Title: A Phase 4, Open-label Study to Evaluate the Immunogenicity and Safety of Intramuscular Injections of BLB-750 in Healthy Adult Subjects

NCT Number: NCT03370289

Protocol Approve Date: 21-Nov-2017

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This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
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- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

Note; This document was translated into English as the language on original version was Japanese.

Post-marketing Study Protocol

<Title>

A Phase 4, Open-label Study to Evaluate
the Immunogenicity and Safety of Intramuscular Injections of BLB-750 in Healthy Adult Subjects

<Short Title>

A Phase 4 Post-marketing Study of Intramuscular Injections of BLB-750 in Healthy Adult Subjects

Name of Sponsor	Takeda Pharmaceutical Company Limited 1-1, Doshomachi 4-chome, Chuo-ku, Osaka		
Protocol number	BLB-750/CCT-901		
IND Number	Not applicable	**EudraCT Number**	Not applicable
Compound	BLB-750 (Cell-Culture Influenza Vaccine H5N1 “Takeda” 1 mL)		
Date:	21 Nov 2017	**Version Number**	Amendment 02

1.0 ADMINISTRATIVE INFORMATION AND PRINCIPLES OF CLINICAL STUDIES

1.1 Contacts and Responsibilities of Study-Related Activities

See the attachments.

1.2 Principles of Clinical Studies

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

1.3 Summary of Changes in the Amended Protocol

The changes in the amended version of the protocol are described below.

The key changes in this amended protocol are summarized below. Details of the changes are described in Appendix C.

1. Addition of requirements to avoid possible bleeding at the intramuscular injection site.
   Reason for the change: To reflect the revised package insert with additional precautionary text, the exclusion criteria and the list of excluded medications and treatments have been updated to include new requirements.

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2.0 STUDY SUMMARY

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Takeda Pharmaceutical Company Limited</td><td colspan="2">Study Drug
BLB-750 (Cell-Culture Influenza Vaccine H5N1 “Takeda” 1 mL)</td></tr>
<tr><td colspan="2">Title of Protocol: A Phase 4, Open-label Study to Evaluate the Immunogenicity and Safety of Intramuscular Injections of BLB-750 in Healthy Adult Subjects</td><td>IIND Number: Not applicable</td><td>EudraCT Number: Not applicable</td></tr>
<tr><td colspan="2">Study Number: BLB-750/CCT-901</td><td colspan="2">Phase: 4</td></tr>
<tr><td colspan="4">Study Design:
This is a phase 4, Open-label study to evaluate the immunogenicity and safety of two intramuscular vaccinations with BLB-750 at a 3-week interval in healthy Japanese adults.
Participants considered eligible as subjects for the study during the eligibility assessment at a visit after providing informed consent will receive the initial intramuscular vaccination with the study drug BLB-750 (Day 1) and the second intramuscular vaccination with BLB-750 during the study visit at 21 days after the initial vaccination (Day 22).
The study duration will be 43 days, starting on the day of initial vaccination (Day 1). Subjects will return to the study site 21 days after the initial vaccination (Day 22) and 21 days after the second vaccination (Day 43).
The total planned number of subjects to receive the study vaccination is 55.</td></tr>
<tr><td colspan="4">Objectives:
To evaluate the immunogenicity and safety of two intramuscular vaccinations with BLB-750 in healthy Japanese adults</td></tr>
<tr><td colspan="4">Study Population: Healthy Japanese adults (male or female)</td></tr>
<tr><td colspan="2">Planned Number of Subjects:
BLB-750: 55 subjects</td><td colspan="2">Planned Number of Study Sites:
1 institution</td></tr>
<tr><td colspan="2">Dose Level(s):
Two doses of BLB-750 at 0.5 mL (HA antigen level of 7.5 μg) will be injected into the upper arm muscle (the deltoid muscle) at a 3-week interval.
As the manufacturing strain for BLB-750, the following attenuated strain (H5N1 influenza virus attenuated using reverse genetics technology) will be used:
● Qinghai RG strain
[A/bar-headed goose/Qinghai/1A/2005(H5N1)
(SJRG-163222)]</td><td colspan="2">Vaccination Route:
Intramuscular injection</td></tr>
<tr><td colspan="2">Duration of Vaccination:
Two doses at a 3-week interval</td><td colspan="2">Period of Evaluation:
43 days</td></tr>
</table>

Inclusion Criteria

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form prior to the initiation of any study procedures.
3. The subject is a healthy Japanese adult man or woman.
4. The subject is aged 20 to 49 years, inclusive, at the time of informed consent.
5. A female subject of childbearing potential who is sexually active with a nonsterilized male partner agrees to use routinely adequate contraception from signing of informed consent throughout the duration of the study.

Exclusion Criteria

1. The subject has received vaccination with any other investigational or study products within 4 months prior to vaccination with the study vaccine.
2. The subject has a history of vaccination with an H5N1 influenza vaccine.
3. The subject has a history of infection with H5N1 virus.
4. The subject is at high risk of contracting H5N1 influenza infection (e.g., poultry workers).
5. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (e.g., spouse, parent, child, sibling) or may consent under duress.
6. The subject has poorly controlled, clinically significant manifestations of neurological, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, endocrine, or other disorders, which may impact their ability to participate as subjects or may potentially confound the study results.
7. The subject has a body temperature (oral) ≥37.5°C prior to vaccination with the study vaccine on Day 1.
8. The subject has any medically diagnosed or suspected immune-deficiency condition.

9. The subject has an immunocompromising condition or disease, or is currently undergoing a form of treatment or was undergoing a form of treatment that can be expected to influence immune response within 30 days prior to vaccination with the study vaccine.
   Such treatments include, but are not limited to, systemic or high dose inhaled corticosteroids (>800 µg/day of beclomethasone dipropionate or equivalent; the use of inhaled and nasal steroids that do not exceed this level will be permitted), radiation treatment or other immunosuppressive or cytotoxic drugs.
10. The subject has received antipyretics within 4 hours prior to vaccination with the study vaccine.
11. The subject has a history of Guillain-Barré Syndrome, demyelinating disorders (including acute disseminated encephalomyelitis [ADEM] and multiple sclerosis), or convulsions.
12. The subject has a functional or anatomic asplenia.
13. The subject has a rash, other dermatologic conditions or tattoos that may interfere with the evaluation of local reaction.
14. The subject has a past or present history of infection with the Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) or Human Immunodeficiency Virus (HIV).
15. The subject has a known hypersensitivity to any component of BLB-750.
16. The subject has a history of severe allergic reactions or anaphylaxis.
17. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol dependence within 1 year prior to vaccination with the study vaccine or is unwilling to agree to abstain from excessive alcohol and drugs throughout the study.
18. The subject has received any blood product (e.g., blood transfusion or immunoglobulin) within 90 days prior to vaccination with the study vaccine.
19. The subject has received any live vaccine within 4 weeks (28 days) prior to vaccination with the study vaccine or any inactivated vaccine within 2 weeks (14 days) prior to vaccination with the study vaccine.
20. The subject is a pregnant or lactating woman or wishes to become pregnant before signing informed consent, during, or within 12 weeks after the last vaccination with the study vaccine or intends to donate ova during such time period
21. For males: The subject has donated whole blood ≥200 mL within 4 weeks (28 days) or ≥400 mL within 12 weeks (84 days) prior to the first vaccination with the study vaccine.

    For females: The subject has donated whole blood ≥200 mL within 4 weeks (28 days) or ≥400 mL within 16 weeks (112 days) prior to the first vaccination with the study vaccine.
22. For males: The subject has donated whole blood ≥800 mL in total within 52 weeks (364 days) prior to the first vaccination with the study vaccine.

    For females: The subject has donated whole blood ≥400 mL in total within 52 weeks (364 days) prior to the first vaccination with the study vaccine.
23. The subject has donated blood components within 2 weeks (14 days) prior to the first vaccination with the study vaccine.
24. In the opinion of the investigator, the subject is unlikely to comply with protocol requirements or is considered ineligible for any other reason.
25. The subject has thrombocytopenia or coagulopathy, or is currently receiving anticoagulant therapy or received anticoagulant therapy within 30 days prior to the first vaccination with the study vaccine.

Main Criteria for Evaluation and Analyses:

[Primary Endpoints]

Immunogenicity:

- Seroprotection rate as measured by SRH antibody titer (defined as the proportion of subjects with SRH antibody titer ≥25 mm^2) for the vaccine strain at 21 days after the second vaccination
- Seroconversion rate as measured by SRH antibody titer (defined as the proportion of subjects with a 50% or more increase in SRH antibody titer from baseline for those who have a baseline value >4 mm^2 or SRH antibody titer ≥25 mm^2 for those who have a baseline value ≤4 mm^2) for the vaccine strain at 21 days after the second vaccination
- Geometric mean fold increase (GMFI) in SRH antibody titer from baseline for the vaccine strain at 21 days after the second vaccination

[Secondary Endpoints]

Immunogenicity:

- Seroprotection rate as measured by SRH antibody titer (defined as the proportion of subjects with SRH antibody titer ≥25 mm^2) for the vaccine strain at 21 days after the initial vaccination
- Seroconversion rate as measured by SRH antibody titer (defined as the proportion of subjects with a 50% or more increase in SRH antibody titer from baseline for those who have a baseline value >4 mm^2 or SRH antibody titer ≥25 mm^2 for those who have a baseline value ≤4 mm^2) for the vaccine strain at 21 days after the initial vaccination
- GMFI in SRH antibody titer from baseline for the vaccine strain at 21 days after the initial vaccination
- Geometric mean titer (GMT) of SRH antibody titer for the vaccine strain at 21 days after each vaccination

Safety:

- Solicited local and systemic adverse events (AEs) to be recorded in the subject diary
- AEs
- Vital signs

[Additional Endpoints]

Immunogenicity:

- Seroprotection rate as measured by MN antibody titer (defined as the proportion of subjects with MN antibody titer ≥20) for the vaccine strain at 21 days after each vaccination
- Seroconversion rate as measured by MN antibody titer (defined as the proportion of subjects with 4-fold or more increase in MN antibody titer from baseline) for the vaccine strain at 21 days after each vaccination
- GMFI in MN antibody titer from baseline for the vaccine strain at 21 days after each vaccination
- GMT of MN antibody titer for the vaccine strain at 21 days after each vaccination

Statistical Considerations:

[Immunogenicity] Using the full analysis set (FAS), frequency tabulations of the SRH antibody titer and the seroprotection and seroconversion rates at 21 days after the second vaccination will be presented, and their point estimates and two-sided 95% confidence intervals will be calculated. For the GMFI in the SRH antibody titer at 21 days after the second vaccination, summary statistics and geometric means with corresponding two-sided 95% confidence intervals of the fold increase in the SRH antibody titer from baseline will be calculated.

Two-sided 95% confidence intervals of the geometric means will be calculated by back-transforming the upper and lower limits of two-sided 95% confidence intervals of the log transformed mean values.

[Safety] Using the safety analysis set, the following analyses will be performed:

For injection site and systemic AEs to be collected in the diary, frequency tabulations, frequency tabulations by severity, and frequency tabulations by vaccination and by timing of onset will be presented.

Treatment-emergent adverse events (TEAEs) are defined as AEs observed after vaccination with the study drug.

For TEAEs, the following analyses will be performed: TEAEs will be coded using the MedDRA and be summarized by System Organ Class and Preferred Term.

- Frequency tabulation of all TEAEs
- Frequency tabulation of TEAEs considered “related” to the study drug
- Frequency tabulation of all TEAEs by severity
- Frequency tabulation of TEAEs considered “related” to the study drug by severity
- Frequency tabulation of serious TEAEs
- Frequency tabulation of all TEAEs by vaccination and by timing of onset

Rationales for the Determination of Sample Size:

The objective of this study is to evaluate the immunogenicity and safety of two intramuscular vaccinations with BLB-750 in healthy Japanese adults. Therefore, the sample size for this study was determined to be 55 subjects, as the number of subjects to be vaccinated, by reference to the “Guidelines for the Development of Prototype Vaccines in Preparedness for Pandemic Influenza.” There are no statistical rationales for the determination of this sample size.

3.0 LIST OF ABBREVIATIONS

ADEM	acute disseminated encephalomyelitis
AE	adverse event
CRO	contract research organization
EDC	electronic data capture
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GMT	geometric mean titer
HA	hemagglutinin
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MN	microneutralization
PMDA	Pharmaceuticals and Medical Devices Agency
SAE	serious adverse event
SRH	single radial hemolysis
SUSARs	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

In Japan's National Action Plan for Pandemic Influenza and New Infectious Diseases [1], pandemic influenza is defined as "an influenza infectious disease in humans caused by newly emerging influenza virus as an etiological agent that acquires the ability of human-to-human transmission." Especially, there are concerns that when the highly pathogenic avian influenza virus H5N1 newly acquires the ability of human-to-human transmission and causes pandemic influenza (H5N1), it can constitute an enormous health hazard due to its high mortality rate. At present, therapeutic strategies for the treatment of pandemic influenza (H5N1) may include administration of anti-influenza virus drugs, such as oseltamivir phosphate and zanamivir hydrate. However, fatality due to acquired drug resistance during the treatment with oseltamivir phosphate has been suggested [2], which warrants the consideration of potential emergence of resistant virus strains before the use of anti-influenza virus drugs. In August 2004, a report by a subcommittee for the review of measures against pandemic influenza of the Section of Infectious Diseases, Health Sciences Council of the Ministry of Health, Labour and Welfare (MHLW) was prepared, in which the development, production, and stabilization of the supply of pandemic influenza vaccines are listed as primary aspects of measures against pandemic influenza.

Takeda Pharmaceutical Company Limited and PPD co-developed a vaccine indicated for "the prevention of pandemic influenza (H5N1)", and approval for the manufacture and marketing of Cell-Culture Influenza Vaccines H5N1 "CCI" and "Takeda" 5 mL was obtained June 2013 (approval withdrawn in September 2016). In March 2014, Takeda Pharmaceutical Company Limited obtained approval for the manufacture and marketing of Cell-Culture Influenza Vaccine H5N1 "Takeda" 1 mL. BLB-750 is an influenza vaccine containing inactivated whole influenza virions as an active ingredient. It is produced by inactivating influenza (H5N1 subtype) viruses that infected and replicated in cultured cells using formaldehyde treatment and ultraviolet irradiation.

4.1.1 Benefit/Risk Profile

Currently there is no established treatment available for pandemic influenza (H5N1), and viral drug resistance associated with the use of anti-influenza virus drugs has been reported. Therefore, it is considered extremely important to prevent the development or aggravation of influenza infectious diseases through vaccination. BLB-750 has been shown to be effective for the prevention of the development of influenza infectious diseases in mice and ferrets. In addition, clinical study results show that the vaccine is immunogenic. Based on these findings, it is expected that vaccination with BLB-750 will be useful for the prevention of the development or aggravation of pandemic influenza (H5N1).

BLB-750 may also be suitable as a vaccine prepared for a pandemic possibly caused by the H5N1 subtype for the following reasons: cell culture technology is applied for the manufacturing of the vaccine, which requires less time for vaccine production than other vaccines manufactured using chicken egg culture method; the manufacturing of BLB-750 is not affected by the availability of chicken eggs; and BLB-750 can be used in those who are allergic to hen's egg.

Frequently observed adverse events of BLB-750 in clinical studies of the vaccine include transient pain, bleeding, and induration for injection site reactions, and headache, fatigue, malaise, hyperhidrosis, myalgia, chills, oropharyngeal pain, pyrexia, and arthralgia for systemic reactions, with no major issues in terms of the tolerability or safety. The safety profile of BLB-750 is similar to that of existing seasonal influenza vaccines, and there considered to be no specific risk associated with vaccination with BLB-750. Although results from clinical studies of BLB-750 indicate the immunogenicity of BLB-750, it may not be effective for the prevention of pandemic influenza (H5N1) in all subjects due to various factors, including differences in the immunoreactivity among vaccinated individuals and between prevalent virus strains and the vaccine strain.

4.2 Rationale for the Proposed Study

As required by the MHLW, a strain attenuated using reverse genetics technology must be used as an H5N1 subtype virus strain for the production of pre-pandemic vaccine stockpiles as one of measures against pandemic influenza.

Clinical studies in Japanese adults for the purpose of the application for the approval of a cell-culture influenza vaccine (H5N1 strain) and clinical studies in the Japanese elderly and in children were conducted using a vaccine manufactured using a wild type strain as an H5N1 subtype virus strain, and there is no clinical experience with a vaccine manufactured using an attenuated strain.

Therefore, we planned a phase 4, open-label study to evaluate the immunogenicity and safety of two intramuscular vaccinations with BLB-750 at a 3-week interval in healthy Japanese adults, in which a cell-culture influenza vaccine (H5N1 strain) manufactured using an attenuated strain will be used..

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

To evaluate the immunogenicity and safety of two intramuscular vaccinations with BLB-750 in healthy Japanese adults

5.2 Endpoints

5.2.1 Primary Endpoints

Immunogenicity:

- Seroprotection rate as measured by SRH antibody titer (defined as the proportion of subjects with SRH antibody titer ≥25 mm^2) for the vaccine strain at 21 days after the second vaccination
- Seroconversion rate as measured by SRH antibody titer (defined as the proportion of subjects with a 50% or more increase in SRH antibody titer from baseline for those who have a baseline value >4 mm^2 or SRH antibody titer ≥25 mm^2 for those who have a baseline value ≤4 mm^2) for the vaccine strain at 21 days after the second vaccination
- Geometric mean fold increase (GMFI) in SRH antibody titer from baseline for the vaccine strain at 21 days after the second vaccination

5.2.2 Secondary Endpoints

Immunogenicity:

- Seroprotection rate as measured by SRH antibody titer (defined as the proportion of subjects with SRH antibody titer ≥25 mm^2) for the vaccine strain at 21 days after the initial vaccination
- Seroconversion rate as measured by SRH antibody titer (defined as the proportion of subjects with a 50% or more increase in SRH antibody titer from baseline for those who have a baseline value >4 mm^2 or SRH antibody titer ≥25 mm^2 for those who have a baseline value ≤4 mm^2) for the vaccine strain at 21 days after the initial vaccination
- GMFI in SRH antibody titer from baseline for the vaccine strain at 21 days after the initial vaccination
- Geometric mean titer (GMT) of SRH antibody titer for the vaccine strain at 21 days after each vaccination

Safety:

- Solicited local and systemic adverse events (AEs) to be recorded in the subject diary
- AEs
- Vital signs

5.2.3 Additional Endpoints

Immunogenicity:

- Seroprotection rate as measured by MN antibody titer (defined as the proportion of subjects with MN antibody titer ≥20) for the vaccine strain at 21 days after each vaccination
- Seroconversion rate as measured by MN antibody titer (defined as the proportion of subjects with 4-fold or more increase in MN antibody titer from baseline) for the vaccine strain at 21 days after each vaccination

- GMFI in MN antibody titer from baseline for the vaccine strain at 21 days after each vaccination
- GMT of MN antibody titer for the vaccine strain at 21 days after each vaccination

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 4, open-label study to evaluate the immunogenicity and safety of two intramuscular vaccinations with BLB-750 at a 3-week interval in healthy Japanese adults.

Subjects considered eligible after providing informed consent will receive the initial intramuscular vaccination with the study drug BLB-750 (Day 1) and the second intramuscular vaccination with BLB-750 during the study visit at 21 days after the initial vaccination (Day 22).

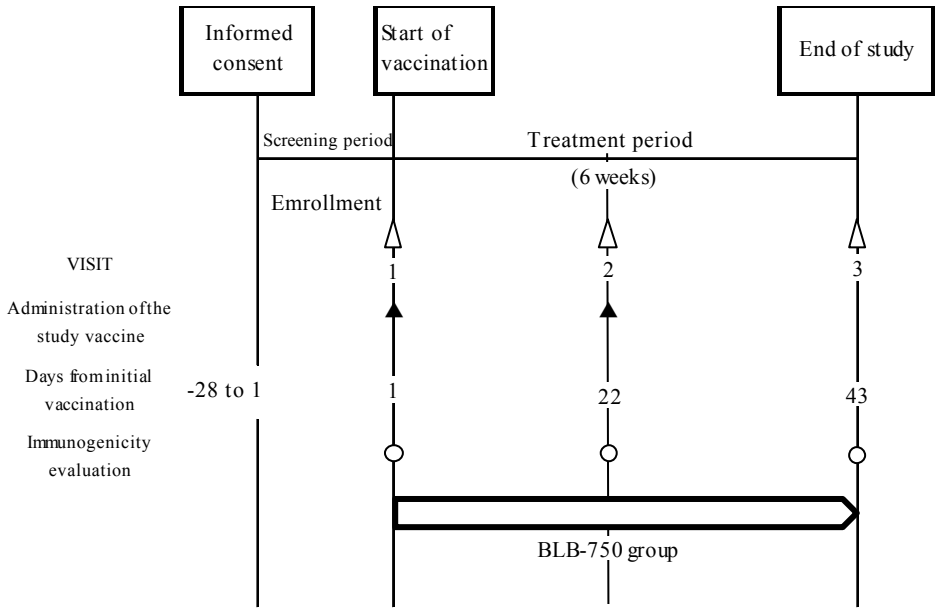
The study duration will be 43 days, starting on the day of initial vaccination (Day 1). Subjects will return to the study site 21 days after the initial vaccination (Day 22) and 21 days after the second vaccination (Day 43).

The total planned number of subjects to receive the study vaccination is 55.

