabin strain)/Haemophilus b (non-toxic mutant diphtheria toxin conjugate) combination vaccine

BK1310 is a syringe formulation that contains, in 0.5 mL, 10 μg of Hib antigen, in terms of the quantity of oligosaccharide, and that also contains the same antigen levels as those contained in TETRABIK.

(2) Control drugs

Name: ActHIB®

Nonproprietary name: Haemophilus influenzae type b conjugate vaccine (tetanus toxoid conjugate)

A formulation that contains 10 μg of Hib antigen, in terms of the polysaccharide content, when reconstituted in 0.5 mL of the diluent.
Name: TETRABIK

Nonproprietary name: Adsorbed-purified pertussis/diphtheria/tetanus/inactivated polio (Sabin strain) combination vaccine
A syringe formulation that contains the following antigens: pertussis-preventing antigen, and diphtheria toxoid, tetanus toxoid, and inactivated poliovirus antigens

7.2 Investigational Product Packaging and Labeling

(1) Packaging

1) Individual Cartons

Cartons containing the following investigational product (2 types)

a) Investigational drug or control drug (TETRABIK): 1 syringe
b) Control drug (ActHIB®) or a placebo: For the control drug (ActHIB®), a single vial and a single of the drug and a single vial of the diluent will be packaged together in a blister pack For the placebo, the carton will contain a buffer material wrapped in buffer paper

2) Outer Cartons

Cartons that contain the individual cartons described in a) and b) above packaged as a set.

(2) Label

Both the individual cartons and the outer cartons will bear the following information.

- The fact that the contents are for use in a clinical study
- The name and address of the study sponsor
- The ID number
- The manufacturing number
- The storage method

- The drug number

More detailed information is provided in the "Investigational Product Control Procedures."

7.3 Storage Method

The investigational product should be stored shielded from light at 2 to 8°C; it should not be allowed to freeze.

7.4 Investigational Product Handling, Storage, and Control

The study sponsor will deliver the investigational products once the contract with the study site has been concluded. The investigational product controller stored and controlled the investigational products and, after the conclusion of the study, will return all the unused investigational products and the empty outer cartons to the monitor according to the "Investigational Product Management Procedures" specified by the sponsor.

Furthermore, investigational product must not be used for any purpose other than those described in this study protocol (e.g., for other clinical studies, animal studies, basic research).

- The investigational product controller will distribute the investigational product to the vaccinator with the packaging of the investigational product still sealed and intact, and the vaccinator will prepare a record of investigational product package opening.
- The vaccinator will administer the investigational product to the subject, taking care not to reveal what investigational product is being administered (the key code) either to the subject's legal guardian or to study site staff members other than unblinded staff members (vaccinators, unblinded CRCs).
- The vaccinator will return only the investigational product empty outer cartons to the investigational product controller. Additionally, the vaccinator will pay careful attention to maintaining the blind, so that the drugs cannot be identified from products/packaging that has been disposed of and, after administering the investigational product, the vaccinator will dispose of all syringes, vials, vial caps, injectors with injection needles, blister packs (blisters and blister films), trays, individual cartons, etc.
- The investigational product controller will retain the empty outer cartons of the investigational products until they are collected by the study sponsor.

7.5 Emergency Unblinding Procedures

If it becomes necessary to identify the group to which a subject belongs in an emergency, such as if the subject develops a serious adverse event, then the principal investigator will handle this situation in accordance with the "Emergency Key Opening Procedures." The principal investigator will also promptly prepare a written record of the reason for opening the key, and will submit this to the study sponsor.

8. Subject Study Methods

8.1 Subject Screening and Preparation of an Enrollment Registry and ID Code List

The principal investigator will prepare a list of all subjects who have been screened (subjects whose legal guardians received an informed consent explanation), and will prepare a subject screening registry. The principal investigator will assign ID codes to subjects whose legal guardians have consented to have subjects participate in the study, and will prepare a subject ID code list. When doing so, the principal investigator will note the information that will serve as the key when referencing the subject's medical records (source documents).

The principal investigator will also prepare a subject registry that lists the sex, date of consent, subject ID codes, etc. of the subjects who have been enrolled in the study (including the subjects whose study treatments have been temporarily or permanently discontinued).

8.2 Enrollment of Subjects

Subjects will be enrolled in accordance with the subject enrollment procedures (see Appendix 2, "Study Procedure Flow Chart").

The (sub)investigator will confirm that subjects from who consent to study participation has been obtained meet the inclusion criteria and do not meet the exclusion criteria at the time of enrollment, and will then enter the required information into the WEB subject enrollment system and provide notice of their enrollment in the study. After a subject's enrollment in the study has been accepted, the (sub)investigator will confirm the result on the WEB subject enrollment system.

When enrollment acceptance has been completed, an e-mail containing the result and the drug number (only for accepted subjects) will be sent to the (sub)investigator and the study sponsor from the WEB subject enrollment system. The (sub)investigator will confirm the drug number and prescribe the investigational product to the subject.

The investigational product controller will distribute the investigational product to the vaccinator with the outer carton packaging of the investigational product still sealed and intact. The vaccinator will administer the investigational product to the subject, taking care to not reveal what investigational product is being administered the subject's legal guardian, or to other (blinded) study site staff members.

Additionally, the notification of subject enrollment may be sent from the WEB subject enrollment system by a clinical research coordinator provided approval has been obtained from the (sub)investigator and the information that is needed for enrollment notification from the (sub)investigator has been recorded in, for example, the treatment records.

Test/Observation Parameters Required at Enrollment

Test and Observation Parameters	Description
Confirmation of inclusion/exclusion criteria	See "3.2 Inclusion Criteria" and "3.3 Exclusion Criteria"
Subject background investigation	Sex, date of birth (Western calendar), complications

8.3 Dose and Vaccination Method

8.3.1 Dose and Vaccination Method

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

- BK1310 group: 0.5 mL per dose
- Control group: Subjects will receive 0.5 mL of each of ActHIB® and TETRABIK

For the primary immunization, subjects will receive 3 doses of investigational product subcutaneously (as a rule, administered at the top part of the upper arm extensor) at intervals of 3 to 8 weeks (standard administration interval: 4 weeks). For the booster immunization, subjects will receive a single dose of investigational product subcutaneously (as a rule, administered at the top part of the upper arm extensor) at 6 to 13 months after the primary immunization. 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.