A schematic of the study design is shown in Figure 6.a

For the testing, observations, and assessment schedule, see Appendix A

Figure 6.a Schematic of Study Design



6.2 Rationales for the Selection of Study Design, Vaccination Dosage, and Endpoints

6.2.1 Rationales for the Selection of Study Design

This study has been designed to evaluate the immunogenicity and safety of BLB-750 given intramuscularly in two doses at an interval of 3 weeks (open-label, uncontrolled study).

Clinical studies in Japanese adults for the purpose of the application for the approval of a cell-culture influenza vaccine (H5N1 strain) and clinical studies in the Japanese elderly and in children were conducted using a vaccine manufactured using a wild type strain as an H5N1 subtype virus strain. For this study, healthy adults were selected as a study population because the immunogenicity and safety of vaccination with a vaccine manufactured using an attenuated strain as an H5N1 subtype virus strain will be evaluated. For an age group for the study, a population

aged between 20 and 49 years was selected as a 20 years and older age group, which was not considered to have a major difference in immunogenicity within the group.

6.2.2 Rationales for the Selection of Vaccination Dosage Regimen and Strain

The package insert [3] specifies the dosage regimen of the cell-culture influenza vaccine (H5N1 strain) as "usually two doses of 0.5 mL should be intramuscularly or subcutaneously injected with an at least 3-week interval," and "as a general rule, intramuscular injection should be used as a vaccination route, with an exception in which subcutaneous injection may be selected based on the state of the subject". Thus, in accordance with the approved dosage regimen, the dosage regimen of BLB-750 in this study was selected to be two doses of 0.5 mL of BLB-750 with the HA content of 7.5 μg as an H5N1 subtype virus strain to be intramuscularly injected at a 3-week interval.

As described in Section 8.1.1.1, BLB-750 (Qinghai RG strain) was selected as the H5N1 subtype virus strain for BLB-750 to be used in this study.

6.2.3 Rationales for the Selection of Endpoints

Immunogenicity

To evaluate the immunogenicity against H5N1 subtype viruses of two intramuscular vaccinations of BLB-750, three endpoints as measured by the SRH antibody titer (seroprotection and seroconversion rates and geometric mean fold increase) specified as immunogenicity endpoints in the Guidelines for the Development of Prototype Vaccines in Preparedness for Pandemic Influenza [4] were selected as primary endpoints. Secondary endpoints included three endpoints as measured by the SRH antibody titer after the initial vaccination with BLB-750 (seroprotection and seroconversion rates and geometric mean fold increase) and the GMT of the SRH antibody titer after each vaccination. Additional endpoints were also selected to perform the exploratory evaluation of the MN antibody titer considered sensitive and specific in the detection of functional/protective antibodies against avian influenza strains [5][6].

Safety

Based on common side effects of influenza vaccines and results of previously conducted overseas clinical studies (with BLB-750 given intramuscularly) and Japanese clinical studies (with BLB-750 given intramuscularly and subcutaneously), injection site reactions (injection site pain, erythema, swelling, induration, and bleeding) and systemic reactions (pyrexia, malaise, chills, fatigue, headache, sweaty, myalgia, and arthralgia) have been reported as expected adverse reactions to BLB-750 vaccination. Data on the occurrence of these events during the study period (especially within 7 days after vaccination) will be collected using a subject diary. As in previously conducted overseas and Japanese studies, the severity of pyrexia and injection site reactions will be assessed by reference to the "FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" [7] (see Section 9.1.11). As safety endpoints commonly used in clinical studies, adverse events and vital signs will also be evaluated.

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the product, such that the risk is no longer acceptable for subjects participating in the study.

Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Site(s)

In the event that the sponsor, an institutional review board (IRB) or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to enrollment in the study.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form prior to the initiation of any study procedures.
3. The subject is a healthy Japanese adult man or woman.
4. The subject is aged 20 to 49 years, inclusive, at the time of informed consent.
5. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use routinely adequate contraception from signing of informed consent throughout the duration of the study.

> *Definitions and acceptable methods of contraception are defined in Section 9.1.8 and reporting responsibilities are defined in Section 9.1.9.

Rationale for the selection of inclusion criteria

Criteria 1 to 5 were selected as standard conditions for the selection of subjects participating in a clinical study in healthy adults. The upper limit of age was determined to be 49 years, which was not considered to make a major difference in immunogenicity within the 20-years-and-older age group.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has received vaccination with any other investigational or study products within 4 months prior to vaccination with the study vaccine.
2. The subject has a history of vaccination with an H5N1 influenza vaccine.
3. The subject has a history of infection with H5N1 virus.
4. The subject is at high risk of contracting H5N1 influenza infection (e.g., poultry workers).
5. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (e.g., spouse, parent, child, sibling) or may consent under duress.
6. The subject has poorly controlled, clinically significant manifestations of neurological, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, endocrine, or other disorders, which may impact their ability to participate as subjects or may potentially confound the study results.
7. The subject has a body temperature (oral) ≥37.5°C prior to vaccination with the study vaccine on Day 1.
8. The subject has any medically diagnosed or suspected immune-deficiency condition.
9. The subject has an immunocompromising condition or disease, or is currently undergoing a form of treatment or was undergoing a form of treatment that can be expected to influence immune response within 30 days prior to vaccination with the study vaccine.
   Such treatments include, but are not limited to, systemic or high dose inhaled corticosteroids (>800 μg/day of beclomethasone dipropionate or equivalent; the use of inhaled and nasal steroids that do not exceed this level will be permitted), radiation treatment or other immunosuppressive or cytotoxic drugs.

10. The subject has received antipyretics within 4 hours prior to vaccination with the study vaccine.
11. The subject has a history of Guillain-Barré Syndrome, demyelinating disorders (including acute disseminated encephalomyelitis [ADEM] and multiple sclerosis), or convulsions.
12. The subject has a functional or anatomic asplenia.
13. The subject has a rash, other dermatologic conditions or tattoos that may interfere with the evaluation of local reaction.
14. The subject has a past or present history of infection with the Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) or Human Immunodeficiency Virus (HIV).
15. The subject has a known hypersensitivity to any component of BLB-750.
16. The subject has a history of severe allergic reactions or anaphylaxis.
17. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol dependence within 1 year prior to vaccination with the study vaccine or is unwilling to agree to abstain from excessive alcohol and drugs throughout the study.
18. The subject has received any blood product (e.g., blood transfusion or immunoglobulin) within 90 days prior to vaccination with the study vaccine.
19. The subject has received any live vaccine within 4 weeks (28 days) prior to vaccination with the study vaccine or any inactivated vaccine within 2 weeks (14 days) prior to vaccination with the study vaccine.
20. The subject is a pregnant or lactating woman or wishes to become pregnant before signing informed consent, during, or within 12 weeks after the last vaccination with the study vaccine or intends to donate ova during such time period
21. For males: The subject has donated whole blood ≥200 mL within 4 weeks (28 days) or ≥400 mL within 12 weeks (84 days) prior to the first vaccination with the study vaccine.

    For females: The subject has donated whole blood ≥200 mL within 4 weeks (28 days) or ≥400 mL within 16 weeks (112 days) prior to the first vaccination with the study vaccine.
22. For males: The subject has donated whole blood ≥800 mL in total within 52 weeks (364 days) prior to the first vaccination with the study vaccine.

    For females: The subject has donated whole blood ≥400 mL in total within 52 weeks (364 days) prior to the first vaccination with the study vaccine.
23. The subject has donated blood components within 2 weeks (14 days) prior to the first vaccination with the study vaccine.
24. In the opinion of the investigator, the subject is unlikely to comply with protocol requirements or is considered ineligible for any other reason.
25. The subject has thrombocytopenia or coagulopathy, or is currently receiving anticoagulant therapy or received anticoagulant therapy within 30 days prior to the first vaccination with the study vaccine.

Rationale for the selection of exclusion criteria

Criterion 1 was selected, by reference to the "General Considerations for Clinical Trials" (PFSB/ELD Notification No. 380 dated April 21, 1998), to ensure the safety of subjects with the use of the period during which the previous study would not affect the present study.

Criteria 2, 3, 4, 8, 9, 12, 18, and 19 were selected to eliminate the possible impact on influenza vaccine evaluation (primarily immunogenicity evaluation).

Criteria 5, 6, 14, 17, 20, and 24 were selected as standard conditions for the selection of subjects participating in a clinical study in healthy adults.

Criteria 7 and 13 were selected to eliminate the possible impact on influenza vaccine evaluation (primarily safety evaluation).

Criterion 10 was selected to eliminate the possible impact on influenza vaccine evaluation (safety and immunogenicity evaluation).

Criteria 11, 15, 16, 21, 22, 23, and 25 were selected to ensure the safety of subjects.

7.3 Excluded Medications and Treatments

The use of medications and therapies shown in Table 7.a will be prohibited from the point specified in the table to the end of study.

Table 7.a Excluded Medications and Treatments

In the past	4 months prior to vaccination (Day 1)	90 days prior to vaccination (Day 1)	30 days prior to vaccination (Day 1)	28 days prior to vaccination (Day 1)	14 days prior to vaccination (Day 1)
• H5N1 influenza vaccines	• Other study medications	• Blood products (transfusion or immunoglobulin)	• Systemic or high-dose inhaled corticosteroids (beclomethasone dipropionate >800 µg/day or equivalent) • Radiotherapy • Immunosuppressives • Cytotoxic drugs • Anticoagulant therapy	• Live vaccines	• Inactivated vaccines

The investigator will instruct subjects not to take any drug (including OTC drugs) other than those prescribed by the investigator without consulting with the investigator.

7.4 Diet, Fluid, Activity Control

1. Diet

   Subjects should be abstemious during the study period.

2. Drinking

   Excessive consumption of alcohol-containing beverages should be avoided during the study period.

3. Smoking

   Smoking will be prohibited from 1 hour prior to each assessment to the end of assessment.

4. Exercise

   Excessive exercise will be prohibited during the study period.

5. Blood donation after the end of study

   Blood donation will be prohibited for at least 12 weeks after the completion of final assessment in this study. The investigator will provide subjects with counseling on the prohibition of blood donation.

6. Others

   The investigator will instruct subjects that if they visit another medical institution during the study period, they must inform the investigator of the reason for the visit and treatments given and must inform the institution of their participation in this study.

   The investigator will also instruct subjects to keep the study drug injection site clean and to avoid scratching or rubbing the injection site without good reason.

   For female subjects of childbearing potential who are sexually active with a nonsterilized male partner, the investigator will instruct them to use adequate contraception from the time of signing of informed consent, throughout the duration of the study, and for 12 weeks after the last vaccination with the study drug.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the case report form ([e]CRF) using the following categories. For subjects who discontinue/is withdrawn before enrollment in this study, see 9.1.12

1. Death
   The subject dies during the study.
   Note: If the subject dies on study, the event will be considered as a serious adverse event (SAE). See Section 10.2.2 for the reporting procedures.

2. Adverse event (AE)
   The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the AE.

3. Protocol deviation
   The discovery after enrollment that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.

4. Lost to follow-up
   The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.

5. Withdrawal by the subject
   The subject wishes to be withdrawn from the study. The reason for withdrawal, if provided, should be recorded in the (e)CRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded. In the case of withdrawal due to an AE, however, consideration should be given to classifying it as "AE(s)" rather than as "voluntary withdrawal by the subject."

6. Study Terminated by sponsor.
   The sponsor terminates the study.

7. Pregnancy
   The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn from the study immediately. The procedure is described in Section 9.1.9.

8. Other

Note: The specific reasons should be recorded in the "specify" field of the (e)CRF.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5 In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit. Subjects who are withdrawn from the study after receiving vaccination with the study drug will not be replaced.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all medication and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

The study drug in this protocol is defined below.

8.1.1.1 Study Drug

1. Dosage form and dose strength
   Substance code: BLB-750
   Trade name: Cell-Culture Influenza Vaccine H5N1 "Takeda" 1 mL
   Manufacturer: Takeda Pharmaceutical Company Limited
   Dosage form: A clear to whitish liquid injection (vial)
   Components and dose strength: One vaccination dosage of 0.5 mL contains components shown in Table 8.a.

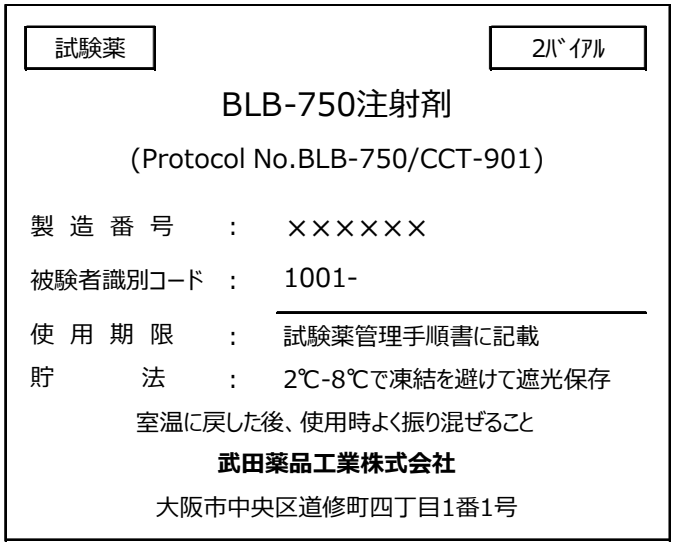
Table 8.a Components and Dose Strength of BLB-750 Injection 0.5 mL

	Component	Dose strength	Function
Active ingredient (vaccine strain)	BLB-750 Qinghai RG strain [A/bar-headed goose/Qinghai/1A/2005 (H5N1) (SJRG-163222)]	7.5 µg	-
Inactive ingredient	Trometamol	1.2 mg	Buffer
	Sodium chloride	4.0 mg	Isotonicifier
	Polysorbate 80	0.63 mg	Aggregation preventer

2. Packaging and labeling
   Two vials of the study drug will be packaged in a box labeled with the following information.

<front side of the box>

Figure 8.a Labeling Sample of the Outer Box for the Study Drug



8.1.1.2 Ancillary Materials

The syringe and injection needle designated by the sponsor should be used for vaccination with the study drug.

8.1.2 Storage

The study drug should be stored at 2°C to 8°C but not frozen, and be protected from light.

The site designee must keep the study drug in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee (CRO). All drugs supplied by the sponsor must be stored under the conditions specified on the label. A daily temperature log of the drug storage area must be maintained every working day.

8.1.3 Dose and Regimen

According to the following procedures, two doses of the study drug 0.5 mL will be injected into the brachial muscle (deltoid muscle) on Days 1 and 22.

- Let the study drug (vial) warm to room temperature.
- Prior to administration, shake the vial for 5-10 seconds to mix the vaccine suspension completely.
- Prior to administration, visually inspect for any insoluble particulate matter or discoloration. The study drug should not be used if any insoluble particulate matter, discoloration, or leakage is observed.
- Using a 1-inch long, 25-gauge needle, inject a dose of 0.5 mL into the arm opposite to the one used for blood collection to obtain a sample for immunogenicity testing wherever possible.
- The following should be noted to avoid the effect of intramuscular vaccination on the tissues and nerves:
- Injecting into a nerve tract should be avoided.
- In the case of intense pain and/or backflow of blood associated with needle insertion, withdraw the needle immediately and inject into another site.

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental vaccination with the study drug at a dose above that assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the (e)CRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with overdose will be documented on an AE page of the CRF(s) in accordance with 10.0 Adverse Events.

SAEs associated with overdose should be reported in accordance with the procedure outlined in 10.2.2.

In the event of drug overdose, the subject should be treated as appropriate by the investigator.

8.2 Study Drug Dispensing Procedures

Subjects will be vaccinated with the study drug according to the study schedule.

8.3 Accountability and Destruction of Sponsor-Supplied Drugs

The site designee will receive the procedures for handling, storage and management of study drugs created by the sponsor, according to which the site designee will appropriately manage the sponsor-supplied drug. The investigator will also receive those procedures from the sponsor. The procedures include those for ensuring appropriate receipt, handling, storage, management, and dispensation of the sponsor-supplied drug, and collection of unused medications as well as their return to the sponsor or their destruction.

The site designee will immediately return unused supplies of the study drug to the sponsor after the study is closed at the site.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The study schedule is provided in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2. Informed consent must be obtained from each subject before any protocol-directed procedures are performed. A unique subject identification number (subject number) will be assigned to each subject at the time that informed consent is explained; this subject number will be used throughout the study; this subject number will be used throughout the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth and sex.

For medical history, clinically significant diseases or symptoms that have healed or resolved within 1 year prior to the first vaccination with study drug will be collected. Ongoing conditions are considered present illnesses (see Section 9.1.7). History of influenza infection within 1 year prior to the first vaccination with study drug will be collected.

Prior treatments to be collected include all drugs discontinued within 4 weeks prior to informed consent. In addition, history of influenza vaccination (including pandemic influenza vaccines and other investigational products) within 1 year prior to informed consent will be collected.

9.1.3 Physical Examination Procedure

A baseline physical examination at baseline (defined as the assessment prior to the first vaccination with study drug), will consist of the following body systems:

(1) eyes; (2) ears, nose; and throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other.

During physical examination after each vaccination with the study drug, the subject will be assessed for any abnormalities considered clinically significant in comparison with pre-vaccination physical findings. During study visits at Days 22 and 43 and at discontinuation, the subject will be assessed for any pyrexia, systemic and injection site reactions, and other events based on the subject diary (see Section 9.1.11).

9.1.4 Weight and Height

A subject should have weight and height measured while wearing indoor clothing on and shoes off. The Takeda standard for collecting height is centimeters without decimal places (rounded to the nearest whole number) and for weight it is kilograms (kg) with 1 decimal place (rounded to one decimal place).

Example: Height = 176 cm, weight = 79.2 kg

9.1.5 Vital Signs Procedure

Vital signs will include body temperature (oral), respiratory rate, sitting blood pressure (resting more than 5-minutes), and pulse (beats per minute). No respiratory rate measurement will be required at Day 43 and at discontinuation.

If blood sampling and vital sign measurement are to be performed at the same point, vital sign measurement should be performed first.

The subject must measure his/her temperature and record it in the subject diary every day on Days 1-7 and 22-28 and as needed on Days 8-22 (before study visit) and 29-43 (before study visit) (see Section 9.1.11). Daily measurements on Days 1-7 and 22-28 should be transcribed to the (e)CRF.

9.1.6 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by Takeda. At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the (e)CRF.

9.1.7 History of Present Illness

A present illness refers to any clinically significant disease or symptom existing at the first vaccination with study drug. All clinically significant laboratory values and abnormal findings observed during examination prior to vaccination with the study drug should be regarded as present illnesses. The details of present illnesses (diagnoses) should be recorded.

9.1.8 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, and for 12 weeks after last dose of study drug, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use adequate contraception. In addition they must be advised not to donate ova during this period.

*A woman is considered a woman of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a post-menopausal state in younger women (e.g. those < 45 year old) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

**Sterilized males should be at least 1 year post vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

Such subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process, and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy during the course of the study.

During the course of the study, regular urine human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures Appendix A In addition to a urine hCG pregnancy test before vaccination on the day of vaccination with the study drug (Day 1), the result of urine hCG test at the end of study (or discontinuation) (Day 43) must be confirmed negative.

In this study, the only acceptable methods of contraception are:

Barrier methods (each time the subject has intercourse):	**Intrauterine devices (IUDs):**	**Hormonal contraceptives:**
• Male condom PLUS spermicide.	• Copper T PLUS condom. • Progesterone T PLUS condom.	• Combined pill.

9.1.9 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug should be immediately discontinued.

If the pregnancy occurs during administration of active study drug, eg, after Day 1 or within 12 weeks of the last dose of active study drug, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed on the attached sheet.

If the female subject agrees to the primary care physician (obstetrician) being informed, the investigator should notify the primary care physician that the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received.

All pregnancies in subjects on active study drug including comparator will be followed up to final outcome, using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.10 Immunogenicity Evaluation

The SRH and MN antibody titers against influenza virus for immunogenicity evaluation will be measured by the laboratory specified in the procedures. As for blood sampling, 20 mL of blood per sampling will be collected from the forearm vein. The blood sample collected will be used for study-specific endpoint measurements as well as immunogenicity evaluation by a government organization, and also may be used for other exploratory immunogenicity evaluations (see Section 9.4). No genetic testing will be performed using the samples collected in this study.

For the immunogenicity evaluation by a government organization, the protocol and the result report will be prepared by the sponsor or the government organization, separately from the protocol and clinical study report for this study. If other exploratory immunogenicity evaluations are performed, their protocols and result reports should also be prepared.

Detailed procedures for handling and transporting samples are found in separately prepared documented procedures for handling of biological samples for immunogenicity evaluation.

9.1.11 Injection Site and Systemic Reactions (Diary-based Assessment)

As AEs related to reactogenicity of vaccination with the study drug, injection site reactions (injection site pain, erythema, swelling, induration, and haemorrhage, hereinafter the same applies) and systemic reactions (pyrexia, malaise, chills, fatigue, headache, sweaty, myalgia, and arthralgia, hereinafter the same applies) occurring between the initial vaccination with study drug and 42 days after the vaccination (Day 43) will be collected via the subject diary.

Injection site and systemic AEs occurring within 21 days after each vaccination (Days 22 and 43) will be collected via the subject diary (Diary 1 for Days 1-7, Diary 2 for Days 8-22, Diary 3 for Days 22-28, and Diary 4 for Days 29-43).

Diaries 1 and 2 will be provided to each subject together with a digital thermometer for oral temperature measurement and a ruler for injection site reaction measurement after vaccination with the study drug on Day 1. These diaries will be collected and reviewed by the investigator at Day 22 visit.

Information to be recorded in Diary 1 (Days 1-7)

- Body temperatures (oral) measured once daily in the evening during the period after vaccination with the study drug (Day 1) until Day 7
- Injection site reactions
- Systemic reactions
- Other AEs

Information to be recorded in Diary 2 (Days 8-22)

- Body temperatures (oral) measured when the subject experiences any AE with pyrexia during the period after Day 8 until Day 22 before study visit
- Other AEs

Diaries 3 and 4 will be provided to each subject at Day 22 visit (or at Day 1 visit) and will be collected and reviewed by the investigator at Day 43 visit.

Information to be recorded in Diary 3 (Days 22-28) [same as information to be recorded in Diary 1]

- Body temperatures (oral) measured once daily in the evening during the period after vaccination with the study drug (Day 22) until Day 28
- Injection site reactions
- Systemic reactions
- Other AEs

Information to be recorded in Diary 4 (Days 29-43) [same as information to be recorded in Diary 2]

- Body temperatures (oral) measured when the subject experiences any AE with pyrexia during the period after Day 29 until Day 43 before study visit
- Other AEs

For recording of body temperatures (oral) and injection site reactions in the diary, each subject will be asked to follow the instructions below.

<Body temperature (oral) measurement>

- Diary 1 (Days 1-7) and Diary 3 (Days 22-28): Subjects will measure their oral temperatures once daily, in the evening wherever possible, using the oral digital thermometer provided for the study. Subjects will be asked to keep to the same measurement time every day whenever possible. In the case of pyrexia (defined as oral temperature ≥38.0°C), oral temperatures should be measured more than once (approximately every 4-8 hours) wherever possible and recorded in Diary 1 or 3 until the pyrexia resolves (defined as oral temperature <38.0°C). Subjects will record all measurement information (i.e., measurement results and date and time of measurement) obtained on Days 1-7 and Days 22-28 in Diary 1 and 3, respectively.
- Diary 2 (Days 8-22 [before study visit]) and Diary 4 (Days 29-43 [before study visit]): Daily measurement will not be required. Measurements should be obtained using the oral digital thermometer provided for the study only when any symptom suggestive of pyrexia is noted. In the case of pyrexia (defined as oral temperature ≥38.0°C), the subject should measure his/her oral temperature at least once daily, or more than once

(approximately every 4-8 hours) wherever possible, and record it in Diary 2 or 4 until the pyrexia resolves (defined as oral temperature <38.0°C) to confirm the end date. Subjects will record measurement information (i.e., measurement results and date and time of measurement) obtained on Days 8-22 (before study visit) and Days 29-43 (before study visit) in Diary 2 and 4, respectively.

<Injection site reactions>

- Diary 1 (Days 1-7) and Diary 3 (Days 22-28): If, among injection site reactions, erythema, swelling, or induration is observed after vaccination with the study drug, the subject should measure the longest diameter of the injection site reaction using the ruler provided for the study and record it in Diary 1 or 3.
- Diary 2 (Days 8-22 [before study visit]) and Diary 4 (Days 29-43 [before study visit]): All newly observed injection site reactions and all other injection site reactions observed any time during Days 1-7 or Days 22-28 but that have not resolved during these periods should be recorded in Diary 2 or 4. The longest diameter should also be measured and recorded.

Based on records from each subject's diary collected at Day 22 and 43 visits, the investigator will capture all AEs occurring during Days 1-22 and Days 22-43, and record these AEs on the (e)CRF together with the severity and causality assessment for each event.

As for pyrexia, the start date is defined as the date on which the first oral temperature measurement ≥38.0°C is obtained, and the end date is defined as the date on which the first oral temperature measurement <38.0°C is obtained after the onset. Daily oral temperature measurements on Days 1-7 and Days 22-28 recorded in Diaries 1 and 3 should be transcribed to the (e)CRF even if they are <38.0°C. If two or more temperature measurements are recorded for the same day, the highest temperature of that day should be transcribed to the (e)CRF.

The severity of pyrexia and injection site reactions will be assessed using the criteria shown below, by reference to the "FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"[7] For other AEs (including solicited systemic reactions to be recorded in the subject diary), assessment will be performed as specified in Section 10.1.5.

Pyrexia:

Mild: ≥38.0°C and <38.5°C

Moderate: ≥38.5°C and <39.0°C

Severe: ≥39.0°C

Measurable injection site reactions (injection site erythema, swelling, and induration):

Mild: ≥2.5 cm and <5.1 cm

Moderate: ≥5.1 cm and <10.1 cm

Severe: ≥10.1 cm

*Injection site reactions <2.5 cm will not be regarded as AEs. However, the longest diameter recorded in the diary will be transcribed to the (e)CRF separately from AEs, regardless of whether it is ≥2.5 cm or <2.5 cm.

Injection site pain and haemorrhage:

Mild: No interference with upper extremity movement

Moderate: Interference with upper extremity movement present.

Severe: Upper extremity impairment/dysfunction

9.1.12 Documentation of Subjects Failure before Enrollment in the Study

The investigator accounts for all subjects who sign informed consent.

If the subject is found to be not eligible before the start of vaccination with the study drug, the investigator should complete the (e)CRF.

The primary reason for subjects failure before the start of vaccination with the study drug is recorded in the (e)CRF using the following categories:

- Death
- Adverse Event
- Screen failure (failed inclusion criteria or did meet exclusion criteria)
- Protocol deviation
- Lost to follow-up
- Withdrawal by subject <specify reason>
- Study terminated by sponsor
- Pregnancy
- Sample size sufficient
- Other <specify reason>

Subject numbers assigned to subjects who fail screening should not be reused.

9.1.13 Documentation of Enrollment in the Study

Subjects will be enrolled in the study and receive vaccination with the study drug only if they meet all the inclusion criteria and do not meet any of the exclusion criteria.

For subjects who did not receive vaccination with the study drug, the investigator should record the primary reason for failure on the applicable (e)CRF.

9.2 Vaccination Status in Subjects

The study vaccine will be administered under observation at the study site. The investigator will observe the subjects for any abnormalities for at least 30 minutes after vaccination with the study drug at the study site. The date of vaccination will be recorded in the subjects' source documents and (e)CRFs. The inventory of the study drugs dispensed will be controlled and recorded in the investigational product accountability log or equivalent document by a study site pharmacist or a person designated by the investigator.

9.3 Schedule of Observations and Procedures

The schedule for all testing, observation, and assessments is provided in Appendix A. The following testing, observation, and assessments should be completed at the designated time points.

9.3.1 <Screening Period/Day 1 (Starting before the Initial Vaccination and Ending after the Completion of the Initial Vaccination)>

Enrollment in the study will be performed on Day 1, and the following testing, observation, and assessments will be performed: Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0.

- Informed consent
- Demographics, medical history, and medication history procedure
- Physical examination
- Vital signs (body temperature [oral], blood pressure, and pulse and respiratory rates)
- Weight and height
- Documentation of concomitant medications
- Present illness
- Pregnancy test (only for female subjects of childbearing potential)
- Blood sampling for the immunogenicity evaluation

Subjects meeting all the inclusion criteria and not meeting any of the exclusion criteria will be enrolled in the study. Subjects will receive vaccination with the study drug under the supervision of the investigator at the study site. For the procedures for the recording of subjects withdrawn from the study prior to the start of vaccination with the study drug, see Section 9.1.12.

9.3.2 <Treatment Period/Day 1 (after the Initial Vaccination) to Day 22 (before Visiting the Study Site)>

During the period from Day 1 (after the initial vaccination) to Day 22 (before visiting the study site), the following testing, observation, and assessments will be performed: Day 1 (the day of initial vaccination) will be the day of study visit, and subjects will monitor themselves at home during the period after the completion of Day 1 visit until before Day 22 visit (see Section 9.1.11).

- Physical Examination

  Time point: Day 1 (after the initial vaccination)

  The investigator will monitor for any acute hypersensitivity reaction, etc., for 30 minutes after vaccination.

- Vital signs (blood pressure and pulse and respiratory rates)

  Time point: Day 1 (after the initial vaccination)

  Vital signs will be measured 30 minutes after vaccination.

- Vital signs (body temperature [oral])

  From Days 1 to 7, subjects will measure their body temperature (oral) and record it in the subject diary. From Days 8 to 22 (before visiting the study site), subjects will measure their body temperature (oral) only if they develop pyrexia (or any symptoms suggestive of pyrexia) (see Section 9.1.11).

- Supply of the subject diary

  Time point: Day 1 (Diaries 1 and 2) (Diaries 3 and 4 may be supplied on Day 1)

- Completion of the subject diary (by subjects)

  Time points: From Day 1 (after the initial vaccination) to Day 7 (Diary 1) and from Day 8 to Day 22 (before visiting the study site) (Diary 2)

During the periods from Day 1 (after the completion of study visit) to Day 7 and from Day 8 to Day 22 (before visiting the study site), subjects will monitor for and record any systemic reactions, injection site reactions, etc. (see Section 9.1.11).

9.3.3 <Treatment Period/Day 22 (Starting before the Second Vaccination and Ending after the Completion of the Second Vaccination)>

The following tests, observations, and assessments will be performed on Day 22 (starting before the second vaccination and ending after the completion of the second vaccination).

- Physical Examination
- Vital signs (body temperature [oral], blood pressure, and pulse and respiratory rates)
- Collection of concomitant medications and AEs
- Blood sampling for the immunogenicity evaluation
- Collection of the subject diary (Diaries 1 and 2)

Subjects will receive vaccination with the study drug under the supervision of the investigator at the study site.

9.3.4 <Treatment Period/Day 22 (after the Second Vaccination) to Day 43 (before Visiting the Study Site)>

During the period from Day 22 (after the second vaccination) to Day 43 (before visiting the study site), the following testing, observation, and assessments will be performed: Subjects will monitor themselves at home during the period after the completion of Day 22 visit until before Day 43 visit (see Section 9.1.11).

- Physical Examination

  Time point: Day 22 (after vaccination)

  The investigator will monitor for any acute hypersensitivity reaction, etc., for 30 minutes after vaccination.

- Vital signs (blood pressure and pulse and respiratory rates)

  Time point: Day 22 (after vaccination)

  Vital signs will be measured 30 minutes after vaccination.

- Vital signs (body temperature [oral])

  Form Days 22 to 28, subjects will measure their body temperature (oral) and record it in the subject diary. Form Days 29 to 43 (before visiting the study site), subjects will measure their body temperature (oral) only if they develop pyrexia (or any symptoms suggestive of pyrexia) (see Section 9.1.11).

- Supply of the subject diary

  Time point: Day 22 (Diaries 3 and 4) (Diaries 3 and 4 may be supplied on Day 1)

- Completion of the subject diary (by subjects)

  Time point: From Day 22 (after vaccination) to Day 28 (Diary 3) and from Day 29 to Day 43 (before visiting the study site) (Diary 4)

During the periods from Day 22 (after the completion of study visit) to Day 28 and from Day 29 to Day 43 (before visiting the study site), subjects will monitor for and record any systemic reactions, injection site reactions, etc. (see Section 9.1.11).

9.3.5 <Treatment Period/at the End of Study/Day 43>

The following testing, observation, and assessments will be performed at the final study visit (for observation) (Day 43).

- Physical Examination
- Vital signs (body temperature [oral], blood pressure, and pulse rate)
- Pregnancy test (only for female subjects of childbearing potential)
- Blood sampling for the immunogenicity evaluation
- Collection of the subject diary (Diaries 3 and 4)
- Collection of concomitant medications and AEs

For all subjects receiving the study drug, the investigator must complete the Subject Status (e)CRF page.

9.3.6 <Treatment Period/at Discontinuation>

For subjects withdrawn from the study, reasons for study discontinuation must be recorded in the subject's source documents and CRF, and the following testing, observation, and assessments should be performed wherever possible.

- Physical Examination
- Vital signs (body temperature [oral], blood pressure, and pulse rate)
- Pregnancy test (only for female subjects of childbearing potential)
- Blood sampling for the immunogenicity evaluation
- Collection of the subject diary
- Collection of concomitant medications and AEs

For all subjects receiving the study drug, the investigator must complete the Subject Status (e)CRF page.

9.4 Biological Sample Retention and Destruction

The remainder of serum samples collected in accordance with Section 9.1.10, "Immunogenicity Evaluation" will be stored. Serum samples will be discarded after they will no longer be used. Details on sample retention will be provided in separately prepared handling procedures.

9.5 Amount and Frequency of Blood Collection

The total amount of blood to be collected from each subject will be as shown in Table 9.a.

Table 9.a Amount and Frequency of Blood Collection

Test	Amount to be collected per collection	Frequency of collection	Total amount to be collected
Immunogenicity testing	20 mL	Three times	60 mL
Total amount to be collected			60 mL

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study; it does not necessarily have to have a causal relationship with this treatment or study participation.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the study participation whether or not it is considered related to the drug or study procedures.

10.1.2 Additional Points to Consider for AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying diseases should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or dose adjustment of the study drug or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

AEs caused by a study procedure (e.g., a bruise after blood draw) should be recorded as an AE.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. However, each solicited local or systemic AE to be recorded in the subject diary should be recorded as a single event. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).

Pre-existing conditions:

- Pre-existing conditions (present since before the first vaccination with study drug) are considered present illnesses and should NOT be recorded as AEs. However, if the present illness worsens after the first vaccination with study drug, it should be appropriately recorded as an AE. The investigator should ensure that the AE term to be reported reflects a change from baseline (e.g., “worsening of…”).
- If a subject has a pre-existing episodic condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as an AE if the episodes become more frequent, serious or severe in nature, that is, investigators should ensure that the AE term recorded captures the change in the condition from Baseline (eg “worsening of…”).
- If a subject has a degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as an AE if occurring to a greater extent to that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (eg, “worsening of…”).

Change in severity of AEs:

- If the subject experiences a change in severity of an AE that is not related to starting the study drug or changing in the dose or regimen, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that are scheduled prior to signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (e.g., as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- The occurrence of overdose with no associated events should NOT be considered an AE, but instead will be documented on an Overdose page of the (e)CRF. Any event associated with overdose should be considered AEs and will be recorded on the AE page of the (e)CRF.

10.1.3 SAEs

An SAE is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product (including a study drug), which:

1. Results in DEATH.
2. Is LIFE THREATENING.

- The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:

- May require intervention to prevent items 1 through 5 above.
- May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
- Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Acute liver failure
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure (including seizure and epilepsy)	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis (including interstitial lung disease)
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
Hepatic necrosis	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death

Note: The terms listed in this table may be "important medical events" that require the reporting of SAEs and are therefore broadly defined medical terms.

7. The following important medical events associated with the use of an influenza vaccine: neuritis, encephalitis, vasculitis, Guillain-Barre syndrome, Bell's palsy (facial palsy), and demyelinating disorder (including acute disseminated encephalomyelitis [ADEM] and multiple sclerosis)

10.1.4 AEs of Special Interest

An AE of Special Interest (regardless of whether it is serious or not) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand them.

10.1.5 Severity of AEs

The different categories of intensity are characterized as follows:

Mild: The event is transient and easily tolerated by the subject.

Moderate: The event causes the subject interrupts the subject's usual activities.

Severe: The event causes considerable interference with the subject's usual activities.

However, pyrexia and injection site reactions (injection site pain, erythema, swelling, induration, and haemorrhage) should be assessed according to the classification specified in 9.1.11.

10.1.6 Causality of AEs

The relationship of each AE to study drug(s) will be assessed using the following categories:

Related: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, present illness, concomitant medications and concurrent treatments, may also be responsible.

Not related: An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, present illness, concomitant medications and concurrent treatments.

10.1.7 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.8 Start Date

The start date of the AE is the date that the first signs/symptoms were noted by the subject and/or investigator.

The start date of AEs will be determined using the following criteria;

AEs	Start Date
Any signs/symptoms/diseases (diagnosis)	The date that the first signs/symptoms were noted by the subject and/or the investigator should be recorded.
Asymptomatic diseases	The date when examination was performed for diagnosis and diagnosis was confirmed should be recorded. The date when diagnosis was confirmed should also be recorded even when values or findings showed previous values or findings or the onset time can be estimated.
Worsening of present illnesses	The date when diagnosis was confirmed should also be recorded even when values or findings showed previous values or findings or the onset time can be estimated.

10.1.9 End Date

The end date of the AE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.1.10 Pattern of Adverse Events

Episodic AEs (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.11 Action Taken with Study Treatment

Actions concerning the study drug will be classified and defined as follows:

- Drug withdrawn — A study drug is stopped due to the particular AE.
- Dose not changed — The particular AE did not require stopping a study drug.
- Unknown — Only to be used if it has not been possible to determine what action has been taken.
- Not applicable — A study drug was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, vaccination with study drug was already stopped before the onset of the AE.

10.1.12 Outcome of Event

• Recovered/resolved	Subject returned to first assessment status with respect to the AE.
• Recovering/resolving	The intensity is lowered by one or more stages: The diagnosis or signs/symptoms has almost disappeared; The abnormal laboratory value improved, but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving".
• Not recovered/not resolved	There is no change in the diagnosis, signs or symptoms; The intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved".
• Recovered/Resolved with sequelae	The subject recovered from an acute AE but was left with permanent/significant impairment (e.g, recovered from a cardiovascular accident but with some persisting paresis.
• Fatal	The AEs which are considered as the cause of death.
• Unknown	The course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 AE Collection Period

The collection of AEs will be started at the initial vaccination with the study drug (Day 1) and continued until the end of study (Day 43).

10.2.1.2 AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study.

All subjects experiencing AEs after the first exposure to study drug, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the (e)CRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term
2. Start and end date
3. Pattern
4. Severity
5. Investigator's opinion of the causality between the event and administration of study drug(s)
6. Investigator's opinion of the causality to study procedure(s), including the details of the suspected procedure

7. Action taken with study treatment
8. Outcome of event
9. Seriousness
10. Treatment emergent (After the first exposure to study drug)
11. For pyrexia, the maximum body temperature and the presence or absence of a 24-hour or longer persistence
12. For injection site erythema, swelling, and induration, the longest diameter

10.2.1.3 AEs of Special Interest Reporting

In this study, AEs of special interest will include the following AEs:

Hypersensitivity and anaphylaxis or any events suggestive of hypersensitivity

If this AE of special interest, which occurs during the treatment period or the follow-up period, is considered to be clinically significant, it should be reported to the sponsor (described in the separate contact information list) immediately or within 1 business day of first onset or subject's notification of the event. The study-specific Solicited AE Form or SAE Form should be completed, signed and/or sealed by the principal investigator, and reported to appropriate personnel in the separate contact information list within 10 business days.

The AE of special interest have to be recorded as AEs in the (e)CRF. An evaluation form (the original copy of Solicited AE Form or SAE Form) along with all other required documentation must be submitted to the sponsor.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

An SAE should be reported to the sponsor (described in the separate contact information list) within 1 business day of first onset or subject's notification of the event. The principal investigator should submit the completed SAE form within 10 calendar days. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious
- Subject identification number
- Investigator's name
- Name of the study drug(s)
- Causality assessment

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

The investigator should report any AEs to the sponsor and submit the form within the appropriate period as specified by the sponsor.

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event.

10.3.1 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities investigators and IRBs /the head of the study site, as applicable in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of a study drug or that would be sufficient to consider changes in the study drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs and medical history including present illness will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 CRFs

Completed (e)CRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. (e)CRFs must be completed in English. Data are transcribed directly onto eCRFs.

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal investigator must review the (e)CRFs for completeness and accuracy and must sign the appropriate (e)CRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the (e)CRFs.

The following data will be recorded directly into the (e)CRFs. However, this will not apply if the subject's medical records contain the data.

- Subject eligibility assessment
- AE terms, the start and end dates, ongoing/not ongoing at the end of study, onset pattern, severity, causal relationship with the study procedures, causal relationship with the study drug, action taken with the study drug, outcome, and seriousness
- The status of the subject in terms of vaccination with the study drug and the completion of the study
- Reason for the use of concomitant medications and ongoing/not ongoing at the end of study

The following data will not be recorded on the (e)CRFs:

- Immunogenicity testing results

After the lock of the clinical study database, any change of, modification of or addition to the data on the (e)CRFs should be made by the investigator with use of change and modification records of the Data Clarification Form provided by the sponsor. The principal investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date.

(e)CRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the (e)CRFs. The completed (e)CRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator and the head of the institution agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees.

Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, the investigator and the head of the institution are required to retain essential relevant documents until the day of completion of BLB-750 reexamination. However, if the sponsor requests a longer time period for retention, the head of the institution should discuss how long and how to retain those documents with the sponsor.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized by the statistician prior to the data lock. The SAP will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A data review will be conducted prior to the data lock. This data review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

In this study, two kinds of analysis sets are defined: FAS, and safety analysis set. The FAS used as an immunogenicity analysis set and the safety analysis set will be defined as “all subjects who received at least one dose of the study drug for the treatment period." The definition of each analysis set will be detailed in the separate “SAP.”

13.1.2 Analysis of Demographics and Other Baseline Characteristics

In this study, major subject background data in the FAS will be tabulated.