Rationale

These parameters were established in accordance with the "Immunization Guidelines."

The amount of Hib antigen in the investigational drug has been set at 10 μg on the basis of the results of study BK1310-J01.

For the route of administration, it was decided that the investigational product would be administered by subcutaneous injection, because this is the standard method of administering vaccinations in Japan, and one that is familiar to health care professionals.

8.3.2 Precautions About Dose and Administration Method

(1) As a rule, BK1310, the investigational drug, and the control drug TETRABIK will be administered into the upper part of the upper arm extensor, and the control drug ActHIB® will be administered into the lower part of the upper arm extension on the same side.

(2) A method will be used to ensure that the subjects' legal guardians will not be able to confirm the exact conditions of vaccination (for example, the legal guardians may be asked to wait in a separate room).

(3) Unblinded staff will affix an adhesive bandage of the same type as that used to cover the site of vaccination to the lower part of the upper arm extensor on the same side as that to which BK1310 has been administered for subjects who have been randomized to the BK1310 group, as well. Also, all adhesive bandages will be replaced with new ones by an unblinded staff after it has been confirmed that bleeding has stopped and before the subjects are examined by the (sub)investigator 30 minutes after administration.

Rationale

(2)(3) Because investigational products will be administered to the BK1310 groups at 1 place and to the control group at 2 places, in order to improve the quality of the blind as much as possible when assessing safety (local reactions), and in order to eliminate observer bias as much as possible, it has been decided that measures should be adopted for preventing the observers and legal guardians from finding out to what groups the subjects have been assigned based on, for example, the number of administration sites and scabs.

8.4 Treatment period

4 doses, 68 weeks maximum

Rationale

These parameters were established in accordance with the "Immunization Guidelines."

8.5 Concomitant Drugs/Therapies

8.5.1 Prohibited Concomitant Medication/Therapy

The concomitant use of the following drugs and therapies will be prohibited during the study periods (Visit 1 through Visit 6).

(1) Hib, pertussis, diphtheria, tetanus, or polio vaccines other than the investigational products

(2) Immunoglobulin preparations

(3) Corticosteroids at prednisolone equivalent doses of 2 mg/kg/day or higher (except for topical drugs)

(4) Immunosuppressants (except for topical drugs)

(5) Blood transfusions

(6) Immunosuppressant therapies

(7) Investigational products other than BK1310, ActHIB®, and TETRABIK

The concomitant use of the following drugs will be prohibited from 27 days before until 14 days after the vaccination with investigational product.

(8) Live vaccines (e.g., BCG, measles, rubella, mumps, varicella, rotavirus*)

*: Simultaneous vaccination with the investigational product will be permitted only for a rotavirus vaccine

The concomitant use of the following drugs will be prohibited from 6 days before until 14 days after the vaccination with investigational product.

(9) Inactivated vaccines (e.g., Pneumococcal,** influenza, Japanese encephalitis, hepatitis A, hepatitis B**)

**: Simultaneous vaccination with the investigational product will be permitted only for the pneumococcal and hepatitis B vaccines. The site of vaccination will be the thigh or the arm on the opposite side from that used to administer the investigational product.

Rationale

(1) This criterion was established because of the potential effects on the assessments of efficacy.

(2)(5) These criteria were established because of the potential effects on the assessments of efficacy, since they might contain antibodies to the active ingredients of the investigational drug.

(3)(4)(6) These criteria were established because of the potential effects on the assessments of efficacy and safety, since these drugs could suppress immune function.

(7) This criterion was established because of safety and ethics considerations.

(8)(9) These criteria were established because of safety and ethics considerations, in accordance with the vaccination intervals for other vaccines described in the Routine Immunization Guidelines. It was also decided that the concomitant use of other vaccines should be prohibited up until 14 days after

vaccination with the investigational product in order to check the effects on safety of combining the vaccines.

8.5.2 Records of Concomitant Drugs and Therapies

The (sub)investigator will record in the "Concomitant Drugs" and "Concomitant Therapies" columns of the case report form the following information about all drugs and therapies used concomitantly during the period from Visit 1 to Visit 4 and during the period from Visit 5 to Visit 6. However, saline solutions and similar products used to dissolve injectable products will not be recorded.

- Concomitant drugs: Drug name, daily dose,* route of administration, treatment period, objective of use
- Concomitant therapies: Therapy name, duration, objective of use

*: This information will be recorded only for corticosteroids (except for topical agents).

In addition, if a prohibited concomitant drug was used during the period from Visit 4 to Visit 5, then this will be recorded in the specified column of the case report form.

8.6 Subject Management

(1) Lifestyle Guidance

The (sub)investigator or a clinical research coordinator will provide lifestyle guidance to the legal guardian and request that they comply with the following rules.

1) Subjects are expected to undergo the observations/tests on the specified days. If a subject cannot come in to the study site on the specified day, the legal guardian must notify the (sub)investigator or a clinical research coordinator and follow his or her instructions.
2) The legal guardian must carry around a clinical study participation card and present it when the subject is examined at another hospital or department. In addition, if the subject uses any drugs that have been prescribed by a doctor outside of this study, or even any drugs that have been purchased by the legal guardian at a drug store, the legal guardian must be sure to inform the (sub)investigator or a clinical research coordinator. Also, if the subject is going to use a new drug during the study, the legal guardian must notify the (sub)investigator or a clinical research coordinator in advance.
3) In order to be able to respond to emergency symptoms, such as anaphylaxis, during the 30 minutes after vaccination with the investigational product, the subject will for this period remain in a location within the hospital that can be immediately contacted by the (sub)investigator.
4) If the subject develops any abnormalities, or if the subject's condition seems to be different from normal, then the (sub)investigator must be contacted.
5) Following vaccination, the site of vaccination must be kept clean.
6) During the term of the study, and particularly until 14 days after vaccination, the legal guardian must take care for the subject to avoid undue physical or mental burdening situations.

(2) Instructions for Filling Out the Health Monitoring Diary

The (sub)investigator or a clinical research coordinator will instruct the legal guardian to enter in the health monitoring diary information about the parameters specified in Section 9.2.4.1 every day up through Day 14 after vaccination with the investigational product. If the subject's pyrexia or symptoms do not return to normal by Day 14 after vaccination with the investigational product then, as a rule, the legal guardian will be instructed to enter information about them in the health monitoring diary until they return to normal.