13.1.3 Immunogenicity Analysis

(1) Primary Endpoints and Their Analyses

(Primary Endpoints)

Immunogenicity:

Seroprotection rate as measured by SRH antibody titer (defined as the proportion of subjects with SRH antibody titer ≥25 mm^2) for the vaccine strain at 21 days after the second vaccination

Seroconversion rate as measured by SRH antibody titer (defined as the proportion of subjects with a 50% or more increase in SRH antibody titer from baseline for those who have a baseline value >4 mm^2 or SRH antibody titer ≥25 mm^2 for those who have a baseline value ≤4 mm^2) for the vaccine strain at 21 days after the second vaccination

Geometric mean fold increase (GMFI) in SRH antibody titer from baseline for the vaccine strain at 21 days after the second vaccination

[Analysis Methods]

Using the FAS, frequency tabulations of the SRH antibody titer and the seroprotection and seroconversion rates at 21 days after the second vaccination will be presented, and their point estimates and two-sided 95% confidence intervals will be calculated. For the geometric mean fold increase in the SRH antibody titer at 21 days after the second vaccination, summary statistics and geometric means with corresponding two-sided 95% confidence intervals of the fold increase in the SRH antibody titer from baseline will be calculated. Two-sided 95% confidence intervals of the geometric means will be calculated by back-transforming the upper and lower limits of two-sided 95% confidence intervals of the log transformed mean values.

(2) Secondary Endpoints and Their Analyses

(Secondary Endpoints)

Immunogenicity:

Seroprotection rate as measured by SRH antibody titer (defined as the proportion of subjects with SRH antibody titer ≥25 mm^2) for the vaccine strain at 21 days after the initial vaccination

Seroconversion rate as measured by SRH antibody titer (defined as the proportion of subjects with a 50% or more increase in SRH antibody titer from baseline for those who have a baseline value >4 mm^2 or SRH antibody titer ≥25 mm^2 for those who have a baseline value ≤4 mm^2) for the vaccine strain at 21 days after the initial vaccination

GMFI in SRH antibody titer from baseline for the vaccine strain at 21 days after the initial vaccination

Geometric mean titer (GMT) of SRH antibody titer for the vaccine strain at 21 days after each vaccination

[Analysis Methods]

Using the FAS, frequency tabulations of the SRH antibody titer and the seroprotection and seroconversion rates at 21 days after the initial vaccination will be presented, and their point estimates and two-sided 95% confidence intervals will be calculated. For the geometric mean fold increase in the SRH antibody titer at 21 days after the initial vaccination, summary statistics and geometric means with corresponding two-sided 95% confidence intervals of the fold increase in the SRH antibody titer from baseline will be calculated. For GMT of the SRH antibody titer at 21 days after each vaccination, summary statistics and geometric means with corresponding two-sided 95% confidence intervals will be calculated. Two-sided 95% confidence intervals of geometric means will be calculated using the method specified in 13.1.3(1).

(3) Additional Endpoints

See Section 5.2.3.

(4) Methods of Data Transformation and Handling of Missing Data

The details will be provided in the separate "SAP."

(5) Confidence Coefficient

Confidence coefficient: 95% (two-sided estimation)

13.1.4 Safety Analysis

Secondary Endpoints and Their Analyses

- Solicited local and systemic adverse events (AEs) to be recorded in the subject diary
- AEs
- Vital signs

Using the safety analysis set, the following analyses will be performed:

For injection site and systemic AEs to be collected from the diaries, frequency tabulations, frequency tabulations by severity, and frequency tabulations by vaccination and by timing of onset will be presented. For vital signs, summary statistics of measurement values and the changes in post-vaccination values from baseline at each assessment point will be calculated. In addition, the changes in each test item over time will be graphically presented.

Treatment-emergent adverse events (TEAEs) are defined as AEs observed after the start of vaccination with the study drug.

For TEAEs, the following analyses will be performed: TEAEs will be coded using the MedDRA and summarized by System Organ Class and Preferred Term.

- Frequency tabulation of all TEAEs
- Frequency tabulation of TEAEs considered "related" to the study drug
- Frequency tabulation of all TEAEs by severity

- Frequency tabulation of TEAEs considered "related" to the study drug by severity
- Frequency tabulation of serious TEAEs
- Frequency tabulation of all TEAEs by vaccination and by timing of onset

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

The number of subjects to be vaccinated: 55

The objective of this study is to evaluate the immunogenicity and safety of two intramuscular vaccinations with BLB-750 in healthy Japanese adults. Therefore, the sample size for this study was determined to be 55 subjects, as the number of subjects to be vaccinated, by reference to the Notification issued by the Director of the Evaluation and Licensing Division of the Pharmaceutical and Food Safety Bureau on October 31, 2011: "Guidelines for the Development of Prototype Vaccines in Preparedness for Pandemic Influenza" [4]. There are no statistical rationales for the determination of this sample size.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the (e)CRFs. Source documents are defined as original documents, data, and records. The investigator and head of the study site guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, and review of (e)CRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviation

The investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from IRB. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the study site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the study site as soon as possible and an approval from IRB should be obtained.

The investigator should document all protocol deviations. Significant deviations from the protocol must be recorded on the (e)CRFs and reviewed by the sponsor or designee. Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare Products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and head of the study site guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB Approval

IRBs must be constituted according to the applicable local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study. The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will notify site once the sponsor has confirmed the adequacy of site regulatory documentation. Until the site receives [notification no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of the investigator's final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB approval of the informed consent form. The informed consent form must be approved by both the IRB and the sponsor prior to use.

The informed consent form must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

The subject must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject determines he or she will participate in the study, then the informed consent

form must be signed and dated by the subject at the time of consent and prior to the subject entering into the study. The subject should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator will also sign and date the informed consent form before the subject enters into the study.

Once signed, the original informed consent form will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's [e]CRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator.

The investigator needs to obtain a prior written approval from the sponsor to publish any information from the study externally such as to a professional association.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with the study site's name, city, country, and recruiting status will be registered and available for public viewing.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov and other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

[1] "National Action Plan for Pandemic Influenza and New Infectious Diseases" revised on June 7, 2013, http://www.cas.go.jp/jp/seisaku/ful/keikaku.html

[2] Menno D. de Jong, M.D., Ph.D., Tran Tan Thanh,et al. Oseltamivir Resistance during Treatment of Influenza A (H5N1) Infection. N Engl J Med. 2005;353:2667-2672.

[3] Takeda Pharmaceutical Company Limited. The Package Insert for Cell-Culture Influenza Vaccine (H5N1 strain) created in June 2017 (version 1)

[4] "Guidelines for the Development of Prototype Vaccines in Preparedness for Pandemic Influenza" (PFSB Notification No. 1031-[1] dated October 31, 2011)

[5] Thomas R., Robert A., Jean H., et al. Detection of Antibody to Avian Influenza A(H5N1) Virus in Human Serum by Using a Combination of Serologic Assays.J Clin Microbiol.April 1999;37(4):937-943.

[6] Iain S. , Karl G.,Anthony C., et al.Boosting immunity to influenza H5N1 with MF59-adjuvanted H5N3 A/Duck/Singapore/97 vaccine in a primed human population.ELSEVIER.April 2003;21(15):1687-1693

[7] Food and Drug Administration. Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent volunteers Enrolled in Preventive Vaccine Clinical Trials. U.S.Department of Health and Drug administration Center for Biologics Evaluation and Research. September 2007

Appendix A Schedule of Study Procedures

	Screening	Treatment				
Visit number	Visit 1		Visit 2			Visit 3/at discontinuation[12)]
Day[1)]	1	1 to 22	22		22 to 43	43/-
Days after the initial vaccination	0	0 to 21	21		21 to 42	42 (Visit 2 + 21)/-
Acceptable time window for visit (day)	-	-	+0 to 2		-	Visit 2 + 19 to Visit 2 + 23 /date of discontinuation + 28
	Pre-vaccination	Post-vaccination		Pre-vaccination	Post-vaccination		-
Informed Consent	X[2)]						
Demographics	X						
Past history, present illness, and prior treatments	X[3)]						
Height and weight	X						
Vital signs (blood pressure and pulse and respiratory rates)	X	X[4)]		X	X[4)]		X[5)]
Vital signs (body temperature [oral])	X		X[6) 7)]	X		X[6) 7)]	X
Pregnancy test[9)]	X						X
Physical examination	X	X[9)]		X	X[9)]		X
Eligibility assessment	X						
Enrollment	X						
Blood sampling (immunogenicity evaluation)[10)]	X			X			X
Vaccination with the study drug	X			X			
Diaries 1 and 2		To be provided	To be recorded	To be collected			(To be collected, if not yet collected)
Diaries 3 and 4					To be provided[11)]	To be recorded	To be collected
Adverse events	←	———	———	———	———	———	→
Concomitant medications	←	———	———	———	———	———	→

1) The day before vaccination with the study drug is defined as Day -1, and the day of vaccination with the study drug (Visit 1) is defined as Day 1.
2) Informed consent must be obtained before any study procedure is performed. Informed consent is considered valid if it is obtained within 28 days prior to Visit 1 (Day -28).
3) Prior treatments include those given before signing the informed consent form, and past history and present illness include those occurring before the first vaccination of study drug.
4) On the day of vaccination with study drug, blood pressure, pulse rate, and respiratory rate will be measured before vaccination and approximately 30 minutes after vaccination.
5) No respiratory rate measurement will be required at Day 43 and at discontinuation.
6) Among vital signs, body temperature will be measured by each subject every day in the evening wherever possible for 7 days after vaccination (after vaccination on Day 1 until Day 7 and after vaccination on Day 22 until Day 28) and be recorded in the diary provided to each subject.

7) During Days 8-22 (before study visit) and Days 29-43 (before study visit), body temperature will be measured by each subject and be recorded in the diary provided to each subject only if any symptom of pyrexia occurs. Measurements should be obtained approximately every 4-8 hours until the pyrexia resolves and should be recorded in the diary.
8) Pregnancy test will be performed in female subjects of childbearing potential.
9) The investigator will monitor for any acute hypersensitivity reaction, etc., for 30 minutes after vaccination.
10) Blood sampling should be performed after vital sign measurement.
11) Provision of Diaries 3 and 4 may take place at Visit 1.
12) The study discontinuation visit should be performed wherever possible.

Appendix B Responsibilities of the Investigator

1. Conduct the appropriate study in accordance with the protocol and GCP considering the rights, safety and wellbeing of human subjects.
2. When a part of the important activities related to the study are delegated to the investigator or the study collaborator, prepare the lists of activities to be delegated and responsible personnel, submit the lists to the director of the site in advance to get them accepted.
3. Prepare a written informed consent form and other written information, and update as appropriate.
4. Confirm the contents of the clinical study agreement.
5. Provide necessary information on the protocol, medications and responsibilities of individual personnel to the investigator and study collaborator, and provide guidance and supervision.
6. Screen subjects who meet the requirements of the protocol, provide the explanation of the study in writing and obtain the written consent.
7. Assume responsibility for all the medical judgement related to the study.
8. Ensure in collaboration with the director of the site that sufficient information on all clinically significant adverse events related to the study are provided to subjects throughout and beyond the period when subjects participate in the study.
9. If a subject consults other medical institution or other department, notify the physician of the medical institution or department of the subject's participation in the study upon obtaining the consent of the subject, as well as the end and termination of the study in writing, and document such records.
10. In case of urgent report of a SAE, immediately notify the director of the site and the sponsor in writing.
11. Prepare correct and complete (e)CRFs, and submit them to the sponsor with electronic signature.
12. Check and confirm the contents of (e)CRFs prepared by the investigator or transcribed from the source data by the study collaborator, and submit them to the sponsor with electronic signature.
13. Discuss any proposal from the sponsor including update of the protocol.
14. Notify the director of the site of the end of the study in writing.

Appendix C Details of Amendments

Specific changes in the amended protocol are described below.

Section 2.0 (Exclusion Criteria) on Page 9 and Section 7.2 on Page 21

After change

25. The subject has thrombocytopenia or coagulopathy, or is currently receiving anticoagulant therapy or received anticoagulant therapy within 30 days prior to the first vaccination with the study vaccine.

Reason for the change

Addition of an exclusion criterion to reflect the revised package insert with additional precautionary text.

Section 7.2 on Page 21

Before change

Criteria 11, 15, 16, 21, 22, *and* 23 were selected to ensure the safety of subjects.

After change

Criteria 11, 15, 16, 21, 22, 23, **and 25** were selected to ensure the safety of subjects.

Reason for the change

Addition of an exclusion criterion to reflect the revised package insert with additional precautionary text.

Section 7.3 (Table 7.a) on Page 23

Before change

- Systemic or high-dose inhaled corticosteroids (beclomethasone dipropionate >800 μg/day or equivalent)
- Radiotherapy
- Immunosuppressives
- Cytotoxic drugs

After change

- Systemic or high-dose inhaled corticosteroids (beclomethasone dipropionate >800 μg/day or equivalent)
- Radiotherapy
- Immunosuppressives
- Cytotoxic drugs
- **Anticoagulant therapy**

Reason for the change

Addition of anticoagulant therapy to the list of excluded medications and treatments to reflect the revised package insert with additional precautionary text.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Science Approval	19-Jan-2018 03:55 UTC

Post-marketing Study Protocol

<Title>

A Phase 4, Open-label Study to Evaluate
the Immunogenicity and Safety of Intramuscular Injections of BLB-750 in Healthy Adult Subjects

<Short Title>

A Phase 4 Post-marketing Study of Intramuscular Injections of BLB-750 in Healthy Adult Subjects

Name of Sponsor	Takeda Pharmaceutical Company Limited 1-1, Doshomachi 4-chome, Chuo-ku, Osaka		
Protocol number	BLB-750/CCT-901		
IND Number	Not applicable	**EudraCT Number**	Not applicable
Compound	BLB-750 (Cell-Culture Influenza Vaccine H5N1 “Takeda” 1 mL)		
Date:	25 Oct 2017	**Version Number**	Amendment 01

1.0 ADMINISTRATIVE INFORMATION AND PRINCIPLES OF CLINICAL STUDIES

1.1 Contacts and Responsibilities of Study-Related Activities

See the attachments.

1.2 Principles of Clinical Studies

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

1.3 Summary of Changes in the Amended Protocol

The changes in the amended version of the protocol are described below.

The key changes in this amended protocol are summarized below. Details of the changes are described in Appendix C.

1. The study is conducted in an open-label manner, not a randomized, double-blind, parallel-group comparative manner.
   Reason for the change: Because of changes to the study objectives, the study design was changed from a randomized study to an open-label study.
2. This study uses a single group, not three groups.
   Reason for the change: Because of changes to the study objectives, the number of the groups was changed from three to one.
3. Only BLB-750 (Qinghai RG strain) is used as the study drug.
   Reason for the change: Because the number of the groups was changed from three to one due to changes to the study objectives.
4. Deletion of the secondary objectives.
   Reason for the change: Because the number of the groups was changed from three to one due to changes to the study objectives.

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2.0 STUDY SUMMARY

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Takeda Pharmaceutical Company Limited</td><td colspan="2">Study Drug
BLB-750 (Cell-Culture Influenza Vaccine H5N1 “Takeda” 1 mL)</td></tr>
<tr><td colspan="2">Title of Protocol: A Phase 4, Open-label Study to Evaluate the Immunogenicity and Safety of Intramuscular Injections of BLB-750 in Healthy Adult Subjects</td><td>IIND Number: Not applicable</td><td>EudraCT Number: Not applicable</td></tr>
<tr><td colspan="2">Study Number: BLB-750/CCT-901</td><td colspan="2">Phase: 4</td></tr>
<tr><td colspan="4">Study Design:
This is a phase 4, Open-label study to evaluate the immunogenicity and safety of two intramuscular vaccinations with BLB-750 at a 3-week interval in healthy Japanese adults.
Participants considered eligible as subjects for the study during the eligibility assessment at a visit after providing informed consent will receive the initial intramuscular vaccination with the study drug BLB-750 (Day 1) and the second intramuscular vaccination with BLB-750 during the study visit at 21 days after the initial vaccination (Day 22).
The study duration will be 43 days, starting on the day of initial vaccination (Day 1). Subjects will return to the study site 21 days after the initial vaccination (Day 22) and 21 days after the second vaccination (Day 43).
The total planned number of subjects to receive the study vaccination is 55.</td></tr>
<tr><td colspan="4">Objectives:
To evaluate the immunogenicity and safety of two intramuscular vaccinations with BLB-750 in healthy Japanese adults</td></tr>
<tr><td colspan="4">Study Population: Healthy Japanese adults (male or female)</td></tr>
<tr><td colspan="2">Planned Number of Subjects:
BLB-750: 55 subjects</td><td colspan="2">Planned Number of Study Sites:
1 institution</td></tr>
<tr><td colspan="2">Dose Level(s):
Two doses of BLB-750 at 0.5 mL (HA antigen level of 7.5 μg) will be injected into the upper arm muscle (the deltoid muscle) at a 3-week interval.
As the manufacturing strain for BLB-750, the following attenuated strain (H5N1 influenza virus attenuated using reverse genetics technology) will be used:
● Qinghai RG strain
[A/bar-headed goose/Qinghai/1A/2005(H5N1)
(SJRG-163222)]</td><td colspan="2">Vaccination Route:
Intramuscular injection</td></tr>
<tr><td colspan="2">Duration of Vaccination:
Two doses at a 3-week interval</td><td colspan="2">Period of Evaluation:
43 days</td></tr>
</table>

Inclusion Criteria

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form prior to the initiation of any study procedures.
3. The subject is a healthy Japanese adult man or woman.
4. The subject is aged 20 to 49 years, inclusive, at the time of informed consent.
5. A female subject of childbearing potential who is sexually active with a nonsterilized male partner agrees to use routinely adequate contraception from signing of informed consent throughout the duration of the study.

Exclusion Criteria

1. The subject has received vaccination with any other investigational or study products within 4 months prior to vaccination with the study vaccine.
2. The subject has a history of vaccination with an H5N1 influenza vaccine.
3. The subject has a history of infection with H5N1 virus.
4. The subject is at high risk of contracting H5N1 influenza infection (e.g., poultry workers).
5. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (e.g., spouse, parent, child, sibling) or may consent under duress.
6. The subject has poorly controlled, clinically significant manifestations of neurological, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, endocrine, or other disorders, which may impact their ability to participate as subjects or may potentially confound the study results.
7. The subject has a body temperature (oral) ≥37.5°C prior to vaccination with the study vaccine on Day 1.
8. The subject has any medically diagnosed or suspected immune-deficiency condition.

9. The subject has an immunocompromising condition or disease, or is currently undergoing a form of treatment or was undergoing a form of treatment that can be expected to influence immune response within 30 days prior to vaccination with the study vaccine.
   Such treatments include, but are not limited to, systemic or high dose inhaled corticosteroids (>800 µg/day of beclomethasone dipropionate or equivalent; the use of inhaled and nasal steroids that do not exceed this level will be permitted), radiation treatment or other immunosuppressive or cytotoxic drugs.
10. The subject has received antipyretics within 4 hours prior to vaccination with the study vaccine.
11. The subject has a history of Guillain-Barré Syndrome, demyelinating disorders (including acute disseminated encephalomyelitis [ADEM] and multiple sclerosis), or convulsions.
12. The subject has a functional or anatomic asplenia.
13. The subject has a rash, other dermatologic conditions or tattoos that may interfere with the evaluation of local reaction.
14. The subject has a past or present history of infection with the Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) or Human Immunodeficiency Virus (HIV).
15. The subject has a known hypersensitivity to any component of BLB-750.
16. The subject has a history of severe allergic reactions or anaphylaxis.
17. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol dependence within 1 year prior to vaccination with the study vaccine or is unwilling to agree to abstain from excessive alcohol and drugs throughout the study.
18. The subject has received any blood product (e.g., blood transfusion or immunoglobulin) within 90 days prior to vaccination with the study vaccine.
19. The subject has received any live vaccine within 4 weeks (28 days) prior to vaccination with the study vaccine or any inactivated vaccine within 2 weeks (14 days) prior to vaccination with the study vaccine.
20. The subject is a pregnant or lactating woman or wishes to become pregnant before signing informed consent, during, or within 12 weeks after the last vaccination with the study vaccine or intends to donate ova during such time period
21. For males: The subject has donated whole blood ≥200 mL within 4 weeks (28 days) or ≥400 mL within 12 weeks (84 days) prior to the first vaccination with the study vaccine.

    For females: The subject has donated whole blood ≥200 mL within 4 weeks (28 days) or ≥400 mL within 16 weeks (112 days) prior to the first vaccination with the study vaccine.
22. For males: The subject has donated whole blood ≥800 mL in total within 52 weeks (364 days) prior to the first vaccination with the study vaccine.

    For females: The subject has donated whole blood ≥400 mL in total within 52 weeks (364 days) prior to the first vaccination with the study vaccine.
23. The subject has donated blood components within 2 weeks (14 days) prior to the first vaccination with the study vaccine.
24. In the opinion of the investigator, the subject is unlikely to comply with protocol requirements or is considered ineligible for any other reason.