1) Measurement of body temperature

The subject's legal guardian will measure the subject's axillary body temperature, and enter the result in the health monitoring diary. Furthermore, if multiple measurements are performed on the

same day because, for example, the subject has a pyrexia, then the highest measured body temperature will be entered.

2) Observation of symptoms

The legal guardian will monitor the subject's vaccination site reactions as well as any reactions other than vaccination site reactions (systemic reactions), and enter them in the health monitoring diary. When doing so, the legal guardian will also enter into the health monitoring diary the long axis for any redness, swelling, or induration at the vaccination site.

Furthermore, if the subject is examined or treated at another medical institution or by another treating department, the details thereof will be explained to the (sub)investigator or a clinical research coordinator.

9. Tests/Observations

9.1 Test/Observation Schedule

	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			←											→		
Health monitoring 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 monitoring 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 monitoring diary until the symptoms return to normal.

9.2 Test/Observation Parameters and Time Points

9.2.1 Subject Characteristics

The (sub)investigator will investigate the following subject characteristics and record the results in the case report form.

(1) Sex

(2) Date of birth (Western calendar)

(3) Complications (at the time of the first dose of the investigational product)

Investigation time point: The day of the first vaccination with the investigational product

9.2.2 Vaccination Status

The (sub)investigator or a clinical research coordinator will record the following information in the case report form.

(1) Drug number

(2) Day of vaccination with investigational product

(3) Body temperature (axillary) prior to vaccination with the investigational product

(4) Site of vaccination with the investigational product

(5) Status of simultaneous immunization with a vaccine other than the investigational product (day of vaccination, type of vaccine simultaneously administered, site of vaccination)

9.2.3 Efficacy Endpoints

9.2.3.1 Antibody Titers

The (sub)investigator or a clinical research coordinator will take blood samples at the following time points in order to measure the subject's antibody titers. The (sub)investigator will record the days of blood sample collection in the case report form.

(1) Sample Collection

1) Blood sample collection time points, and volumes collected

(a) Times of blood sample collection: Before the first vaccination with the investigational product, at Post-vaccination Examination 1, before the administration of the fourth dose of the investigational product, at Post-vaccination Examination 2, or at discontinuation (only when discontinuation occurs after the vaccination of the third or fourth dose of the investigational product)

Volume of blood collected: Around 3 mL, as a rule

(b) Number of samples collected: 4

2) Blood processing

The processing of blood will be performed in accordance with the separately prepare "Sample Collection Guidelines."

(2) Shipment of samples

The samples (serum) for antibody titer measurement will be collected by the antibody titer measurement sample transportation organization, and sent to the antibody titer measurement organization.

(3) Measurement Parameters

Hib	Anti-PRP antibody concentration
Diphtheria	Anti-diphtheria antibody concentration
Pertussis	Anti-pertussis antibody concentration
	Anti-FHA antibody concentration
Tetanus	Anti-tetanus antibody concentration
Polio	Attenuated anti-poliovirus antibody titers* (types 1, 2, and 3)

*: Sabin strains

(4) Handling of Remaining Samples

If a new measurement method is established for any of the aforementioned parameters, then the study sponsor will be able to use any remaining samples to measure the antibody titers.

9.2.4 Safety Endpoints

9.2.4.1 Health Monitoring Diary

The (sub)investigator or a clinical research coordinator will have the legal guardian enter information for the following parameters in the health monitoring diary every day until Day 14 after vaccination with the investigational product. If the subject's pyrexia or symptoms do not return to normal by Day 14 after vaccination with the investigational product then, as a rule, the legal guardian will be instructed to enter information about them in the health monitoring diary until they return to normal. In addition, the (sub)investigator or a clinical research coordinator will transcribe (1) and (2) above into the case report form.

(1) Body temperature (axillary)

(2) The presence or absence of investigational product (investigational substance or control substance) vaccination site reactions (redness, swelling, induration, pain), and size (redness, swelling, induration) or severity thereof

(3) The presence or absence of systemic reactions (irritability, crying, decreased appetite, decreased sleep, increased sleep), and the severity thereof

9.2.4.2 Adverse Events

An adverse event is any clinically undesirable or unintended sign (including clinically significant test value abnormalities), symptom, or disease that occurs during the safety assessment period following vaccination with the investigational product, regardless of whether or not it is causally related to the investigational product.

Furthermore, vaccination site reactions (redness, swelling, induration, pain) and systemic reactions (pyrexia, irritability, crying, decreased appetite, decreased sleep, increased sleep), which are reactions that are specific to vaccination, that occur in the period up through Day 14 after vaccination with the investigational product will be considered pre-specified adverse events. Vaccination site reactions to other

vaccines that were administered at the same time will be considered normal adverse events, and will not be considered pre-specified adverse events. Axillary body temperature ≥ 37.5°C will be handled as the adverse event "pyrexia." In addition, adverse events that occur within 30 minutes after vaccination with the investigational product will be considered immediate reactions.

(1) Symptoms or diseases

The (sub)investigator will confirm the presence or absence of adverse events based on the contents of the health monitoring diary that has been filled out by the legal guardian, as well as by questioning of the legal guardian and observation of the subject.

(2) Clinical laboratory test abnormalities

The (sub)investigator will handle as an adverse event any event that is judged to be a clinically significant abnormality.*

*: A "clinically significant test value abnormality" will be determined based on the following criteria.

- When there is a relationship to a clinical sign or symptom

  However, if these symptoms or signs have been reported as separate adverse events, then there is no need to handle this test value abnormality as an adverse event.
- When a medical or surgical treatment has been administered for the test value abnormality in this clinical laboratory tests
- When the investigational product vaccination method has been changed (e.g., a change in the dose, treatment interruption, treatment discontinuation) because of the test value abnormality
- When the (sub)investigator determines for some other reason that the finding is a clinically significant abnormality

(3) Safety assessment period

The period from the first vaccination with the investigational product until Post-vaccination Examination 2 will be considered the safety assessment period. However, the collection of all adverse events will be performed for the period from the first vaccination with the investigational product until Post-vaccination Examination 1, and also for the period from the vaccination of the fourth dose of the investigational product until Post-vaccination Examination 2. Additionally, information about serious adverse events will be collected throughout the entire safety assessment period.

(4) Adverse event assessment and criteria

1) Day of onset

The day of onset will be the day on which the symptom is observed or the day on which the clinical test value abnormality was observed.

2) Severity

Adverse event severity will be classified using the following categories.

Event	Mild	Moderate	Severe
Vaccination site redness	long axis ≤ 2.0 cm	long axis > 2.0 cm, ≤ 5.0 cm	long axis > 5.0 cm
Vaccination site swelling			
Vaccination site induration			
Administration site pain	Whimpers when the vaccination site is touched	Cries when the vaccination site is touched	Cries when vaccinated arm is moved
Pyrexia	≥ 37.5°C, < 38.5°C	≥ 38.5°C, < 40.0°C	≥ 40.0°C
Decreased appetite	A little decreased	Half or less of normal	Hardly eats at all

Adverse event severity other than that described above will be classified using the following categories.

1. Mild: No effect on the subject's activities of daily living
2. Moderate: The event impacts the subject's activities of daily living
3. Severe: The event prevents the subject from performing activities of daily living

3) Seriousness

The seriousness of adverse events will be classified using the following categories.

1. Not serious: Anything other than 2 below
2. Serious: Any of a) through f) below
   a) Death
   b) A life-threatening event
   c) Necessitates admission to a hospital or clinic for treatment, or the prolongation of a hospital stay
   d) Disability
   e) A serious outcome comparable to those listed in a) through d) above
   f) Congenital disease or abnormality in the next generation

4) Causal relationship to the investigational product

For events other than vaccination site reaction, which are pre-specified adverse events, the (sub)investigator will assess whether or not there is a "reasonable possibility" that the investigational product caused the adverse event in question. This assessment is made in consideration of the underlying disease, concomitant medical diseases, and other aspects of the natural course of the primary disease, concomitant therapies risk factors and factors other than the investigational product, and the temporal relationship between investigational product dosing and adverse event onset. For all vaccination site reactions (vaccination site redness, swelling, induration, and pain), which are pre-specified adverse events, the causal relationship to the investigational product will be classified as "there is a reasonable possibility." 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.

1. Reasonable possibility

2. No reasonable possibility

5) Outcome

The outcomes of adverse events will be classified using the following 6 categories.

1. Recovered
2. Recovering
3. Did not recover
4. Recovered, but with sequelae
5. Death
6. Unknown

6) Day of outcome

The day of outcome will be classified according to the following criteria.

Recovered	: The day of resolution. However, if the day on which the subject recovered cannot be identified, then the day of outcome will be the day on which the outcome was confirmed or determined.
Recovering	: The day on which it was confirmed or determined that the subject was recovering.
Did not recover	: The day on which it was confirmed or determined that the subject had not recovered.
Recovered with sequelae	: The day on which it was confirmed or determined that sequelae were present.
Death	: The day of death. However, if the day of death cannot be determined, then this will be the day on which the death was confirmed or determined.
Unknown	: The day of death if the subject died due to a cause other than the adverse event in question and the outcome was unknown. Otherwise, this will be the day on which the outcome was confirmed or determined.

7) Follow-up

Adverse events that occur during the safety assessment period will be followed until 28 days after Post-vaccination Examination 1 or Post-vaccination Examination 2, and the findings recorded in the case report form. Furthermore, if there is a valid reason for stopping the investigation partway, then this reason will be entered in, for example, the source documents, and the follow-up investigation will be concluded. The day of the outcome that is recorded on the case report form for adverse events that are recovering or have not recovered at the end of the follow-up investigation period will be considered the day of the final observations in the follow-up investigation period. For adverse drug reactions that are recovering or have not recovered at the end of the follow-up investigation period, the subsequent courses of these reactions will be investigated.

Furthermore, serious adverse events that occur in the period from Post-vaccination Examination 1 until the vaccination of the fourth dose of the investigational product will be followed until 28 days after Post-vaccination Examination 2.

(5) Information recorded in the case report form

When an adverse event occurs, the (sub)investigator will record the following information in the adverse events section of the case report form: name of the adverse event;* if the administration site reaction is that other than a pre-specified adverse event, then the site of onset; if the adverse event is "pyrexia," then the highest axillary body temperature measured during the period of pyrexia emergence;

day of onset; severity; seriousness; causal relationship to the investigational product; actions taken with respect to the investigational product; a description of other actions taken, if any (e.g., names of drugs or therapies); outcome; and date of outcome. In addition, for immediate reactions, the presence or absence of any such reactions, as well as the details thereof, will be confirmed, and the information recorded in the immediate reactions section of the case report form.

*: The adverse event terms will conform to the following criteria.

- As a rule, the diagnosis term will be used.
- If the diagnosis term is unclear, the symptom name will be used.
- If multiple symptoms emerge, and if they indicate a single diagnosis term, then this diagnosis term will be used.

Surgical procedures, etc. will not be considered adverse events; if an illness and/or symptom requiring a surgical procedure, etc. is confirmed, then this will be considered an adverse event.

Furthermore, for vaccination site reactions (vaccination site redness, swelling, induration, and pain), which are pre-specified adverse drug reactions, that have been recorded in the health monitoring diary by the subject's legal guardian and transcribed into the case report form by the (sub)investigator or a clinical research coordinator, the study sponsor will establish the date of onset, date of outcome, and outcome of the adverse event in accordance with the criteria shown below. Further details are provided in separate written procedures.

1) Definition of date of onset to date of outcome

From the first day after vaccination with the investigational product on which "Yes" was entered for the vaccination site reaction until the last day "Yes" was entered.