Main Criteria for Evaluation and Analyses:

[Primary Endpoints]

Immunogenicity:

- Seroprotection rate as measured by SRH antibody titer (defined as the proportion of subjects with SRH antibody titer ≥25 mm^2) for the vaccine strain at 21 days after the second vaccination
- Seroconversion rate as measured by SRH antibody titer (defined as the proportion of subjects with a 50% or more increase in SRH antibody titer from baseline for those who have a baseline value >4 mm^2 or SRH antibody titer ≥25 mm^2 for those who have a baseline value ≤4 mm^2) for the vaccine strain at 21 days after the second vaccination
- Geometric mean fold increase (GMFI) in SRH antibody titer from baseline for the vaccine strain at 21 days after the second vaccination

[Secondary Endpoints]

Immunogenicity:

- Seroprotection rate as measured by SRH antibody titer (defined as the proportion of subjects with SRH antibody titer ≥25 mm^2) for the vaccine strain at 21 days after the initial vaccination
- Seroconversion rate as measured by SRH antibody titer (defined as the proportion of subjects with a 50% or more increase in SRH antibody titer from baseline for those who have a baseline value >4 mm^2 or SRH antibody titer ≥25 mm^2 for those who have a baseline value ≤4 mm^2) for the vaccine strain at 21 days after the initial vaccination
- GMFI in SRH antibody titer from baseline for the vaccine strain at 21 days after the initial vaccination
- Geometric mean titer (GMT) of SRH antibody titer for the vaccine strain at 21 days after each vaccination

Safety:

- Solicited local and systemic adverse events (AEs) to be recorded in the subject diary
- AEs
- Vital signs

[Additional Endpoints]

Immunogenicity:

- Seroprotection rate as measured by MN antibody titer (defined as the proportion of subjects with MN antibody titer ≥20) for the vaccine strain at 21 days after each vaccination
- Seroconversion rate as measured by MN antibody titer (defined as the proportion of subjects with 4-fold or more increase in MN antibody titer from baseline) for the vaccine strain at 21 days after each vaccination
- GMFI in MN antibody titer from baseline for the vaccine strain at 21 days after each vaccination
- GMT of MN antibody titer for the vaccine strain at 21 days after each vaccination

Statistical Considerations:

[Immunogenicity] Using the full analysis set (FAS), frequency tabulations of the SRH antibody titer and the seroprotection and seroconversion rates at 21 days after the second vaccination will be presented, and their point estimates and two-sided 95% confidence intervals will be calculated. For the GMFI in the SRH antibody titer at 21 days after the second vaccination, summary statistics and geometric means with corresponding two-sided 95% confidence intervals of the fold increase in the SRH antibody titer from baseline will be calculated.

Two-sided 95% confidence intervals of the geometric means will be calculated by back-transforming the upper and lower limits of two-sided 95% confidence intervals of the log transformed mean values.

[Safety] Using the safety analysis set, the following analyses will be performed:

For injection site and systemic AEs to be collected in the diary, frequency tabulations, frequency tabulations by severity, and frequency tabulations by vaccination and by timing of onset will be presented.

Treatment-emergent adverse events (TEAEs) are defined as AEs observed after vaccination with the study drug.

For TEAEs, the following analyses will be performed: TEAEs will be coded using the MedDRA and be summarized by System Organ Class and Preferred Term.

- Frequency tabulation of all TEAEs
- Frequency tabulation of TEAEs considered “related” to the study drug
- Frequency tabulation of all TEAEs by severity
- Frequency tabulation of TEAEs considered “related” to the study drug by severity
- Frequency tabulation of serious TEAEs
- Frequency tabulation of all TEAEs by vaccination and by timing of onset

Rationales for the Determination of Sample Size:

The objective of this study is to evaluate the immunogenicity and safety of two intramuscular vaccinations with BLB-750 in healthy Japanese adults. Therefore, the sample size for this study was determined to be 55 subjects, as the number of subjects to be vaccinated, by reference to the “Guidelines for the Development of Prototype Vaccines in Preparedness for Pandemic Influenza.” There are no statistical rationales for the determination of this sample size.

3.0 LIST OF ABBREVIATIONS

ADEM	acute disseminated encephalomyelitis
AE	adverse event
CRO	contract research organization
EDC	electronic data capture
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GMT	geometric mean titer
HA	hemagglutinin
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MN	microneutralization
PMDA	Pharmaceuticals and Medical Devices Agency
SAE	serious adverse event
SRH	single radial hemolysis
SUSARs	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

In Japan's National Action Plan for Pandemic Influenza and New Infectious Diseases [1], pandemic influenza is defined as "an influenza infectious disease in humans caused by newly emerging influenza virus as an etiological agent that acquires the ability of human-to-human transmission." Especially, there are concerns that when the highly pathogenic avian influenza virus H5N1 newly acquires the ability of human-to-human transmission and causes pandemic influenza (H5N1), it can constitute an enormous health hazard due to its high mortality rate. At present, therapeutic strategies for the treatment of pandemic influenza (H5N1) may include administration of anti-influenza virus drugs, such as oseltamivir phosphate and zanamivir hydrate. However, fatality due to acquired drug resistance during the treatment with oseltamivir phosphate has been suggested [2], which warrants the consideration of potential emergence of resistant virus strains before the use of anti-influenza virus drugs. In August 2004, a report by a subcommittee for the review of measures against pandemic influenza of the Section of Infectious Diseases, Health Sciences Council of the Ministry of Health, Labour and Welfare (MHLW) was prepared, in which the development, production, and stabilization of the supply of pandemic influenza vaccines are listed as primary aspects of measures against pandemic influenza.

Takeda Pharmaceutical Company Limited and PPD co-developed a vaccine indicated for "the prevention of pandemic influenza (H5N1)", and approval for the manufacture and marketing of Cell-Culture Influenza Vaccines H5N1 "CCI" and "Takeda" 5 mL was obtained June 2013 (approval withdrawn in September 2016). In March 2014, Takeda Pharmaceutical Company Limited obtained approval for the manufacture and marketing of Cell-Culture Influenza Vaccine H5N1 "Takeda" 1 mL. BLB-750 is an influenza vaccine containing inactivated whole influenza virions as an active ingredient. It is produced by inactivating influenza (H5N1 subtype) viruses that infected and replicated in cultured cells using formaldehyde treatment and ultraviolet irradiation.

4.1.1 Benefit/Risk Profile

Currently there is no established treatment available for pandemic influenza (H5N1), and viral drug resistance associated with the use of anti-influenza virus drugs has been reported. Therefore, it is considered extremely important to prevent the development or aggravation of influenza infectious diseases through vaccination. BLB-750 has been shown to be effective for the prevention of the development of influenza infectious diseases in mice and ferrets. In addition, clinical study results show that the vaccine is immunogenic. Based on these findings, it is expected that vaccination with BLB-750 will be useful for the prevention of the development or aggravation of pandemic influenza (H5N1).

BLB-750 may also be suitable as a vaccine prepared for a pandemic possibly caused by the H5N1 subtype for the following reasons: cell culture technology is applied for the manufacturing of the vaccine, which requires less time for vaccine production than other vaccines manufactured using chicken egg culture method; the manufacturing of BLB-750 is not affected by the availability of chicken eggs; and BLB-750 can be used in those who are allergic to hen's egg.

Frequently observed adverse events of BLB-750 in clinical studies of the vaccine include transient pain, bleeding, and induration for injection site reactions, and headache, fatigue, malaise, hyperhidrosis, myalgia, chills, oropharyngeal pain, pyrexia, and arthralgia for systemic reactions, with no major issues in terms of the tolerability or safety. The safety profile of BLB-750 is similar to that of existing seasonal influenza vaccines, and there considered to be no specific risk associated with vaccination with BLB-750. Although results from clinical studies of BLB-750 indicate the immunogenicity of BLB-750, it may not be effective for the prevention of pandemic influenza (H5N1) in all subjects due to various factors, including differences in the immunoreactivity among vaccinated individuals and between prevalent virus strains and the vaccine strain.

4.2 Rationale for the Proposed Study

As required by the MHLW, a strain attenuated using reverse genetics technology must be used as an H5N1 subtype virus strain for the production of pre-pandemic vaccine stockpiles as one of measures against pandemic influenza.

Clinical studies in Japanese adults for the purpose of the application for the approval of a cell-culture influenza vaccine (H5N1 strain) and clinical studies in the Japanese elderly and in children were conducted using a vaccine manufactured using a wild type strain as an H5N1 subtype virus strain, and there is no clinical experience with a vaccine manufactured using an attenuated strain.

Therefore, we planned a phase 4, open-label study to evaluate the immunogenicity and safety of two intramuscular vaccinations with BLB-750 at a 3-week interval in healthy Japanese adults, in which a cell-culture influenza vaccine (H5N1 strain) manufactured using an attenuated strain will be used..

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

To evaluate the immunogenicity and safety of two intramuscular vaccinations with BLB-750 in healthy Japanese adults

5.2 Endpoints

5.2.1 Primary Endpoints

Immunogenicity:

- Seroprotection rate as measured by SRH antibody titer (defined as the proportion of subjects with SRH antibody titer ≥25 mm^2) for the vaccine strain at 21 days after the second vaccination
- Seroconversion rate as measured by SRH antibody titer (defined as the proportion of subjects with a 50% or more increase in SRH antibody titer from baseline for those who have a baseline value >4 mm^2 or SRH antibody titer ≥25 mm^2 for those who have a baseline value ≤4 mm^2) for the vaccine strain at 21 days after the second vaccination
- Geometric mean fold increase (GMFI) in SRH antibody titer from baseline for the vaccine strain at 21 days after the second vaccination

5.2.2 Secondary Endpoints

Immunogenicity:

- Seroprotection rate as measured by SRH antibody titer (defined as the proportion of subjects with SRH antibody titer ≥25 mm^2) for the vaccine strain at 21 days after the initial vaccination
- Seroconversion rate as measured by SRH antibody titer (defined as the proportion of subjects with a 50% or more increase in SRH antibody titer from baseline for those who have a baseline value >4 mm^2 or SRH antibody titer ≥25 mm^2 for those who have a baseline value ≤4 mm^2) for the vaccine strain at 21 days after the initial vaccination
- GMFI in SRH antibody titer from baseline for the vaccine strain at 21 days after the initial vaccination
- Geometric mean titer (GMT) of SRH antibody titer for the vaccine strain at 21 days after each vaccination

Safety:

- Solicited local and systemic adverse events (AEs) to be recorded in the subject diary
- AEs
- Vital signs

5.2.3 Additional Endpoints

Immunogenicity:

- Seroprotection rate as measured by MN antibody titer (defined as the proportion of subjects with MN antibody titer ≥20) for the vaccine strain at 21 days after each vaccination
- Seroconversion rate as measured by MN antibody titer (defined as the proportion of subjects with 4-fold or more increase in MN antibody titer from baseline) for the vaccine strain at 21 days after each vaccination

- GMFI in MN antibody titer from baseline for the vaccine strain at 21 days after each vaccination
- GMT of MN antibody titer for the vaccine strain at 21 days after each vaccination

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 4, open-label study to evaluate the immunogenicity and safety of two intramuscular vaccinations with BLB-750 at a 3-week interval in healthy Japanese adults.

Subjects considered eligible after providing informed consent will receive the initial intramuscular vaccination with the study drug BLB-750 (Day 1) and the second intramuscular vaccination with BLB-750 during the study visit at 21 days after the initial vaccination (Day 22).

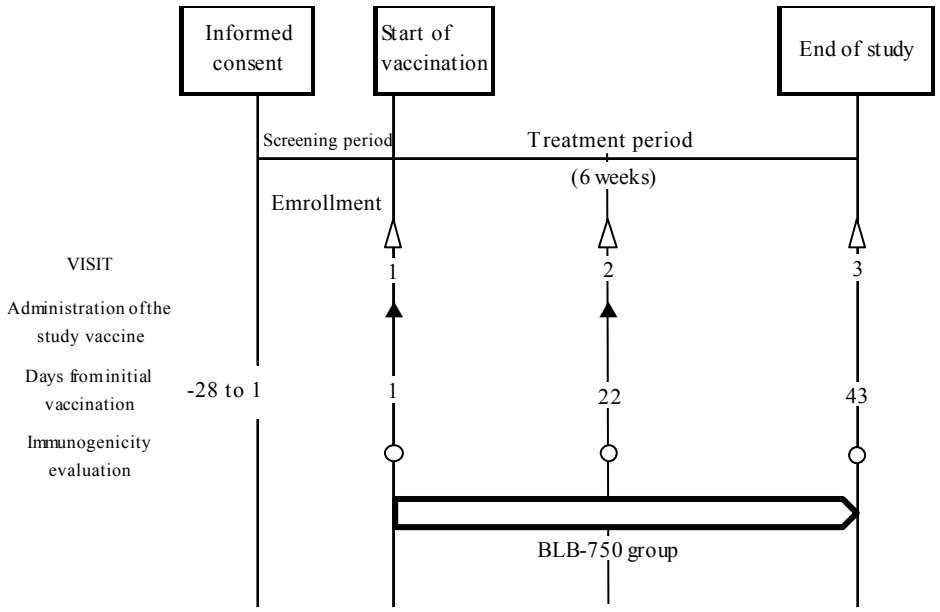
The study duration will be 43 days, starting on the day of initial vaccination (Day 1). Subjects will return to the study site 21 days after the initial vaccination (Day 22) and 21 days after the second vaccination (Day 43).

The total planned number of subjects to receive the study vaccination is 55.

A schematic of the study design is shown in Figure 6.a

For the testing, observations, and assessment schedule, see Appendix A

Figure 6.a Schematic of Study Design



6.2 Rationales for the Selection of Study Design, Vaccination Dosage, and Endpoints

6.2.1 Rationales for the Selection of Study Design

This study has been designed to evaluate the immunogenicity and safety of BLB-750 given intramuscularly in two doses at an interval of 3 weeks (open-label, uncontrolled study).

Clinical studies in Japanese adults for the purpose of the application for the approval of a cell-culture influenza vaccine (H5N1 strain) and clinical studies in the Japanese elderly and in children were conducted using a vaccine manufactured using a wild type strain as an H5N1 subtype virus strain. For this study, healthy adults were selected as a study population because the immunogenicity and safety of vaccination with a vaccine manufactured using an attenuated strain as an H5N1 subtype virus strain will be evaluated. For an age group for the study, a population

aged between 20 and 49 years was selected as a 20 years and older age group, which was not considered to have a major difference in immunogenicity within the group.

6.2.2 Rationales for the Selection of Vaccination Dosage Regimen and Strain

The package insert [3] specifies the dosage regimen of the cell-culture influenza vaccine (H5N1 strain) as "usually two doses of 0.5 mL should be intramuscularly or subcutaneously injected with an at least 3-week interval," and "as a general rule, intramuscular injection should be used as a vaccination route, with an exception in which subcutaneous injection may be selected based on the state of the subject". Thus, in accordance with the approved dosage regimen, the dosage regimen of BLB-750 in this study was selected to be two doses of 0.5 mL of BLB-750 with the HA content of 7.5 μg as an H5N1 subtype virus strain to be intramuscularly injected at a 3-week interval.

As described in Section 8.1.1.1, BLB-750 (Qinghai RG strain) was selected as the H5N1 subtype virus strain for BLB-750 to be used in this study.

6.2.3 Rationales for the Selection of Endpoints

Immunogenicity

To evaluate the immunogenicity against H5N1 subtype viruses of two intramuscular vaccinations of BLB-750, three endpoints as measured by the SRH antibody titer (seroprotection and seroconversion rates and geometric mean fold increase) specified as immunogenicity endpoints in the Guidelines for the Development of Prototype Vaccines in Preparedness for Pandemic Influenza [4] were selected as primary endpoints. Secondary endpoints included three endpoints as measured by the SRH antibody titer after the initial vaccination with BLB-750 (seroprotection and seroconversion rates and geometric mean fold increase) and the GMT of the SRH antibody titer after each vaccination. Additional endpoints were also selected to perform the exploratory evaluation of the MN antibody titer considered sensitive and specific in the detection of functional/protective antibodies against avian influenza strains [5][6].

Safety

Based on common side effects of influenza vaccines and results of previously conducted overseas clinical studies (with BLB-750 given intramuscularly) and Japanese clinical studies (with BLB-750 given intramuscularly and subcutaneously), injection site reactions (injection site pain, erythema, swelling, induration, and bleeding) and systemic reactions (pyrexia, malaise, chills, fatigue, headache, sweaty, myalgia, and arthralgia) have been reported as expected adverse reactions to BLB-750 vaccination. Data on the occurrence of these events during the study period (especially within 7 days after vaccination) will be collected using a subject diary. As in previously conducted overseas and Japanese studies, the severity of pyrexia and injection site reactions will be assessed by reference to the "FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" [7] (see Section 9.1.11). As safety endpoints commonly used in clinical studies, adverse events and vital signs will also be evaluated.

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the product, such that the risk is no longer acceptable for subjects participating in the study.

Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Site(s)

In the event that the sponsor, an institutional review board (IRB) or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to enrollment in the study.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form prior to the initiation of any study procedures.
3. The subject is a healthy Japanese adult man or woman.
4. The subject is aged 20 to 49 years, inclusive, at the time of informed consent.
5. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use routinely adequate contraception from signing of informed consent throughout the duration of the study.

> *Definitions and acceptable methods of contraception are defined in Section 9.1.8 and reporting responsibilities are defined in Section 9.1.9.

Rationale for the selection of inclusion criteria

Criteria 1 to 5 were selected as standard conditions for the selection of subjects participating in a clinical study in healthy adults. The upper limit of age was determined to be 49 years, which was not considered to make a major difference in immunogenicity within the 20-years-and-older age group.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has received vaccination with any other investigational or study products within 4 months prior to vaccination with the study vaccine.
2. The subject has a history of vaccination with an H5N1 influenza vaccine.
3. The subject has a history of infection with H5N1 virus.
4. The subject is at high risk of contracting H5N1 influenza infection (e.g., poultry workers).
5. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (e.g., spouse, parent, child, sibling) or may consent under duress.
6. The subject has poorly controlled, clinically significant manifestations of neurological, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, endocrine, or other disorders, which may impact their ability to participate as subjects or may potentially confound the study results.
7. The subject has a body temperature (oral) ≥37.5°C prior to vaccination with the study vaccine on Day 1.
8. The subject has any medically diagnosed or suspected immune-deficiency condition.
9. The subject has an immunocompromising condition or disease, or is currently undergoing a form of treatment or was undergoing a form of treatment that can be expected to influence immune response within 30 days prior to vaccination with the study vaccine.
   Such treatments include, but are not limited to, systemic or high dose inhaled corticosteroids (>800 μg/day of beclomethasone dipropionate or equivalent; the use of inhaled and nasal steroids that do not exceed this level will be permitted), radiation treatment or other immunosuppressive or cytotoxic drugs.

10. The subject has received antipyretics within 4 hours prior to vaccination with the study vaccine.
11. The subject has a history of Guillain-Barré Syndrome, demyelinating disorders (including acute disseminated encephalomyelitis [ADEM] and multiple sclerosis), or convulsions.
12. The subject has a functional or anatomic asplenia.
13. The subject has a rash, other dermatologic conditions or tattoos that may interfere with the evaluation of local reaction.
14. The subject has a past or present history of infection with the Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) or Human Immunodeficiency Virus (HIV).
15. The subject has a known hypersensitivity to any component of BLB-750.
16. The subject has a history of severe allergic reactions or anaphylaxis.
17. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol dependence within 1 year prior to vaccination with the study vaccine or is unwilling to agree to abstain from excessive alcohol and drugs throughout the study.
18. The subject has received any blood product (e.g., blood transfusion or immunoglobulin) within 90 days prior to vaccination with the study vaccine.
19. The subject has received any live vaccine within 4 weeks (28 days) prior to vaccination with the study vaccine or any inactivated vaccine within 2 weeks (14 days) prior to vaccination with the study vaccine.
20. The subject is a pregnant or lactating woman or wishes to become pregnant before signing informed consent, during, or within 12 weeks after the last vaccination with the study vaccine or intends to donate ova during such time period
21. For males: The subject has donated whole blood ≥200 mL within 4 weeks (28 days) or ≥400 mL within 12 weeks (84 days) prior to the first vaccination with the study vaccine.

    For females: The subject has donated whole blood ≥200 mL within 4 weeks (28 days) or ≥400 mL within 16 weeks (112 days) prior to the first vaccination with the study vaccine.
22. For males: The subject has donated whole blood ≥800 mL in total within 52 weeks (364 days) prior to the first vaccination with the study vaccine.

    For females: The subject has donated whole blood ≥400 mL in total within 52 weeks (364 days) prior to the first vaccination with the study vaccine.
23. The subject has donated blood components within 2 weeks (14 days) prior to the first vaccination with the study vaccine.
24. In the opinion of the investigator, the subject is unlikely to comply with protocol requirements or is considered ineligible for any other reason.

Rationale for the selection of exclusion criteria

Criterion 1 was selected, by reference to the "General Considerations for Clinical Trials" (PFSB/ELD Notification No. 380 dated April 21, 1998), to ensure the safety of subjects with the use of the period during which the previous study would not affect the present study.

Criteria 2, 3, 4, 8, 9, 12, 18, and 19 were selected to eliminate the possible impact on influenza vaccine evaluation (primarily immunogenicity evaluation).

Criteria 5, 6, 14, 17, 20, and 24 were selected as standard conditions for the selection of subjects participating in a clinical study in healthy adults.

Criteria 7 and 13 were selected to eliminate the possible impact on influenza vaccine evaluation (primarily safety evaluation).

Criterion 10 was selected to eliminate the possible impact on influenza vaccine evaluation (safety and immunogenicity evaluation).

Criteria 11, 15, 16, 21, 22, and 23 were selected to ensure the safety of subjects.

7.3 Excluded Medications and Treatments

The use of medications and therapies shown in Table 7.a will be prohibited from the point specified in the table to the end of study.

Table 7.a Excluded Medications and Treatments

In the past	4 months prior to vaccination (Day 1)	90 days prior to vaccination (Day 1)	30 days prior to vaccination (Day 1)	28 days prior to vaccination (Day 1)	14 days prior to vaccination (Day 1)
• H5N1 influenza vaccines	• Other study medications	• Blood products (transfusion or immunoglobulin)	• Systemic or high-dose inhaled corticosteroids (beclomethasone dipropionate >800 µg/day or equivalent) • Radiotherapy • Immunosuppressives • Cytotoxic drugs	• Live vaccines	• Inactivated vaccines

The investigator will instruct subjects not to take any drug (including OTC drugs) other than those prescribed by the investigator without consulting with the investigator.

7.4 Diet, Fluid, Activity Control

1. Diet

   Subjects should be abstemious during the study period.

2. Drinking

   Excessive consumption of alcohol-containing beverages should be avoided during the study period.

3. Smoking

   Smoking will be prohibited from 1 hour prior to each assessment to the end of assessment.

4. Exercise

   Excessive exercise will be prohibited during the study period.

5. Blood donation after the end of study

Blood donation will be prohibited for at least 12 weeks after the completion of final assessment in this study. The investigator will provide subjects with counseling on the prohibition of blood donation.

6. Others

   The investigator will instruct subjects that if they visit another medical institution during the study period, they must inform the investigator of the reason for the visit and treatments given and must inform the institution of their participation in this study.

   The investigator will also instruct subjects to keep the study drug injection site clean and to avoid scratching or rubbing the injection site without good reason.

   For female subjects of childbearing potential who are sexually active with a nonsterilized male partner, the investigator will instruct them to use adequate contraception from the time of signing of informed consent, throughout the duration of the study, and for 12 weeks after the last vaccination with the study drug.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the case report form ([e]CRF) using the following categories. For subjects who discontinue/is withdrawn before enrollment in this study, see 9.1.12

1. Death
   The subject dies during the study.
   Note: If the subject dies on study, the event will be considered as a serious adverse event (SAE). See Section 10.2.2 for the reporting procedures.
2. Adverse event (AE)
   The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the AE.
3. Protocol deviation
   The discovery after enrollment that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
4. Lost to follow-up
   The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
5. Withdrawal by the subject
   The subject wishes to be withdrawn from the study. The reason for withdrawal, if provided, should be recorded in the (e)CRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded. In the case of withdrawal due to an AE, however, consideration should be given to classifying it as "AE(s)" rather than as "voluntary withdrawal by the subject."
6. Study Terminated by sponsor.
   The sponsor terminates the study.
7. Pregnancy
   The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn from the study immediately. The procedure is described in Section 9.1.9.
8. Other

   Note: The specific reasons should be recorded in the "specify" field of the (e)CRF.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5 In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit. Subjects who are withdrawn from the study after receiving vaccination with the study drug will not be replaced.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all medication and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

The study drug in this protocol is defined below.

8.1.1.1 Study Drug

1. Dosage form and dose strength
   Substance code: BLB-750
   Trade name: Cell-Culture Influenza Vaccine H5N1 "Takeda" 1 mL
   Manufacturer: Takeda Pharmaceutical Company Limited
   Dosage form: A clear to whitish liquid injection (vial)
   Components and dose strength: One vaccination dosage of 0.5 mL contains components shown in Table 8.a.

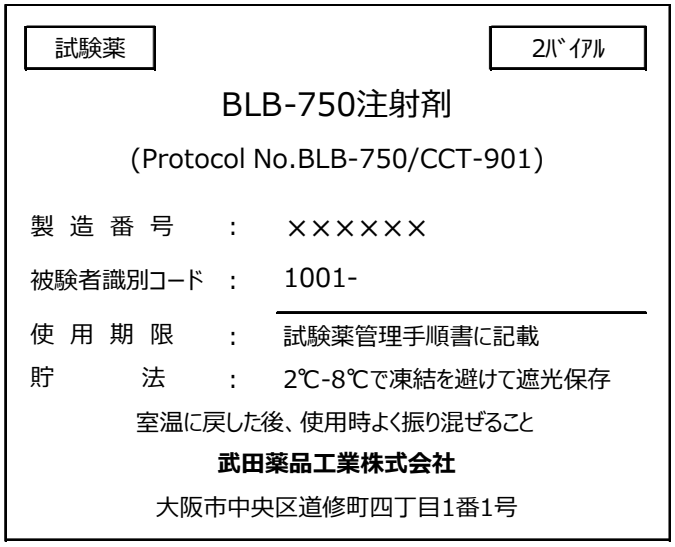
Table 8.a Components and Dose Strength of BLB-750 Injection 0.5 mL

	Component	Dose strength	Function
Active ingredient (vaccine strain)	BLB-750 Qinghai RG strain [A/bar-headed goose/Qinghai/1A/2005 (H5N1) (SJRG-163222)]	7.5 µg	-
Inactive ingredient	Trometamol	1.2 mg	Buffer
	Sodium chloride	4.0 mg	Isotonicifier
	Polysorbate 80	0.63 mg	Aggregation preventer

2. Packaging and labeling
   Two vials of the study drug will be packaged in a box labeled with the following information.

<front side of the box>

Figure 8.a Labeling Sample of the Outer Box for the Study Drug



8.1.1.2 Ancillary Materials

The syringe and injection needle designated by the sponsor should be used for vaccination with the study drug.

8.1.2 Storage

The study drug should be stored at 2°C to 8°C but not frozen, and be protected from light.

The site designee must keep the study drug in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee (CRO) . All drugs supplied by the sponsor must be stored under the conditions specified on the label. A daily temperature log of the drug storage area must be maintained every working day.

8.1.3 Dose and Regimen

According to the following procedures, two doses of the study drug 0.5 mL will be injected into the brachial muscle (deltoid muscle) on Days 1 and 22.

- Let the study drug (vial) warm to room temperature.
- Prior to administration, shake the vial for 5-10 seconds to mix the vaccine suspension completely.
- Prior to administration, visually inspect for any insoluble particulate matter or discoloration. The study drug should not be used if any insoluble particulate matter, discoloration, or leakage is observed.
- Using a 1-inch long, 25-gauge needle, inject a dose of 0.5 mL into the arm opposite to the one used for blood collection to obtain a sample for immunogenicity testing wherever possible.
- The following should be noted to avoid the effect of intramuscular vaccination on the tissues and nerves:
- Injecting into a nerve tract should be avoided.
- In the case of intense pain and/or backflow of blood associated with needle insertion, withdraw the needle immediately and inject into another site.

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental vaccination with the study drug at a dose above that assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the (e)CRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with overdose will be documented on an AE page of the CRF(s) in accordance with 10.0 Adverse Events.

SAEs associated with overdose should be reported in accordance with the procedure outlined in 10.2.2.

In the event of drug overdose, the subject should be treated as appropriate by the investigator.

8.2 Study Drug Dispensing Procedures

Subjects will be vaccinated with the study drug according to the study schedule.

8.3 Accountability and Destruction of Sponsor-Supplied Drugs

The site designee will receive the procedures for handling, storage and management of study drugs created by the sponsor, according to which the site designee will appropriately manage the sponsor-supplied drug. The investigator will also receive those procedures from the sponsor. The procedures include those for ensuring appropriate receipt, handling, storage, management, and dispensation of the sponsor-supplied drug, and collection of unused medications as well as their return to the sponsor or their destruction.

The site designee will immediately return unused supplies of the study drug to the sponsor after the study is closed at the site.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The study schedule is provided in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2. Informed consent must be obtained from each subject before any protocol-directed procedures are performed. A unique subject identification number (subject number) will be assigned to each subject at the time that informed consent is explained; this subject number will be used throughout the study; this subject number will be used throughout the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth and sex.

For medical history, clinically significant diseases or symptoms that have healed or resolved within 1 year prior to the first vaccination with study drug will be collected. Ongoing conditions are considered present illnesses (see Section 9.1.7). History of influenza infection within 1 year prior to the first vaccination with study drug will be collected.

Prior treatments to be collected include all drugs discontinued within 4 weeks prior to informed consent. In addition, history of influenza vaccination (including pandemic influenza vaccines and other investigational products) within 1 year prior to informed consent will be collected.

9.1.3 Physical Examination Procedure

A baseline physical examination at baseline (defined as the assessment prior to the first vaccination with study drug), will consist of the following body systems:

(1) eyes; (2) ears, nose; and throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other.

During physical examination after each vaccination with the study drug, the subject will be assessed for any abnormalities considered clinically significant in comparison with pre-vaccination physical findings. During study visits at Days 22 and 43 and at discontinuation, the subject will be assessed for any pyrexia, systemic and injection site reactions, and other events based on the subject diary (see Section 9.1.11).

9.1.4 Weight and Height

A subject should have weight and height measured while wearing indoor clothing on and shoes off. The Takeda standard for collecting height is centimeters without decimal places (rounded to the nearest whole number) and for weight it is kilograms (kg) with 1 decimal place (rounded to one decimal place).

Example: Height = 176 cm, weight = 79.2 kg

9.1.5 Vital Signs Procedure

Vital signs will include body temperature (oral), respiratory rate, sitting blood pressure (resting more than 5-minutes), and pulse (beats per minute). No respiratory rate measurement will be required at Day 43 and at discontinuation.

If blood sampling and vital sign measurement are to be performed at the same point, vital sign measurement should be performed first.

The subject must measure his/her temperature and record it in the subject diary every day on Days 1-7 and 22-28 and as needed on Days 8-22 (before study visit) and 29-43 (before study visit) (see Section 9.1.11). Daily measurements on Days 1-7 and 22-28 should be transcribed to the (e)CRF.

9.1.6 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by Takeda. At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the (e)CRF.

9.1.7 History of Present Illness

A present illness refers to any clinically significant disease or symptom existing at the first vaccination with study drug. All clinically significant laboratory values and abnormal findings observed during examination prior to vaccination with the study drug should be regarded as present illnesses. The details of present illnesses (diagnoses) should be recorded.

9.1.8 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, and for 12 weeks after last dose of study drug, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use adequate contraception. In addition they must be advised not to donate ova during this period.

*A woman is considered a woman of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a post-menopausal state in younger women (e.g. those < 45 year old) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

**Sterilized males should be at least 1 year post vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

Such subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process, and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy during the course of the study.

During the course of the study, regular urine human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures Appendix A In addition to a urine hCG pregnancy test before vaccination on the day of vaccination with the study drug (Day 1), the result of urine hCG test at the end of study (or discontinuation) (Day 43) must be confirmed negative.

In this study, the only acceptable methods of contraception are:

Barrier methods (each time the subject has intercourse):	**Intrauterine devices (IUDs):**	**Hormonal contraceptives:**
• Male condom PLUS spermicide.	• Copper T PLUS condom. • Progesterone T PLUS condom.	• Combined pill.

9.1.9 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug should be immediately discontinued.

If the pregnancy occurs during administration of active study drug, eg, after Day 1 or within 12 weeks of the last dose of active study drug, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed on the attached sheet.

If the female subject agrees to the primary care physician (obstetrician) being informed, the investigator should notify the primary care physician that the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received.

All pregnancies in subjects on active study drug including comparator will be followed up to final outcome, using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.10 Immunogenicity Evaluation

The SRH and MN antibody titers against influenza virus for immunogenicity evaluation will be measured by the laboratory specified in the procedures. As for blood sampling, 20 mL of blood per sampling will be collected from the forearm vein. The blood sample collected will be used for study-specific endpoint measurements as well as immunogenicity evaluation by a government organization, and also may be used for other exploratory immunogenicity evaluations (see Section 9.4). No genetic testing will be performed using the samples collected in this study.

For the immunogenicity evaluation by a government organization, the protocol and the result report will be prepared by the sponsor or the government organization, separately from the protocol and clinical study report for this study. If other exploratory immunogenicity evaluations are performed, their protocols and result reports should also be prepared.

Detailed procedures for handling and transporting samples are found in separately prepared documented procedures for handling of biological samples for immunogenicity evaluation.

9.1.11 Injection Site and Systemic Reactions (Diary-based Assessment)

As AEs related to reactogenicity of vaccination with the study drug, injection site reactions (injection site pain, erythema, swelling, induration, and haemorrhage, hereinafter the same applies) and systemic reactions (pyrexia, malaise, chills, fatigue, headache, sweaty, myalgia, and arthralgia, hereinafter the same applies) occurring between the initial vaccination with study drug and 42 days after the vaccination (Day 43) will be collected via the subject diary.

Injection site and systemic AEs occurring within 21 days after each vaccination (Days 22 and 43) will be collected via the subject diary (Diary 1 for Days 1-7, Diary 2 for Days 8-22, Diary 3 for Days 22-28, and Diary 4 for Days 29-43).

Diaries 1 and 2 will be provided to each subject together with a digital thermometer for oral temperature measurement and a ruler for injection site reaction measurement after vaccination with the study drug on Day 1. These diaries will be collected and reviewed by the investigator at Day 22 visit.

Information to be recorded in Diary 1 (Days 1-7)

- Body temperatures (oral) measured once daily in the evening during the period after vaccination with the study drug (Day 1) until Day 7
- Injection site reactions
- Systemic reactions
- Other AEs

Information to be recorded in Diary 2 (Days 8-22)

- Body temperatures (oral) measured when the subject experiences any AE with pyrexia during the period after Day 8 until Day 22 before study visit
- Other AEs

Diaries 3 and 4 will be provided to each subject at Day 22 visit (or at Day 1 visit) and will be collected and reviewed by the investigator at Day 43 visit.

Information to be recorded in Diary 3 (Days 22-28) [same as information to be recorded in Diary 1]

- Body temperatures (oral) measured once daily in the evening during the period after vaccination with the study drug (Day 22) until Day 28
- Injection site reactions
- Systemic reactions
- Other AEs

Information to be recorded in Diary 4 (Days 29-43) [same as information to be recorded in Diary 2]

- Body temperatures (oral) measured when the subject experiences any AE with pyrexia during the period after Day 29 until Day 43 before study visit
- Other AEs

For recording of body temperatures (oral) and injection site reactions in the diary, each subject will be asked to follow the instructions below.

<Body temperature (oral) measurement>

- Diary 1 (Days 1-7) and Diary 3 (Days 22-28): Subjects will measure their oral temperatures once daily, in the evening wherever possible, using the oral digital thermometer provided for the study. Subjects will be asked to keep to the same measurement time every day whenever possible. In the case of pyrexia (defined as oral temperature ≥38.0°C), oral temperatures should be measured more than once (approximately every 4-8 hours) wherever possible and recorded in Diary 1 or 3 until the pyrexia resolves (defined as oral temperature <38.0°C). Subjects will record all measurement information (i.e., measurement results and date and time of measurement) obtained on Days 1-7 and Days 22-28 in Diary 1 and 3, respectively.
- Diary 2 (Days 8-22 [before study visit]) and Diary 4 (Days 29-43 [before study visit]): Daily measurement will not be required. Measurements should be obtained using the oral digital thermometer provided for the study only when any symptom suggestive of pyrexia is noted. In the case of pyrexia (defined as oral temperature ≥38.0°C), the subject should measure his/her oral temperature at least once daily, or more than once

(approximately every 4-8 hours) wherever possible, and record it in Diary 2 or 4 until the pyrexia resolves (defined as oral temperature <38.0°C) to confirm the end date. Subjects will record measurement information (i.e., measurement results and date and time of measurement) obtained on Days 8-22 (before study visit) and Days 29-43 (before study visit) in Diary 2 and 4, respectively.

<Injection site reactions>

- Diary 1 (Days 1-7) and Diary 3 (Days 22-28): If, among injection site reactions, erythema, swelling, or induration is observed after vaccination with the study drug, the subject should measure the longest diameter of the injection site reaction using the ruler provided for the study and record it in Diary 1 or 3.
- Diary 2 (Days 8-22 [before study visit]) and Diary 4 (Days 29-43 [before study visit]): All newly observed injection site reactions and all other injection site reactions observed any time during Days 1-7 or Days 22-28 but that have not resolved during these periods should be recorded in Diary 2 or 4. The longest diameter should also be measured and recorded.

Based on records from each subject's diary collected at Day 22 and 43 visits, the investigator will capture all AEs occurring during Days 1-22 and Days 22-43, and record these AEs on the (e)CRF together with the severity and causality assessment for each event.

As for pyrexia, the start date is defined as the date on which the first oral temperature measurement ≥38.0°C is obtained, and the end date is defined as the date on which the first oral temperature measurement <38.0°C is obtained after the onset. Daily oral temperature measurements on Days 1-7 and Days 22-28 recorded in Diaries 1 and 3 should be transcribed to the (e)CRF even if they are <38.0°C. If two or more temperature measurements are recorded for the same day, the highest temperature of that day should be transcribed to the (e)CRF.

The severity of pyrexia and injection site reactions will be assessed using the criteria shown below, by reference to the "FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"[7] For other AEs (including solicited systemic reactions to be recorded in the subject diary), assessment will be performed as specified in Section 10.1.5.

Pyrexia:

Mild: ≥38.0°C and <38.5°C

Moderate: ≥38.5°C and <39.0°C

Severe: ≥39.0°C

Measurable injection site reactions (injection site erythema, swelling, and induration):

Mild: ≥2.5 cm and <5.1 cm

Moderate: ≥5.1 cm and <10.1 cm

Severe: ≥10.1 cm

*Injection site reactions <2.5 cm will not be regarded as AEs. However, the longest diameter recorded in the diary will be transcribed to the (e)CRF separately from AEs, regardless of whether it is ≥2.5 cm or <2.5 cm.

Injection site pain and haemorrhage:

Mild: No interference with upper extremity movement

Moderate: Interference with upper extremity movement present.

Severe: Upper extremity impairment/dysfunction

9.1.12 Documentation of Subjects Failure before Enrollment in the Study

The investigator accounts for all subjects who sign informed consent.

If the subject is found to be not eligible before the start of vaccination with the study drug, the investigator should complete the (e)CRF.

The primary reason for subjects failure before the start of vaccination with the study drug is recorded in the (e)CRF using the following categories:

- Death
- Adverse Event
- Screen failure (failed inclusion criteria or did meet exclusion criteria)
- Protocol deviation
- Lost to follow-up
- Withdrawal by subject <specify reason>
- Study terminated by sponsor
- Pregnancy
- Sample size sufficient
- Other <specify reason>

Subject numbers assigned to subjects who fail screening should not be reused.

9.1.13 Documentation of Enrollment in the Study

Subjects will be enrolled in the study and receive vaccination with the study drug only if they meet all the inclusion criteria and do not meet any of the exclusion criteria.

For subjects who did not receive vaccination with the study drug, the investigator should record the primary reason for failure on the applicable (e)CRF.

9.2 Vaccination Status in Subjects

The study vaccine will be administered under observation at the study site. The investigator will observe the subjects for any abnormalities for at least 30 minutes after vaccination with the study drug at the study site. The date of vaccination will be recorded in the subjects' source documents and (e)CRFs. The inventory of the study drugs dispensed will be controlled and recorded in the investigational product accountability log or equivalent document by a study site pharmacist or a person designated by the investigator.

9.3 Schedule of Observations and Procedures

The schedule for all testing, observation, and assessments is provided in Appendix A. The following testing, observation, and assessments should be completed at the designated time points.

9.3.1 <Screening Period/Day 1 (Starting before the Initial Vaccination and Ending after the Completion of the Initial Vaccination)>

Enrollment in the study will be performed on Day 1, and the following testing, observation, and assessments will be performed: Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0.

- Informed consent
- Demographics, medical history, and medication history procedure
- Physical examination
- Vital signs (body temperature [oral], blood pressure, and pulse and respiratory rates)
- Weight and height
- Documentation of concomitant medications
- Present illness
- Pregnancy test (only for female subjects of childbearing potential)
- Blood sampling for the immunogenicity evaluation

Subjects meeting all the inclusion criteria and not meeting any of the exclusion criteria will be enrolled in the study. Subjects will receive vaccination with the study drug under the supervision of the investigator at the study site. For the procedures for the recording of subjects withdrawn from the study prior to the start of vaccination with the study drug, see Section 9.1.12.

9.3.2 <Treatment Period/Day 1 (after the Initial Vaccination) to Day 22 (before Visiting the Study Site)>

During the period from Day 1 (after the initial vaccination) to Day 22 (before visiting the study site), the following testing, observation, and assessments will be performed: Day 1 (the day of initial vaccination) will be the day of study visit, and subjects will monitor themselves at home during the period after the completion of Day 1 visit until before Day 22 visit (see Section 9.1.11).

- Physical Examination

  Time point: Day 1 (after the initial vaccination)

  The investigator will monitor for any acute hypersensitivity reaction, etc., for 30 minutes after vaccination.

- Vital signs (blood pressure and pulse and respiratory rates)

  Time point: Day 1 (after the initial vaccination)

  Vital signs will be measured 30 minutes after vaccination.

- Vital signs (body temperature [oral])

  From Days 1 to 7, subjects will measure their body temperature (oral) and record it in the subject diary. From Days 8 to 22 (before visiting the study site), subjects will measure their body temperature (oral) only if they develop pyrexia (or any symptoms suggestive of pyrexia) (see Section 9.1.11).