2) Outcome definitions:

(a) Redness, swelling, and induration

Recovered: When "No" was entered for vaccination site reactions
Recovering: When the last long axis value entered is less than the maximum value

Did not recover: When the last long axis value entered is equal to or more than the maximum value

(b) Pain

Recovered: When "No" was entered for vaccination site reactions

Recovering: When the last severity rating entered indicates improvement compared to the worst rating entered

Did not recover: When the last pain rating entered indicates no improvement compared to the worst rating entered

10. Assessment Methods and Criteria

10.1 Efficacy

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

Measurement Parameters		Measurement Method	Reference Value
Hib	Anti-PRP antibody concentration	Enzyme-linked immunosorbent assay (ELISA)	≥ 1 μg/mL[14), 15)]
			≥ 0.15 μg/mL[15)]
Diphtheria	Anti-diphtheria antibody concentration	Neutralization method	≥ 0.1 IU/mL[16)]
Pertussis	Anti-pertussis antibody concentration	Enzyme-linked immunosorbent assay (ELISA)	≥ 10.0 IU/mL[16)]
	Anti-FHA antibody concentration		≥ 10.0 IU/mL[17)]
Tetanus	Anti-tetanus antibody concentration	Indirect agglutination (KPA)	≥ 0.01 IU/mL[18)]
Polio	Attenuated anti-poliovirus antibody titers* (types 1, 2, and 3)	Neutralization method	≥ 8-fold[19)]

*: Sabin strains

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

10.2 Safety

Adverse events and adverse drug reactions (for details, see "9.2.4.2 Adverse Events")

11. Ensuring Subject Safety

11.1 Handling of Serious Adverse Events

If serious adverse events occur during the treatment period, the (sub)investigator will immediately provide the subject with appropriate treatment irrespective of the presence or absence of a causal relationship to the investigational product.

The (sub)investigator will immediately report the occurrence of any serious adverse events to the monitor (as a rule, in writing), and will provide the study sponsor with a more detailed written report within 7 days of the initial report using Attachment 6, "Serious Adverse Event Report Form" (Standard Form 12) and Attachment 7, "Serious Adverse Event or Issue Information Form" (Standard Form 14). The principal investigator will also immediately report the aforementioned serious adverse events to the head of the study site. In addition, if the study site has its own forms for this purpose, then these forms may be used.

Furthermore, if no serious adverse events have occurred, but vaccination with an investigational product which had an issue could result in the emergence of a serious adverse event, then this will be reported to the study sponsor and the head of the study site in accordance with the same procedure that should be followed when a serious adverse event has occurred.

Serious Adverse Event Definition

(1) Death

(2) A life-threatening event

(3) An event that necessitates admission to a hospital or clinic for treatment, or the prolongation of a hospital stay

(4) Disability

(5) An event with a level of seriousness comparable to those listed in (1) through (4) above

(6) A congenital disease or abnormality in the next generation

11.2 Clinically Significant Adverse Event

In this study, no "clinically significant adverse event" designation has been established.

11.3 Informing the Subject's Other Doctors

The (sub)investigator will check whether or not the subject is being treated outside the context of this study both at written informed consent obtainment and during the study. If a subject is being treated by another doctor, this doctor will be informed, with the legal guardian's consent, of the subject's participation in this study. In addition, the (sub)investigator of a clinical research coordinator will give the legal guardian a study participation card or the like and instruct the legal guardian to present it to other hospitals or departments to inform other doctors of the subject's participation in the study.

12. Subject Study Discontinuation Criteria and Procedures

12.1 Subject Discontinuation Criteria

If any of the following discontinuation criteria are met, the subject will be discontinued from the study.

(1) If the legal guardian requests discontinuation.

(2) If it is determined that the subject is clearly ineligible to participate in the study.

(3) If the (sub)investigator determines that it would be difficult for the subject to continue the study because of the emergence of, for example, an adverse event.

(4) If the (sub)investigator determines that the subject should be discontinued from the study for some other reason.

Rationale

These criteria were established to allow the study to be ethically conducted and in consideration of subject safety.

12.2 Discontinuation Procedures

If a subject is discontinued from the study during the term of the study, the (sub)investigator will take whatever actions are appropriate for the subject, and will inform the monitor in question that the subject has been discontinued from the study.

The day of study discontinuation will be the day on which the (sub)investigator made the decision to discontinue the subject from the study.

The (sub)investigator will perform follow-up by examining the subject as much as possible to investigate the presence or absence of adverse events in the 2 weeks after vaccination with the investigational product (in the period up until the day of discontinuation if the day of discontinuation is more than 2 weeks after vaccination with the investigational product). If the subject is discontinued from the study after the third or fourth dose (except for subjects discontinued in the period from after Post-vaccination Examination 1 to before the fourth vaccination), blood samples for antibody titer measurement will be collected whenever possible 4 to 6 weeks after vaccination. If a subject has not completed all of the vaccinations, the subject's legal guardian will be given a full explanation of the vaccinations that the subject will receive after the subject has been discontinued from the study.

The concomitant medications will be confirmed at discontinuation, at the time of blood sample collection, or at 2 weeks after vaccination, whichever comes last.

The (sub)investigator will record the day of discontinuation and the reason for discontinuation* in the case report form.

For subjects for whom the specified observations/tests cannot be performed at discontinuation, or who did not come in for any study visits after discontinuation, the reasons for this, the subject's subsequent course, etc. will be followed up either in writing (correspondence) or by telephone or the like.

If the subject does not come in for a visit, the (sub)investigator or a clinical research coordinator will ask the subject's guardian to fill out the health monitoring diary as much as possible.

*: The "reason for discontinuation" will be selected from among the following.

1. Adverse event
2. Death
3. Clearly unsuitable as a subject for the study

4. Study protocol deviation
5. Technical problem
6. Subject's legal guardian requested discontinuation
7. Study could not be continued (study could not be continued because of the subject's personal circumstances [e.g., the subject moved])
8. The (sub)investigator determined that the study should be discontinued
9. The study sponsor discontinued the clinical study at the study site
10. The study sponsor discontinued the entire study
11. Some other reason

13. Statistical Analysis

13.1 Analysis Sets

The analysis of efficacy will be 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.

(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 initial primary immunization had not been collected within the specified time window for the post-vaccination tests after the third vaccination (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 vaccination dose levels, numbers of vaccinations, or vaccination intervals were not as specified during the primary immunization

(2) Safety analysis population

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

13.2 Handling of Data

13.2.1 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 then, as a rule, this parameter will be handled as a missing value.

13.2.2 Handling of Time Point Data When Tabulating the Data by Time Point

More detailed information about the allowable time windows and handling of the data used in the tabulations by time point for the test and observation parameters is provided separately in the statistical analysis plan.

13.3 Statistical Analysis Plan

The descriptions in this study protocol of the statistical analysis methods are only as detailed as they need to be to describe the objectives of the study. A more detailed description of the technical aspects of the statistical analysis methods will be provided in the statistical analysis plan before the database lock.

13.3.1 Investigation of Demographic and Other Baseline Characteristics

The key demographic and other baseline characteristics of the analysis populations will be summarized by vaccination group. Depending on the type of the data, the frequency distributions (numbers and proportions of subjects) or descriptive statistics (numbers of subjects, mean values, SDs, minimums, maximums, medians) will be calculated.