- Supply of the subject diary

  Time point: Day 1 (Diaries 1 and 2) (Diaries 3 and 4 may be supplied on Day 1)

- Completion of the subject diary (by subjects)

  Time points: From Day 1 (after the initial vaccination) to Day 7 (Diary 1) and from Day 8 to Day 22 (before visiting the study site) (Diary 2)

During the periods from Day 1 (after the completion of study visit) to Day 7 and from Day 8 to Day 22 (before visiting the study site), subjects will monitor for and record any systemic reactions, injection site reactions, etc. (see Section 9.1.11).

9.3.3 <Treatment Period/Day 22 (Starting before the Second Vaccination and Ending after the Completion of the Second Vaccination)>

The following tests, observations, and assessments will be performed on Day 22 (starting before the second vaccination and ending after the completion of the second vaccination).

- Physical Examination
- Vital signs (body temperature [oral], blood pressure, and pulse and respiratory rates)
- Collection of concomitant medications and AEs
- Blood sampling for the immunogenicity evaluation
- Collection of the subject diary (Diaries 1 and 2)

Subjects will receive vaccination with the study drug under the supervision of the investigator at the study site.

9.3.4 <Treatment Period/Day 22 (after the Second Vaccination) to Day 43 (before Visiting the Study Site)>

During the period from Day 22 (after the second vaccination) to Day 43 (before visiting the study site), the following testing, observation, and assessments will be performed: Subjects will monitor themselves at home during the period after the completion of Day 22 visit until before Day 43 visit (see Section 9.1.11).

- Physical Examination

  Time point: Day 22 (after vaccination)

  The investigator will monitor for any acute hypersensitivity reaction, etc., for 30 minutes after vaccination.

- Vital signs (blood pressure and pulse and respiratory rates)

  Time point: Day 22 (after vaccination)

  Vital signs will be measured 30 minutes after vaccination.

- Vital signs (body temperature [oral])

  Form Days 22 to 28, subjects will measure their body temperature (oral) and record it in the subject diary. Form Days 29 to 43 (before visiting the study site), subjects will measure their body temperature (oral) only if they develop pyrexia (or any symptoms suggestive of pyrexia) (see Section 9.1.11).

- Supply of the subject diary

  Time point: Day 22 (Diaries 3 and 4) (Diaries 3 and 4 may be supplied on Day 1)

- Completion of the subject diary (by subjects)

  Time point: From Day 22 (after vaccination) to Day 28 (Diary 3) and from Day 29 to Day 43 (before visiting the study site) (Diary 4)

During the periods from Day 22 (after the completion of study visit) to Day 28 and from Day 29 to Day 43 (before visiting the study site), subjects will monitor for and record any systemic reactions, injection site reactions, etc. (see Section 9.1.11).

9.3.5 <Treatment Period/at the End of Study/Day 43>

The following testing, observation, and assessments will be performed at the final study visit (for observation) (Day 43).

- Physical Examination
- Vital signs (body temperature [oral], blood pressure, and pulse rate)
- Pregnancy test (only for female subjects of childbearing potential)
- Blood sampling for the immunogenicity evaluation
- Collection of the subject diary (Diaries 3 and 4)
- Collection of concomitant medications and AEs

For all subjects receiving the study drug, the investigator must complete the Subject Status (e)CRF page.

9.3.6 <Treatment Period/at Discontinuation>

For subjects withdrawn from the study, reasons for study discontinuation must be recorded in the subject's source documents and CRF, and the following testing, observation, and assessments should be performed wherever possible.

- Physical Examination
- Vital signs (body temperature [oral], blood pressure, and pulse rate)
- Pregnancy test (only for female subjects of childbearing potential)
- Blood sampling for the immunogenicity evaluation
- Collection of the subject diary
- Collection of concomitant medications and AEs

For all subjects receiving the study drug, the investigator must complete the Subject Status (e)CRF page.

9.4 Biological Sample Retention and Destruction

The remainder of serum samples collected in accordance with Section 9.1.10, "Immunogenicity Evaluation" will be stored. Serum samples will be discarded after they will no longer be used. Details on sample retention will be provided in separately prepared handling procedures.

9.5 Amount and Frequency of Blood Collection

The total amount of blood to be collected from each subject will be as shown in Table 9.a.

Table 9.a Amount and Frequency of Blood Collection

Test	Amount to be collected per collection	Frequency of collection	Total amount to be collected
Immunogenicity testing	20 mL	Three times	60 mL
Total amount to be collected			60 mL

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study; it does not necessarily have to have a causal relationship with this treatment or study participation.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the study participation whether or not it is considered related to the drug or study procedures.

10.1.2 Additional Points to Consider for AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying diseases should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or dose adjustment of the study drug or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

AEs caused by a study procedure (e.g., a bruise after blood draw) should be recorded as an AE.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. However, each solicited local or systemic AE to be recorded in the subject diary should be recorded as a single event. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).

Pre-existing conditions:

- Pre-existing conditions (present since before the first vaccination with study drug) are considered present illnesses and should NOT be recorded as AEs. However, if the present illness worsens after the first vaccination with study drug, it should be appropriately recorded as an AE. The investigator should ensure that the AE term to be reported reflects a change from baseline (e.g., “worsening of…”).
- If a subject has a pre-existing episodic condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as an AE if the episodes become more frequent, serious or severe in nature, that is, investigators should ensure that the AE term recorded captures the change in the condition from Baseline (eg “worsening of…”).
- If a subject has a degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as an AE if occurring to a greater extent to that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (eg, “worsening of…”).

Change in severity of AEs:

- If the subject experiences a change in severity of an AE that is not related to starting the study drug or changing in the dose or regimen, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that are scheduled prior to signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (e.g., as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- The occurrence of overdose with no associated events should NOT be considered an AE, but instead will be documented on an Overdose page of the (e)CRF. Any event associated with overdose should be considered AEs and will be recorded on the AE page of the (e)CRF.

10.1.3 SAEs

An SAE is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product (including a study drug), which:

1. Results in DEATH.
2. Is LIFE THREATENING.

- The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:

- May require intervention to prevent items 1 through 5 above.
- May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
- Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Acute liver failure
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure (including seizure and epilepsy)	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis (including interstitial lung disease)
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
Hepatic necrosis	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death

Note: The terms listed in this table may be "important medical events" that require the reporting of SAEs and are therefore broadly defined medical terms.

7. The following important medical events associated with the use of an influenza vaccine: neuritis, encephalitis, vasculitis, Guillain-Barre syndrome, Bell's palsy (facial palsy), and demyelinating disorder (including acute disseminated encephalomyelitis [ADEM] and multiple sclerosis)

10.1.4 AEs of Special Interest

An AE of Special Interest (regardless of whether it is serious or not) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand them.

10.1.5 Severity of AEs

The different categories of intensity are characterized as follows:

Mild: The event is transient and easily tolerated by the subject.

Moderate: The event causes the subject interrupts the subject's usual activities.

Severe: The event causes considerable interference with the subject's usual activities.

However, pyrexia and injection site reactions (injection site pain, erythema, swelling, induration, and haemorrhage) should be assessed according to the classification specified in 9.1.11.

10.1.6 Causality of AEs

The relationship of each AE to study drug(s) will be assessed using the following categories:

Related: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, present illness, concomitant medications and concurrent treatments, may also be responsible.

Not related: An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, present illness, concomitant medications and concurrent treatments.

10.1.7 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.8 Start Date

The start date of the AE is the date that the first signs/symptoms were noted by the subject and/or investigator.

The start date of AEs will be determined using the following criteria;

AEs	Start Date
Any signs/symptoms/diseases (diagnosis)	The date that the first signs/symptoms were noted by the subject and/or the investigator should be recorded.
Asymptomatic diseases	The date when examination was performed for diagnosis and diagnosis was confirmed should be recorded. The date when diagnosis was confirmed should also be recorded even when values or findings showed previous values or findings or the onset time can be estimated.
Worsening of present illnesses	The date when diagnosis was confirmed should also be recorded even when values or findings showed previous values or findings or the onset time can be estimated.

10.1.9 End Date

The end date of the AE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.1.10 Pattern of Adverse Events

Episodic AEs (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.11 Action Taken with Study Treatment

Actions concerning the study drug will be classified and defined as follows:

- Drug withdrawn — A study drug is stopped due to the particular AE.
- Dose not changed — The particular AE did not require stopping a study drug.
- Unknown — Only to be used if it has not been possible to determine what action has been taken.
- Not applicable — A study drug was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, vaccination with study drug was already stopped before the onset of the AE.

10.1.12 Outcome of Event

• Recovered/resolved	Subject returned to first assessment status with respect to the AE.
• Recovering/resolving	The intensity is lowered by one or more stages: The diagnosis or signs/symptoms has almost disappeared; The abnormal laboratory value improved, but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving".
• Not recovered/not resolved	There is no change in the diagnosis, signs or symptoms; The intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved".
• Recovered/Resolved with sequelae	The subject recovered from an acute AE but was left with permanent/significant impairment (e.g, recovered from a cardiovascular accident but with some persisting paresis.
• Fatal	The AEs which are considered as the cause of death.
• Unknown	The course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 AE Collection Period

The collection of AEs will be started at the initial vaccination with the study drug (Day 1) and continued until the end of study (Day 43).

10.2.1.2 AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study.

All subjects experiencing AEs after the first exposure to study drug, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the (e)CRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term
2. Start and end date
3. Pattern
4. Severity
5. Investigator's opinion of the causality between the event and administration of study drug(s)
6. Investigator's opinion of the causality to study procedure(s), including the details of the suspected procedure

7. Action taken with study treatment
8. Outcome of event
9. Seriousness
10. Treatment emergent (After the first exposure to study drug)
11. For pyrexia, the maximum body temperature and the presence or absence of a 24-hour or longer persistence
12. For injection site erythema, swelling, and induration, the longest diameter

10.2.1.3 AEs of Special Interest Reporting

In this study, AEs of special interest will include the following AEs:

Hypersensitivity and anaphylaxis or any events suggestive of hypersensitivity

If this AE of special interest, which occurs during the treatment period or the follow-up period, is considered to be clinically significant, it should be reported to the sponsor (described in the separate contact information list) immediately or within 1 business day of first onset or subject's notification of the event. The study-specific Solicited AE Form or SAE Form should be completed, signed and/or sealed by the principal investigator, and reported to appropriate personnel in the separate contact information list within 10 business days.

The AE of special interest have to be recorded as AEs in the (e)CRF. An evaluation form (the original copy of Solicited AE Form or SAE Form) along with all other required documentation must be submitted to the sponsor.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

An SAE should be reported to the sponsor (described in the separate contact information list) within 1 business day of first onset or subject's notification of the event. The principal investigator should submit the completed SAE form within 10 calendar days. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious
- Subject identification number
- Investigator's name
- Name of the study drug(s)
- Causality assessment

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

The investigator should report any AEs to the sponsor and submit the form within the appropriate period as specified by the sponsor.

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event.

10.3.1 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities investigators and IRBs /the head of the study site, as applicable in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of a study drug or that would be sufficient to consider changes in the study drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs and medical history including present illness will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 CRFs

Completed (e)CRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. (e)CRFs must be completed in English. Data are transcribed directly onto eCRFs.

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal investigator must review the (e)CRFs for completeness and accuracy and must sign the appropriate (e)CRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the (e)CRFs.

The following data will be recorded directly into the (e)CRFs. However, this will not apply if the subject's medical records contain the data.

- Subject eligibility assessment
- AE terms, the start and end dates, ongoing/not ongoing at the end of study, onset pattern, severity, causal relationship with the study procedures, causal relationship with the study drug, action taken with the study drug, outcome, and seriousness
- The status of the subject in terms of vaccination with the study drug and the completion of the study
- Reason for the use of concomitant medications and ongoing/not ongoing at the end of study

The following data will not be recorded on the (e)CRFs:

- Immunogenicity testing results

After the lock of the clinical study database, any change of, modification of or addition to the data on the (e)CRFs should be made by the investigator with use of change and modification records of the Data Clarification Form provided by the sponsor. The principal investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date.

(e)CRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the (e)CRFs. The completed (e)CRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator and the head of the institution agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees.

Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, the investigator and the head of the institution are required to retain essential relevant documents until the day of completion of BLB-750 reexamination. However, if the sponsor requests a longer time period for retention, the head of the institution should discuss how long and how to retain those documents with the sponsor.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized by the statistician prior to the data lock. The SAP will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A data review will be conducted prior to the data lock. This data review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

In this study, two kinds of analysis sets are defined: FAS, and safety analysis set. The FAS used as an immunogenicity analysis set and the safety analysis set will be defined as “all subjects who received at least one dose of the study drug for the treatment period." The definition of each analysis set will be detailed in the separate “SAP.”

13.1.2 Analysis of Demographics and Other Baseline Characteristics

In this study, major subject background data in the FAS will be tabulated.

13.1.3 Immunogenicity Analysis

(1) Primary Endpoints and Their Analyses

(Primary Endpoints)

Immunogenicity:

Seroprotection rate as measured by SRH antibody titer (defined as the proportion of subjects with SRH antibody titer ≥25 mm^2) for the vaccine strain at 21 days after the second vaccination

Seroconversion rate as measured by SRH antibody titer (defined as the proportion of subjects with a 50% or more increase in SRH antibody titer from baseline for those who have a baseline value >4 mm^2 or SRH antibody titer ≥25 mm^2 for those who have a baseline value ≤4 mm^2) for the vaccine strain at 21 days after the second vaccination

Geometric mean fold increase (GMFI) in SRH antibody titer from baseline for the vaccine strain at 21 days after the second vaccination

[Analysis Methods]

Using the FAS, frequency tabulations of the SRH antibody titer and the seroprotection and seroconversion rates at 21 days after the second vaccination will be presented, and their point estimates and two-sided 95% confidence intervals will be calculated. For the geometric mean fold increase in the SRH antibody titer at 21 days after the second vaccination, summary statistics and geometric means with corresponding two-sided 95% confidence intervals of the fold increase in the SRH antibody titer from baseline will be calculated. Two-sided 95% confidence intervals of the geometric means will be calculated by back-transforming the upper and lower limits of two-sided 95% confidence intervals of the log transformed mean values.

(2) Secondary Endpoints and Their Analyses

(Secondary Endpoints)

Immunogenicity:

Seroprotection rate as measured by SRH antibody titer (defined as the proportion of subjects with SRH antibody titer ≥25 mm^2) for the vaccine strain at 21 days after the initial vaccination

Seroconversion rate as measured by SRH antibody titer (defined as the proportion of subjects with a 50% or more increase in SRH antibody titer from baseline for those who have a baseline value >4 mm^2 or SRH antibody titer ≥25 mm^2 for those who have a baseline value ≤4 mm^2) for the vaccine strain at 21 days after the initial vaccination

GMFI in SRH antibody titer from baseline for the vaccine strain at 21 days after the initial vaccination

Geometric mean titer (GMT) of SRH antibody titer for the vaccine strain at 21 days after each vaccination

[Analysis Methods]

Using the FAS, frequency tabulations of the SRH antibody titer and the seroprotection and seroconversion rates at 21 days after the initial vaccination will be presented, and their point estimates and two-sided 95% confidence intervals will be calculated. For the geometric mean fold increase in the SRH antibody titer at 21 days after the initial vaccination, summary statistics and geometric means with corresponding two-sided 95% confidence intervals of the fold increase in the SRH antibody titer from baseline will be calculated. For GMT of the SRH antibody titer at 21 days after each vaccination, summary statistics and geometric means with corresponding two-sided 95% confidence intervals will be calculated. Two-sided 95% confidence intervals of geometric means will be calculated using the method specified in 13.1.3(1).

(3) Additional Endpoints

See Section 5.2.3.

(4) Methods of Data Transformation and Handling of Missing Data

The details will be provided in the separate "SAP."

(5) Confidence Coefficient

Confidence coefficient: 95% (two-sided estimation)

13.1.4 Safety Analysis

Secondary Endpoints and Their Analyses

- Solicited local and systemic adverse events (AEs) to be recorded in the subject diary
- AEs
- Vital signs

Using the safety analysis set, the following analyses will be performed:

For injection site and systemic AEs to be collected from the diaries, frequency tabulations, frequency tabulations by severity, and frequency tabulations by vaccination and by timing of onset will be presented. For vital signs, summary statistics of measurement values and the changes in post-vaccination values from baseline at each assessment point will be calculated. In addition, the changes in each test item over time will be graphically presented.

Treatment-emergent adverse events (TEAEs) are defined as AEs observed after the start of vaccination with the study drug.

For TEAEs, the following analyses will be performed: TEAEs will be coded using the MedDRA and summarized by System Organ Class and Preferred Term.

- Frequency tabulation of all TEAEs
- Frequency tabulation of TEAEs considered "related" to the study drug
- Frequency tabulation of all TEAEs by severity

- Frequency tabulation of TEAEs considered "related" to the study drug by severity
- Frequency tabulation of serious TEAEs
- Frequency tabulation of all TEAEs by vaccination and by timing of onset

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

The number of subjects to be vaccinated: 55

The objective of this study is to evaluate the immunogenicity and safety of two intramuscular vaccinations with BLB-750 in healthy Japanese adults. Therefore, the sample size for this study was determined to be 55 subjects, as the number of subjects to be vaccinated, by reference to the Notification issued by the Director of the Evaluation and Licensing Division of the Pharmaceutical and Food Safety Bureau on October 31, 2011: "Guidelines for the Development of Prototype Vaccines in Preparedness for Pandemic Influenza" [4]. There are no statistical rationales for the determination of this sample size.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the (e)CRFs. Source documents are defined as original documents, data, and records. The investigator and head of the study site guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, and review of (e)CRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviation

The investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from IRB. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the study site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the study site as soon as possible and an approval from IRB should be obtained.

The investigator should document all protocol deviations. Significant deviations from the protocol must be recorded on the (e)CRFs and reviewed by the sponsor or designee. Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare Products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and head of the study site guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB Approval

IRBs must be constituted according to the applicable local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study. The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will notify site once the sponsor has confirmed the adequacy of site regulatory documentation. Until the site receives [notification no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of the investigator's final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB approval of the informed consent form. The informed consent form must be approved by both the IRB and the sponsor prior to use.

The informed consent form must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

The subject must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject determines he or she will participate in the study, then the informed consent

form must be signed and dated by the subject at the time of consent and prior to the subject entering into the study. The subject should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator will also sign and date the informed consent form before the subject enters into the study.

Once signed, the original informed consent form will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's [e]CRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator.

The investigator needs to obtain a prior written approval from the sponsor to publish any information from the study externally such as to a professional association.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with the study site's name, city, country, and recruiting status will be registered and available for public viewing.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov and other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

[1] "National Action Plan for Pandemic Influenza and New Infectious Diseases" revised on June 7, 2013, http://www.cas.go.jp/jp/seisaku/ful/keikaku.html

[2] Menno D. de Jong, M.D., Ph.D., Tran Tan Thanh,et al. Oseltamivir Resistance during Treatment of Influenza A (H5N1) Infection. N Engl J Med. 2005;353:2667-2672.

[3] Takeda Pharmaceutical Company Limited. The Package Insert for Cell-Culture Influenza Vaccine (H5N1 strain) created in June 2017 (version 1)

[4] "Guidelines for the Development of Prototype Vaccines in Preparedness for Pandemic Influenza" (PFSB Notification No. 1031-[1] dated October 31, 2011)

[5] Thomas R., Robert A., Jean H., et al. Detection of Antibody to Avian Influenza A(H5N1) Virus in Human Serum by Using a Combination of Serologic Assays.J Clin Microbiol.April 1999;37(4):937-943.

[6] Iain S. , Karl G.,Anthony C., et al.Boosting immunity to influenza H5N1 with MF59-adjuvanted H5N3 A/Duck/Singapore/97 vaccine in a primed human population.ELSEVIER.April 2003;21(15):1687-1693

[7] Food and Drug Administration. Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent volunteers Enrolled in Preventive Vaccine Clinical Trials. U.S.Department of Health and Drug administration Center for Biologics Evaluation and Research. September 2007

Appendix A Schedule of Study Procedures

	Screening	Treatment				
Visit number	Visit 1		Visit 2			Visit 3/at discontinuation[12)]
Day[1)]	1	1 to 22	22		22 to 43	43/-
Days after the initial vaccination	0	0 to 21	21		21 to 42	42 (Visit 2 + 21)/-
Acceptable time window for visit (day)	-	-	+0 to 2		-	Visit 2 + 19 to Visit 2 + 23 /date of discontinuation + 28
	Pre-vaccination	Post-vaccination		Pre-vaccination	Post-vaccination		-
Informed Consent	X[2)]						
Demographics	X						
Past history, present illness, and prior treatments	X[3)]						
Height and weight	X						
Vital signs (blood pressure and pulse and respiratory rates)	X	X[4)]		X	X[4)]		X[5)]
Vital signs (body temperature [oral])	X		X[6) 7)]	X		X[6) 7)]	X
Pregnancy test[9)]	X						X
Physical examination	X	X[9)]		X	X[9)]		X
Eligibility assessment	X						
Enrollment	X						
Blood sampling (immunogenicity evaluation)[10)]	X			X			X
Vaccination with the study drug	X			X			
Diaries 1 and 2		To be provided	To be recorded	To be collected			(To be collected, if not yet collected)
Diaries 3 and 4					To be provided[11)]	To be recorded	To be collected
Adverse events	←	→	→	→	→	→	→
Concomitant medications	←	←	←	←	←	←	→

1) The day before vaccination with the study drug is defined as Day -1, and the day of vaccination with the study drug (Visit 1) is defined as Day 1.
2) Informed consent must be obtained before any study procedure is performed. Informed consent is considered valid if it is obtained within 28 days prior to Visit 1 (Day -28).
3) Prior treatments include those given before signing the informed consent form, and past history and present illness include those occurring before the first vaccination of study drug.
4) On the day of vaccination with study drug, blood pressure, pulse rate, and respiratory rate will be measured before vaccination and approximately 30 minutes after vaccination.
5) No respiratory rate measurement will be required at Day 43 and at discontinuation.
6) Among vital signs, body temperature will be measured by each subject every day in the evening wherever possible for 7 days after vaccination (after vaccination on Day 1 until Day 7 and after vaccination on Day 22 until Day 28) and be recorded in the diary provided to each subject.