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

13.3.2 Efficacy

13.3.2.1 Primary Endpoints

The anti-PRP antibody seroprotection (antibody titer ≥ 1 μg/mL) rate, and the seroprotection rates for pertussis, diphtheria toxin, tetanus toxin, and attenuated poliovirus after the primary immunization will be calculated by vaccination group, and the point estimates and two-sided 95% confidence intervals will be calculated by vaccination group. Furthermore, for the intergroup comparison of the antibody seroprotection rates in the investigational product group relative to the control group, a noninferiority test will be performed using the Farrington Manning method, with a significance level of 2.5%, one-sided, and a lower noninferiority limit of 10%.

Rationale for the Lower Noninferiority Limit

In the phase 3 confirmatory studies[20), 21)] that have been conducted to assess Hib vaccines and adsorbed-purified pertussis/diphtheria/tetanus combined vaccine, 10% has been used as the lower noninferiority limit for the antibody seroprotection rate. The lower noninferiority limit was therefore set at 10% for this study, as well.

13.3.2.2 Secondary Endpoints

(1) Anti-PRP seroprotection rates at concentrations of 0.15 μg/mL and above after the primary immunization will be calculated.

(2) The geometric mean antibody titers for anti-PRP antibodies, pertussis, diphtheria toxin, tetanus toxin, and attenuated poliovirus after the primary immunization will be calculated.

(3) The anti-PRP antibody seroprotection (antibody titer ≥ 1 μg/mL) rate, and the seroprotection rates for pertussis, diphtheria toxin, tetanus toxin, and attenuated poliovirusat after the booster immunization will be calculated.

(4) Anti-PRP seroprotection rates at concentrations of 0.15 μg/mL and above after the booster immunization will be calculated.

(5) The geometric mean antibody titers for anti-PRP antibodies, pertussis, diphtheria toxin, tetanus toxin, and attenuated poliovirus after the booster immunization will be calculated.

13.3.3 Safety

The numbers and proportions of subjects with adverse events and adverse drug reactions, as well as the confidence intervals, will be calculated by vaccination group.

In addition, the adverse event terms will be reclassified using MedDRA/J.

13.3.4 Significance Level and Confidence Intervals

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%.

13.3.5 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.

13.4 Statistical Analysis Plan Amendments

If the statistical analysis plan described in this section is going to be amended before database lock, the reason for the amendment will be described in the statistical analysis plan and the clinical study report. If the analysis method is going to be changed or an additional analysis performed after database lock, the reason thereof will be described in the statistical analysis plan and the clinical study report, and the results will be distinguished from the results of the analysis that had been planned.

14. Study Protocol Compliance, Deviations, and Changes

14.1 Agreement and Compliance with the Study Protocol

Before agreeing on the study protocol with the study sponsor, the principal investigator must hold discussions with the study sponsor based on the study protocol, the most recent investigator's brochure, and any other necessary documents that have been provided by the study sponsor, and adequately investigate the ethical and scientific appropriateness of conducting the study.

The principal investigator will based on the results of this investigation reach an agreement with the study sponsor regarding the contents of the study protocol, and will sign (or print his or her name and affix his or her personal seal to) and date a memorandum of agreement to show that the principal investigator agrees to comply with the study protocol.

14.2 Deviations From or Changes to the Study Protocol

The (sub)investigator must not deviate from or amend the study protocol without obtaining the advance written consent of the study sponsor and principal investigator or without first obtaining written approval following review performed by the institutional review board. However, if it is medically necessary, in order to avoid an emergency danger to a subject, the (sub)investigator may deviate from or amend the study protocol without the advance written consent of the study sponsor or the advance approval of the institutional review board.

In such cases, the principal investigator must submit the deviation or amendment, as well as the reasons therefor, and also a draft of any proposed revisions to the study protocol, to the study sponsor, the head of the study site, and the institutional review board at soon as possible and have them approved, and must obtain written approval from the head of the study site and written consent from the study sponsor.

The (sub)investigator must record all actions that constitute deviations from the study protocol. The principal investigator must prepare a written record detailing the reasons for all actions that did not conform to the study protocol that were taken either to avoid an emergency danger to a subject or because of some other medically unavoidable reason, and must promptly submit this written record to the study sponsor and the head of the study site, and retain a copy. The principal investigator must promptly submit a written report to the study sponsor, the head of the study site, and the institutional review board of all changes to the study that could substantially impact the conduction of the study or that could increase the risks to the subjects.

15. Revision of the Study Protocol

If the study sponsor determines during the course of the study that the study protocol needs to be changed, then the study sponsor will revise the study protocol. The study sponsor will discuss the proposed changes with the principal investigator and obtain the principal investigator's agreement, and will then notify the head of the study site promptly and in writing, and will obtain the approval of the institutional review board through the head of the study site.

If the head of the study site indicates that the study protocol should be revised, based on the opinion of the institutional review board, the study sponsor will determine whether or not the change in question is appropriate, and will if necessary revise the study protocol. The study sponsor will discuss the proposed revisions with the principal investigator and obtain the principal investigator's agreement, and will then notify the head of the study site promptly and in writing, and will obtain the approval of the institutional review board through the head of the study site.

If it is determined based on discussions held with the principal investigator that the study protocol needs to be revised, then the study sponsor will determine whether or not the changes are appropriate, and will if necessary revise the study protocol. The study sponsor will obtain the principal investigator's agreement to the proposed revisions and will then notify the head of the study site promptly and in writing, and will obtain the approval of the institutional review board through the head of the study site.

16. Study Discontinuation or Interruption

(1) Criteria for temporarily or permanently discontinuing the study

In the following cases, the study sponsor will investigate whether or not the study should be continued at all or some of the study sites.

1) If information about the quality, efficacy, or safety of the investigational products, or any other information that is important to the proper conduction of the study, is obtained.
2) If it becomes necessary to change the study protocol, and study sites cannot adapt to the changes.
3) If the head of a study site, based on the opinion of the institutional review board, request that the study protocol, etc. be revised, and the study sponsor cannot agree to this request.
4) If the head of a study site instructs that the study be permanently discontinued based on the decision of the institutional review board.
5) If the study site commits major or ongoing violations of the GCP, study protocol, or study contract.