7) During Days 8-22 (before study visit) and Days 29-43 (before study visit), body temperature will be measured by each subject and be recorded in the diary provided to each subject only if any symptom of pyrexia occurs. Measurements should be obtained approximately every 4-8 hours until the pyrexia resolves and should be recorded in the diary.
8) Pregnancy test will be performed in female subjects of childbearing potential.
9) The investigator will monitor for any acute hypersensitivity reaction, etc., for 30 minutes after vaccination.
10) Blood sampling should be performed after vital sign measurement.
11) Provision of Diaries 3 and 4 may take place at Visit 1.
12) The study discontinuation visit should be performed wherever possible.

Appendix B Responsibilities of the Investigator

1. Conduct the appropriate study in accordance with the protocol and GCP considering the rights, safety and wellbeing of human subjects.
2. When a part of the important activities related to the study are delegated to the investigator or the study collaborator, prepare the lists of activities to be delegated and responsible personnel, submit the lists to the director of the site in advance to get them accepted.
3. Prepare a written informed consent form and other written information, and update as appropriate.
4. Confirm the contents of the clinical study agreement.
5. Provide necessary information on the protocol, medications and responsibilities of individual personnel to the investigator and study collaborator, and provide guidance and supervision.
6. Screen subjects who meet the requirements of the protocol, provide the explanation of the study in writing and obtain the written consent.
7. Assume responsibility for all the medical judgement related to the study.
8. Ensure in collaboration with the director of the site that sufficient information on all clinically significant adverse events related to the study are provided to subjects throughout and beyond the period when subjects participate in the study.
9. If a subject consults other medical institution or other department, notify the physician of the medical institution or department of the subject's participation in the study upon obtaining the consent of the subject, as well as the end and termination of the study in writing, and document such records.
10. In case of urgent report of a SAE, immediately notify the director of the site and the sponsor in writing.
11. Prepare correct and complete (e)CRFs, and submit them to the sponsor with electronic signature.
12. Check and confirm the contents of (e)CRFs prepared by the investigator or transcribed from the source data by the study collaborator, and submit them to the sponsor with electronic signature.
13. Discuss any proposal from the sponsor including update of the protocol.
14. Notify the director of the site of the end of the study in writing.

Appendix C Details of Amendments

Specific changes in the amended protocol are described below.

Title on Page 1 and Title of Protocol in Section 2.0 on Page 8

Before change

Randomized, Double-Blind, Parallel-Group, Comparative Study

After change

Open-label Study

Reason for the change

Because of changes to the study objectives, the study design was changed from a randomized study to an open-label study.

Section 2.0 (Study Design) on Page 8, Section 4.2 on Page 15, and Section 6.1 on Page 18

Before change

randomized, double-blind, parallel-group, comparative study

After change

Open-label study

Reason for the change

Because of changes to the study objectives, the study design was changed from a randomized study to an open-label study.

Section 6.2.1 on Page 19

Before change

To *objectively* evaluate the immunogenicity and safety….., *a randomized, double-blind, parallel-group, comparison design will be used in this study*.

After change

This study has been designed to evaluate the immunogenicity and safety ….. **(open-label, uncontrolled study)**.

Reason for the change

Because of changes to the study objectives, the study design was changed from a randomized study to an open-label study.

Section 7.0 on Page 21, Section 7.5 on Page 24, Sections 9.1.12 and 9.1.13 on Page 35, Section 9.3.1 on Page 36, and Appendix A on Page 57

Before change

randomization

After change

enrollment in the study

Reason for the change

Because of changes to the study objectives, the study design was changed from a randomized study to an open-label study.

Section 8.2 on Page 28

Before change

Study Drug *Assignment and* Dispensing Procedures

The investigator will assign study drugs to subjects confirmed eligible prior to vaccination in ascending order of drug number and in the order of subject identification numbers as a general rule. The Medication ID Number will be entered onto the (e)CRF.

After change

Study Drug Dispensing Procedures

Subjects will be vaccinated with the study drug according to the study schedule.

Reason for the change

Because of changes to the study objectives, the study design was changed from a randomized study to an open-label study.

Sections 8.3, 8.4, and 8.5 on Pages 28-29

Before change

8.3 Randomization Code Creation and Storage

Randomization personnel of the sponsor or designee will generate the randomization schedule. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 Study Drug Blind Maintenance

The investigator must store the emergency key until the time of emergency blind breaking or the end of study.

Results of SRH and MN antibody titers against the vaccine strain measured for immunogenicity evaluation will be reported to the sponsor after taking necessary measures (i.e., no inclusion of information on the vaccine strain and measured antigens) to maintain the blindness of the study and to ensure that the laboratory's representative will not be able to identify the subject, if these results are disclosed to the sponsor before unblinding the randomization table. Detailed procedures are provided in the separate SOP for the handling of biological samples for immunogenicity evaluation.

8.5 Unblinding Procedure

The study drug blind shall not be broken by the investigator unless information concerning the study drug is necessary for the medical treatment of the subject. In the event of a medical emergency, if possible, sponsor or designee should be contacted before the study drug blind is broken to discuss the need for unblinding.

For unblinding a subject, the study drug blind can be obtained by opening sealed envelope.

The sponsor must be notified as soon as possible if the study drug blind is broken. The date, time, and reason the blind is broken must be recorded in the document called Record of Early Blind-Breaking and the same information (except the time) must be recorded on the (e)CRF.

If any site personnel are unblinded, study drug must be stopped immediately and the subject must be withdrawn from the study.

The investigator must not change subject assessment after unblinding.

After change

Deleted

Reason for the change

Because of changes to the study objectives, the study design was changed from a randomized study to an open-label study.

Section 9.1.9 on Page 32

Before change

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator.

After change

Deleted

Reason for the change

Because of changes to the study objectives, the study design was changed from a randomized study to an open-label study.

Section 9.1.12 on Page 35 and Section 9.3.1 on Page 35

Before change

before/prior to the randomization

After change

before/prior to **the start of vaccination with the study drug**

Reason for the change

Because of changes to the study objectives, the study design was changed from a randomized study to an open-label study.

Section 9.1.13 on Page 35

Before change

Subjects will be *randomized* and receive vaccination with the study drug only if….

If the subject is found to be not eligible for *randomization*, …

After change

Subjects will be **enrolled in the study** and receive vaccination with the study drug only if….

For subjects **who did not receive vaccination with the study drug,** the investigator…..

Reason for the change

Because of changes to the study objectives, the study design was changed from a randomized study to an open-label study.

Section 9.3.1 on Page 35

Before change

…not meeting any of the exclusion criteria will be *randomized in accordance with Section 8.2*.

After change

…not meeting any of the exclusion criteria will be **enrolled in the study**.

Reason for the change

Because of changes to the study objectives, the study design was changed from a randomized study to an open-label study.

Section 13.1 on Page 50

Before change

prior to *unblinding of subject's treatment assignment*

After change

prior to **the data lock**

Reason for the change

Because of changes to the study objectives, the study design was changed from a randomized study to an open-label study.

Section 13.1 on Page 49

Before change

A *blinded* data review will be…

After change

A **data** review will be…

Reason for the change

Because of changes to the study objectives, the study design was changed from a randomized study to an open-label study.

Section 13.1.1 on Page 49

Before change

The FAS used as an immunogenicity analysis set will be defined as "all subjects who were randomized and received at least one dose of the study drug for the treatment period." The safety analysis set will be defined as "all subjects who received at least one dose of the study drug for the treatment period."

After change

The FAS used as an immunogenicity analysis set and the safety analysis set will be defined as "all subjects who received at least one dose of the study drug for the treatment period."

Reason for the change

Because of changes to the study objectives, the study design was changed from a randomized study to an open-label study.

Section 13.1.2 on Page 49

Before change

…of "*all randomized subjects*"

After change

…**in the FAS**

Reason for the change

Because of changes to the study objectives, the study design was changed from a randomized study to an open-label study.

Appendix B on Page 59

Before change

11. Determine the need of emergency key code blinding of a subject in case of emergency.

After change

Deleted

Reason for the change

Because of changes to the study objectives, the study design was changed from a randomized study to an open-label study.

Section 2.0 (Study Design) on Page 8 and Section 6.1 on Page 18

Before change

The immunogenicity and safety of BLB-750 (Qinghai reverse genetics [RG] strain) vaccinations will be evaluated. In addition, the immunogenicity and safety of BLB-750 (Indonesia RG strain) vaccination will be evaluated in comparison with BLB-750 (Indonesia wild type [WT] strain) to be given to a control group.

After change

Deleted

Reason for the change

Because the number of the groups was changed from three to one due to changes to the study objectives.

Section 2.0 (Study Design) on Page 8

Before change

Participants considered eligible as subjects for the study during the eligibility assessment at a visit after providing informed consent will be randomized to either one of the following groups in a 1:1:1 ratio: BLB-750 (Qinghai RG strain), BLB-750 (Indonesia RG strain), and BLB-750 (Indonesia WT strain).

Subjects will receive the initial intramuscular vaccination with BLB-750 (Qinghai RG strain), BLB-750 (Indonesia RG strain), or BLB-750 (Indonesia WT strain) during the first study visit after providing informed consent (Day 1) and the second vaccination with the same BLB-750 during the study visit at 21 days after the initial vaccination (Day 22).

After change

Participants considered eligible as subjects for the study during the eligibility assessment at a visit after providing informed consent will receive the initial intramuscular vaccination with the **study drug BLB-750** (Day 1) and the second intramuscular vaccination with BLB-750 during the study visit at 21 days after the initial vaccination (Day 22).

Reason for the change

Because the number of the groups was changed from three to one due to changes to the study objectives.

Section 2.0 (Study Design) on Page 8 and Section 6.1 on Page 18

Before change

*165 (*55 *per group*)

After change

55

Reason for the change

Because the number of the groups was changed from three to one due to changes to the study objectives.

Section 2.0 (Planned Number of Subjects) on Page 8

Before change

BLB-750 *Qinghai RG strain* group: 55 subjects

BLB-750 Indonesia RG strain group: 55 subjects

BLB-750 Indonesia WT strain group: 55 subjects

The total number of subjects: 165

After change

BLB-750: 55 subjects

Reason for the change

Because the number of the groups was changed from three to one due to changes to the study objectives.

Section 2.0 on Page 8 (Dose Level(s))

Before change

Two doses of BLB-750 *(Qinghai RG strain), BLB-750 (Indonesia RG strain), or BLB-750 (Indonesia WT strain)* at a vaccination dose of 0.5 mL (HA antigen level of 7.5 µg *per strain*) will be injected into the upper arm muscle (the deltoid muscle) at 3-week intervals.

As manufacturing strains for BLB-750, the following attenuated strains (H5N1 influenza virus attenuated using reverse genetics technology) *and wild-type strain* will be used:

- Qinghai RG strain

[A/bar-headed goose/Qinghai/1A/2005 (H5N1) (SJRG-163222)]

- *Indonesia RG strain*

[A/Indonesia/05/2005(H5N1)-PR8-IBCDC-RG2]

- *Indonesia WT strain*

[A/Indonesia/05/2005(H5N1)]

After change

Two doses of BLB-750 at 0.5 mL (HA antigen level of 7.5 µg) will be injected into the upper arm muscle (the deltoid muscle) at a 3-week interval.

As the manufacturing strain for BLB-750, the following attenuated strain (H5N1 influenza virus attenuated using reverse genetics technology) will be used:

- Qinghai RG strain

[A/bar-headed goose/Qinghai/1A/2005(H5N1) (SJRG-163222)]

Reason for the change

Because the number of the groups was changed from three to one due to changes to the study objectives.

Section 2.0 (Statistical Considerations) on Page 8, Section 13.1.3 on Page 49 and Section 13.1.4 on Page 50

Before change

by vaccination group

After change

Deleted

Reason for the change

Because the number of the groups was changed from three to one due to changes to the study objectives.

Section 2.0 (Rationales for the Determination of Sample Size) on Page 8, Section 6.2.1 on Page 19, and Section 13.3 on Page 51

Before change

BLB-750*(Qinghai RG strain), BLB-750(Indonesia RG strain) or BLB-750 (Indonesia WT strain)*

After change

BLB-750

Reason for the change

Because the number of the groups was changed from three to one due to changes to the study objectives.

Section 2.0 (Rationales for the Determination of Sample Size) on Page 8 and Section 13.3 on Page 51

Before change

a total of 165 subjects, 55 subjects per group

After change

55 subjects

Reason for the change

Because the number of the groups was changed from three to one due to changes to the study objectives.

Section 4.2 on Page 15

Before change

In this study, the immunogenicity and safety of BLB-750 (Qinghai RG strain) vaccination will be evaluated. In addition, the immunogenicity and safety of BLB-750 (Indonesia RG strain) vaccination will be evaluated in comparison with BLB-750 (Indonesia WT strain), which was used in previously conducted clinical studies in Japanese adults, as a comparator

After change

Deleted

Reason for the change

Because the number of the groups was changed from three to one due to changes to the study objectives.

Section 6.1 on Page 18

Before change

Subjects considered eligible after providing informed consent will be randomized to *either one of the following groups in a 1:1:1 ratio: BLB-750 (Qinghai RG strain), BLB-750 (Indonesia RG strain), and BLB-750 (Indonesia WT strain)*.

Subjects will receive the initial intramuscular vaccination with *either BLB-750 (Qinghai RG strain), BLB-750 (Indonesia RG strain), or BLB-750 (Indonesia WT strain)* (Day 1) and the second vaccination with *the same BLB-750* during the study visit at 21 days after the initial vaccination (Day 22).

After change

Subjects considered eligible after providing informed consent will receive the initial intramuscular vaccination with **the study drug BLB-750** (Day 1) and the second intramuscular vaccination with **BLB-750** during the study visit at 21 days after the initial vaccination (Day 22).

Reason for the change

Because the number of the groups was changed from three to one due to changes to the study objectives.

Section 6.1 (Figure 6.a) on Page 18

After change

Replaced schematic of study design

Reason for the change

Because the number of the groups was changed from three to one due to changes to the study objectives.

Section 13.1.2 on Page 49

Before change

...will be tabulated *by vaccination group and for the overall population*.

After change

...will be tabulated.

Reason for the change

Because the number of the groups was changed from three to one due to changes to the study objectives.

Section 6.2.2 on Page 19

Before change

As described in *Section 4.2*, BLB-750 *(Qinghai RG strain), BLB-750 (Indonesia RG strain), and BLB-750 (Indonesia WT strain) were selected as H5N1 subtype virus strains for* BLB-750 to be used in this study.

After change

As described in Section **8.1.1.1**, BLB-750 (Qinghai RG strain) was selected as the H5N1 subtype virus strain for BLB-750 to be used in this study.

Reason for the change

Because the number of the groups was changed from three to one due to changes to the study objectives.

Section 8.1.1.1 on Page 26

Before change

Name of *the study drug*: BLB-750 DB *Injection*
Manufacturer: Takeda Pharmaceutical Company Limited
Either one of the following 1), 2), or 3) will be packaged in outer boxes that are indistinguishable in appearance.
1) Code name of the study drug: BLB-750 (Qinghai RG strain) Injection

After change
Substance code: BLB-750
Trade name: Cell-Culture Influenza Vaccine H5N1 "Takeda" 1 mL
Manufacturer: Takeda Pharmaceutical Company Limited

Reason for the change

Because the number of the groups was changed from three to one due to changes to the study objectives.

Section 8.1.1.1 (Table 8.a) on Page 26

Before change

Components and Dose Strength of BLB-750 *(Qinghai RG Strain)* Injection 0.5 mL

After change

Components and Dose Strength of BLB-750 Injection 0.5 mL

Reason for the change

Because the number of the groups was changed from three to one due to changes to the study objectives.

Section 8.1.1.1 on Page 26

Before change

Text from "2) Code name of the study drug" to Table 8.c

After change

Deleted

Reason for the change

Because the number of the groups was changed from three to one due to changes to the study objectives.

Section 8.1.1.1 (Figure 8.a) on Page 26

After change

Replaced labeling sample of the outer box for the study drug

Reason for the change

Because the number of the groups was changed from three to one due to changes to the study objectives.

Section 13.3 on Page 51

Before change

The number of subjects to be vaccinated: *165*

After change

The number of subjects to be vaccinated: **55**

Reason for the change

Because the number of the groups was changed from three to one due to changes to the study objectives.

Section 2.0 (Objectives) on Page 8 and Section 5.1 on Page 16

Before change

Primary Objectives: To evaluate the immunogenicity and safety of two intramuscular vaccinations with BLB-750 *(Qinghai RG strain)* in healthy Japanese adults

After change

Objectives: To evaluate the immunogenicity and safety of two intramuscular vaccinations with BLB-750 in healthy Japanese adults

Reason for the change

Because the number of the groups was changed from three to one due to changes to the study objectives.

Section 2.0 (Secondary Objectives) on Page 8 and Section 5.1.2 on Page 16

Before change

Secondary Objectives: To evaluate the immunogenicity and safety of two intramuscular vaccinations with BLB-750 (Indonesia RG strain) in comparison with two intramuscular vaccinations with BLB-750 (Indonesia WT strain) in healthy Japanese adults

After change

Deleted

Reason for the change

Because the number of the groups was changed from three to one due to changes to the study objectives.

Section 8.1.1.1 on Page 26

Before change

One vial containing the study drug

After change

Two vials of the study drug

Reason for the change

Because the packaging was changed.

Appendix A on Page 57

Before change

Acceptable time window for visit (day) for "Visit 2": +0 to *7*

After change

Acceptable time window for visit (day) for "Visit 2": +0 to **2**

Reason for the change

For consistency with Visit 3.

Section 2.0 (Exclusion Criteria) on Page 8 and Section 7.2 on Page 21

Before change

investigational products

After change

investigational **or study** products

Reason for the change

Editorial improvement.

Section 4.1 on Page 14

Before change

PPD *and Takeda Pharmaceutical Company Limited* co-developed a vaccine indicated for "the prevention of pandemic influenza (H5N1)" *(development code: BLB-750),*...

After change

Takeda Pharmaceutical Company Limited and PPD co-developed a vaccine indicated for "the prevention of pandemic influenza (H5N1)",…

Reason for the change

Editorial improvement.

Section 6.2.2 on Page 19

Before change

According to the package insert [3], which…

After change

Thus, in accordance with the approved dosage regimen…

Reason for the change

Editorial improvement.

Section 6.2.3 on Page 19

Before change

…, *possible adverse events of BLB-750 vaccination include*…

After change

…**have been reported as expected adverse reactions to BLB-750 vaccination**

Reason for the change

Editorial improvement.

Section 9.1.10 on Page 32

Before change

The blood sample collected will be used for study-specific endpoint measurement *and then* for exploratory immunogenicity evaluation (see Section 9.4). Genetic testing will not be included in *exploratory immunogenicity evaluation*.

This exploratory evaluation may be performed as a cooperative study with an external organization. Apart from the protocol and clinical study report for this study, the sponsor and *research collaborators* will create a plan for and a report on exploratory immunogenicity evaluation.

After change

The blood sample collected will be used for study-specific endpoint measurements **as well as immunogenicity evaluation by a government organization, and also** may be used for other exploratory immunogenicity evaluations (see Section 9.4). No genetic testing will be performed **using the samples collected in this study**.

For the immunogenicity evaluation by a government organization, the protocol and the result report will be prepared by the sponsor or **the government organization**, separately from the protocol and clinical study report for this study. **If other** exploratory immunogenicity evaluations are performed, **their** protocols and result reports should **also** be prepared.

Reason for the change

Editorial improvement.

Section 9.4 on Page 38

Before change

The remainder of serum samples collected in accordance with Section 9.1.10, "Immunogenicity Evaluation" will be stored for the exploratory evaluation of immunogenicity endpoints for this study other than SRH and MN antibody titers. Serum samples will be discarded after their use in the exploratory immunogenicity evaluation or after confirming that they will no longer be used.

After change

The remainder of serum samples collected in accordance with Section 9.1.10, "Immunogenicity Evaluation" will be stored. Serum samples will be discarded after they will no longer be used.

Reason for the change

Editorial improvement.

Section 15.4.2 on Page 54

Before change

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, country, and recruiting status will be registered and available for public viewing.

After change

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with **the study site's name**, city, country, and recruiting status will be registered and available for public viewing.

Reason for the change

Editorial improvement.

Section 16.0 on Page 56

Before change

The Package Insert for Cell-Culture Influenza Vaccine (H5N1 strain) created in *May* 2017

After change

The Package Insert for Cell-Culture Influenza Vaccine (H5N1 strain) created in **June** 2017

Reason for the change

Editorial improvement.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Science Approval	14-Dec-2017 07:10 UTC