(2) Temporary or permanent discontinuation of the entire study by the study sponsor

If the study sponsor decides to temporarily or permanently discontinue the entire study, the study sponsor will promptly inform the heads of the study sites and the regulatory authorities of this fact, and of the reasons why, in writing. The heads of the study sites will upon being notified by the study sponsor that the study is being temporarily or permanently discontinued in turn notify the principal investigators and institutional review boards of this fact, and of the reasons why, in detail in writing.

The principal investigators will upon being notified by the study sponsor through the heads of the study sites that the study is being temporarily or permanently discontinued promptly notify the subjects of this fact and ensure that the subjects receive proper treatment.

The actions that should be taken with respect to subjects if the study is being permanently discontinued are described in "12.2 Study Discontinuation Procedures."

(3) The temporary or permanent discontinuation of the study at a study site by the principal investigator or institutional review board

If the study is temporarily or permanently discontinued at the discretion of the principal investigator, the principal investigator will promptly notify the head of the study site of this fact in writing, and of the reasons therefor. The head of the study site will promptly notify the study sponsor and the institutional review board of this fact in writing.

If the institutional review board decides to temporarily or permanently discontinue the study, the board will promptly notify the head of the study site of this fact, and of the reasons therefor, in writing. The head of the study site will promptly notify the principal investigator and study sponsor of this fact in writing.

(4) Permanent discontinuation of the study because of the cancellation of the contract with the study site

If the study sponsor permanently discontinues the study because a study site has committed grave or ongoing violations of the GCP, study protocol, or study contract during the study, the study sponsor will promptly report this to the regulatory authorities.

17. Information in the Case Report Form

17.1 Case Report Form, etc. Formats

In this study, electronic case report forms utilizing an EDC system will be used. The principal investigator will check the electronic case report form, and the electronically signed electronic case report form will be considered the original. The study sponsor will also obtain the results of the antibody titer measurements from the antibody titer measurement organization.

17.2 Information to be Recorded Directly in the Case Report Form and Considered Source Data

The case report form will serve as the source document for the following parameters. However, if the data in question are clearly noted in, for example, the subject's medical records, then the medical records will be considered the source document.

(1) The objectives and times of use of concomitant drugs, and the objectives and times of use of concomitant therapies

(2) Presence or absence of simultaneous immunization with a vaccine other than the investigational product

(3) Presence or absence of immediate reactions

(4) Adverse events (presence or absence, seriousness, severity, outcome, date of outcome, causal relationship to investigational product, and time of onset [information about before or after vaccination, if the day is the same as a vaccination day])

(5) Day of discontinuation, reason for discontinuation

(6) Antibody titer measurement (day of blood sample collection)

Furthermore, for information other than that described above, the documents will be determined separately, before the start of the study, by the study sponsor and the principal investigator.

17.3 Precautions for Case Report Form Preparation

The (sub)investigator or a clinical research coordinator will prepare the case report form in accordance with the following rules. Furthermore, the case report form will be prepared in accordance with the "Case Report Form Amendment or Revision Manuals,"* which will be provided separately by the study sponsor.

*: "Case Report Form Amendment or Revision Manuals": EDC Manual, eCRF Entry Manual

(1) Before the case report forms are filled out, the study sponsor will provide the (sub)investigators and clinical research coordinators with user IDs and passwords, and thereby control who is using the system. The provided user IDs and passwords will be controlled by the (sub)investigator or clinical research coordinator and not shared with anyone. In addition, the data will be entered by (sub)investigators or clinical research coordinators who have been granted access to use the system.

(2) A case report form will be prepared for cases who have received drug numbers from the WEB subject enrollment system.

(3) The principal investigator will be able to fill out all of the fields in the case report form. The subinvestigator will be able to fill out all of the fields in the case report form other than the electronic signature. Clinical research coordinators will be able to transcribe from source documents information that is not accompanied by a medical evaluation, such as information that has been entered on medical records.

(4) If the information in a case report form is going to be amended or revised, the reason for the amendment or revision will be recorded as electronic information.

(5) The principal investigator will confirm that the case report form has been prepared accurately and completely and that the audit trail and electronic signature information can be referenced, and will then affix his or her electronic signature to the case report form using the EDC system.

(6) The principal investigator will retain a copy of the case report form that is stored on recording media (e.g., CD-R) (the copy will be a copy of the electronic case report form that has been checked by the principal investigator and that has been saved in PDF format). Furthermore, after the case report form has been signed electronically and before the recording media (e.g., CD-R) has been provided by the study sponsor, in lieu of a copy, an environment will be maintained that allows the electronic case report form to be accessed (access rights to the EDC system).

(7) If there is some sort of discrepancy between the data that have been entered on the case report form and the source documents, the principal investigator will prepare a record explaining the reasons why and submit it to the study sponsor, and retain a copy thereof.

17.4 Timing of Case Report Form Submission

Furthermore, the (sub)investigator will promptly prepare a case report form and submit this to the study sponsor.

17.5 Handling of Health Monitoring Diary

Each subject's legal guardian will enter into the subject's health monitoring diary the information for the parameters specified in Section 9.2.4.1 every day until Day 14 after vaccination with the investigational product, and if the subject's pyrexia or symptoms do not return to normal by Day 14 after vaccination with the investigational product then, as a rule, the legal guardian will enter the information about them in the health monitoring diary until they return to normal. The (sub)investigator or a clinical research coordinator will check the information that the subject's legal guardian entered into the health monitoring diary, and if there are any doubts about the information that has been entered, the investigator or clinical research coordinator will promptly confirm this information with the subject's legal guardian, and if there are any parts of the health monitoring diary that have not been filled out, will ask the subject's legal guardian to enter the symptoms to the extent possible.

In this study, the presence or absence of vaccination site reactions, and the size or severity thereof, which are safety assessment parameters, will be assessed based on the data entered by the subject's legal guardian and then transcribed into the case report form by the investigator or a clinical research coordinator. Other adverse events will be assessed by the (sub)investigator based on both the information that has been entered into the health monitoring diary by the subject's legal guardian and the (sub)investigator's examination of the subject.

The principal investigator will retain the health monitoring diary recovered from the subject's legal guardian.

18. Direct Access to Source Documents

The principal investigator and the head of the study site will agree to cooperate with the monitoring and auditing of the study sponsor and the inspections of the institutional review board and regulatory authorities, and to provide these parties with direct access to all materials pertaining to the study.

19. Study Quality Control and Quality Assurance

The study sponsor must perform "study quality control" and "study quality assurance" based on Mitsubishi Tanabe Pharma's GCP Standard Operating Procedures, in order to maintain the quality and reliability of this study. In addition, the study sites and the principal investigators must cooperate with the study quality control and quality assurance activities of the study sponsor.

In the study quality control activities, the monitors will directly access the source data, as appropriate, to confirm that the study is being conducted in compliance with the written procedures pertaining to the study of the study site, the most recent version of the study protocol, and the GCP. The monitors will also confirm that the information that has been recorded in the case report form that has been reported by the (sub)investigator is accurate and complete, and can be verified by comparing it against study-related records, such as source documents.

In addition, in order to ensure that the study is being conducted in compliance with the study protocol and the GCP, the audit staff will perform audits in accordance with the GCP Standard Operating Procedures to confirm that quality control is being done properly.

20. Ethics

20.1 Ethical Implementation of the Study

This study must be conducted in accordance with the Pharmaceutical Affairs Law, the GCP, and the study protocol, and in accordance with the ethical principles of the Helsinki Declaration.

20.2 Institutional Review Board

The institutional review board will review the conduction and continuation of the study from ethical, scientific, and medical/pharmacological perspectives based on the information contained in the investigator's brochure, study protocol, and informed consent form/explanation sheet.

20.3 Preservation of Subject Confidentiality

All parties involved in the study will identify the subjects in the subject records and case report forms using the subject ID codes and will protect the confidentiality of the subjects when source documents pertaining to the conduct of the study are being accessed, published in medical journals, submitted to the regulatory authorities, etc.

21. Record Storage

(1) Records stored at the study site

A storage manager appointed by the head of the study site will store the documents or records pertaining to the study that should be stored at the study site until 1) or 2) below, whichever comes later. However, if the study sponsor states that these documents or records should be stored for a longer period, the study site will hold discussions with the study sponsor about the term and method of storage.

If the study sponsor decided not to append the clinical study test result data that have been collected in the course of the study to the approval application form, the study sponsor will inform the study site directors of this fact, and of the reason(s) therefor, in writing. In addition, if marketing approval is obtained for this investigational product, or if the study sponsor decides to discontinue development of this investigational product before approval is obtained, then the study sponsor will inform the study site directors of this fact in writing.

1) Date of marketing approval for the investigational product (if a notification has been received that development is being discontinued or the study results are not being appended to the approval application, then the date on which 3 years have passed since the date this information was received).
2) 3 years after the discontinuation or completion of the study

(2) Records stored at the study sponsor

The study sponsor will store the documents or records pertaining to the study that should be stored at the study sponsor until 1) or 2) below, whichever comes later. However, because this investigational product meets the definition of a product of biological origin, records of its manufacture and use will be kept for at least 10 years from the date of approval.

1) The date marking 5 years since the date of marketing approval for the investigational product (if development is discontinued, the date marking 3 years from the date on which the decision was made to discontinue development) or the date marking the end of reexamination.
2) 3 years after the discontinuation or completion of the study

22. Monetary Payments

Payments of monetary compensation to subjects and study sites will be made in accordance with the contracts or memoranda of agreement between the study sites and the study sponsor.

23. Compensation for Health Injuries, and Insurance

23.1 Compensation for Health Injuries

If a subject suffers a health injury as a result of the conduction of this study, the study sponsor will compensate the subject appropriately, based on predetermined criteria, except in cases where a causal relationship to the study has been ruled out (said compensation will include the subject's medical treatment fee copayments, a medical allowance, and compensation money). In such cases, the subject will be under no burden to prove that there is a causal relationship.

23.2 Insurance

The study sponsor will take out insurance and will take any other necessary actions to ensure that the study sponsor is indemnified against health injuries experienced by subjects in connection with the study.

24. Agreement on Publication

The information that is contained in this study protocol is the property of the study sponsor, and although it will be provided to the institutional review boards and relevant parties, such as the (sub)investigators conducting the study, it must not be divulged to any outside party without the written consent of the study sponsor, unless this is necessary for the implementation of the study.

In addition, if the information that is obtained by the conduction of this study is going to be presented to any outside parties, such as at a specialist conference, by any study site staff involved in the study, such as a (sub)investigator, the consent of the study sponsor must be obtained in advance. Furthermore, the study sponsor may freely report the information obtained in this study to the regulatory authorities or for a purpose such as the appropriate use or marketing of the drug product.

25. References

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3) National Institute of Infectious Diseases ed. Whooping Cough Vaccine. Vaccine Handbook. Tokyo, Maruzen Publishing. 1994; 59-70.

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7) Ebisawa I: Tetanus. Japan Medical Journal, Tokyo, 1988.

8) Matsuda M:The structure of tetanus toxin. Botulinum Neurotoxin and Tetanus Toxin (ed by Simpson LL),69-92,Academic Press, New York, 1989.

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10) Sixth Health Science Council Immunization/Vaccine Committee's Research and Development and Production/Distribution Subcommittee (November 28, 2013)

11) MHLW, Fundamental Plan for Immunization (March 28, 2014)

12) Guidance on Clinical Studies of Drug Products in Pediatric Populations (PFSB/ELD Notification No. 1334, dated December 15, 2000)

13) Prophylactic Vaccine Clinical Study Guidelines (PFSB/ELD Notification No. 0527-5, issued May 27, 2010)

14) WHO Position Paper on Haemophilus influenzae type b conjugate vaccines. Weekly epidemiological record 2006; 47(81): 445-452

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17) Kato T. DPT. The Journal of Pediatric Practice. 1990; 53(10): 2275-81

18) Ministry of Health, Labour and Welfare, Health Service Bureau, Tuberculosis and Infectious Disease Control Division; and the National Institute of Infectious Diseases, Infectious Disease Surveillance Center: Infectious Disease Epidemic Prediction Surveillance Report; 2008. 217-232.

19) WHO Collaborative Study Group on Oral and Inactivated Poliovirus Vaccines. Combined immunization of infants with oral and inactivated poliovirus vaccines: results of a randomized trial in the Gambia, Oman, and Thailand. Bull World Health Organ. 1996; 74: 253-68.

20) Tribik J-NDA Attachment

21) VaxemHIB Aqueous Suspension for Injection J-NDA Attachments