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

Statistical analysis plan Approve Date: 03-Jul-2018

Certain information within this statistical analysis plan has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information or company confidential information.

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.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- 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.

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: BLB-750/CCT-901

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

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

Version: 2nd

Date: 03 July 2018

Prepared by:

PPD

Based on:

Protocol Version: Amendment 02

Protocol Date: 21 Nov 2017

1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
BMI	body mass index
BUN	blood urea nitrogen
CPK	creatine phosphokinase
CRF	case report form
ECG	electrocardiogram
FAS	full analysis set
GMT	geometric mean titer
GGT	γ-glutamyl transferase
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
IVRS	Interactive Voice Response System
LDH	lactate dehydrogenase
LLN	lower limit of normal
LOCF	last observation carried forward
LS means	least square means
MAV	markedly abnormal value
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures analysis
MN	microneutralization
PD	pharmacodynamics
PK	pharmacokinetics
PPS	per protocol set
PRO	patient-reported outcome
QOL	quality-of-life
SAE	serious adverse event
SAP	statistical analysis plan
SDB	standard database
SRH	single radial hemolysis
TLGs	tables, listings, and graphs
ULN	upper limit of normal
WHODrug	World Health Organization Drug Dictionary

4.0 OBJECTIVES

4.1 Primary Objectives

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

4.2 Secondary Objectives

Not applicable.

4.3 Additional Objectives

Not applicable.

4.4 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.

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 21 days after the initial vaccination (Day 22).

The study duration will be 43 days, starting on the day of the 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 4.a.

For the schedule of testing, observations, and assessments, see Appendix A of the protocol.

Schematic of Study Design

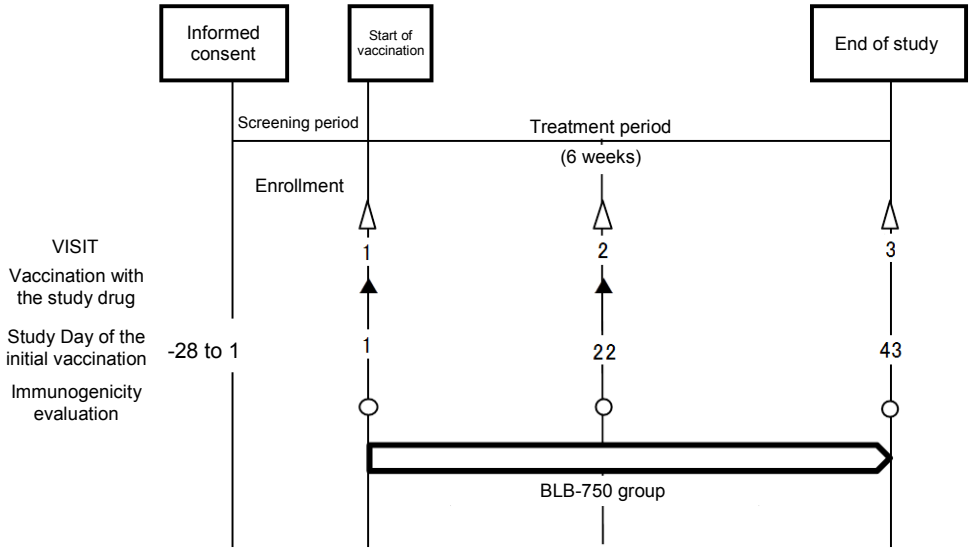

Figure 4.a Schematic of Study Design

5.0 ANALYSIS ENDPOINTS

Primary Efficacy Endpoint

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 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 of >4 mm^2 or SRH antibody titer ≥25 mm^2 for those who have a baseline value of ≤4 mm^2) for the vaccine strain 21 days after the second vaccination
- Geometric mean fold increase (GMFI) in SRH antibody titer from baseline for the vaccine strain 21 days after the second vaccination

Secondary Efficacy 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 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 of >4 mm^2 or SRH antibody titer ≥25 mm^2 for those who have a baseline value of ≤4 mm^2) for the vaccine strain 21 days after the initial vaccination
- GMFI in SRH antibody titer from baseline for the vaccine strain 21 days after the initial vaccination
- Geometric mean titer (GMT) of SRH antibody titer for the vaccine strain 21 days after each vaccination

Safety:

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

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

6.0 DETERMINATION OF SAMPLE SIZE

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" [1]. There are no statistical rationales for the determination of this sample size.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

7.1.1 Study Definitions

- Treatment-emergent adverse event (TEAE): Any AE observed after the start of vaccination with the study drug.
- Pretreatment event (PTE): Any untoward medical occurrence in a subject who has signed informed consent to participate in a study but prior to vaccination with the study drug.
- Summary statistics (antibody titers): Number of subjects, geometric standard deviation, maximum, minimum, and quartiles.
- Summary statistics (other than antibody titers): Number of subjects, mean, standard deviation, maximum, minimum, and quartiles.
- Seroprotection rate as measured by SRH antibody titer: Subjects with an SRH antibody titer ≥25 mm^2 are defined as seroprotected subjects, and the proportion of seroprotected subjects will be calculated.

  Seroprotection rate (%) = (Number of seroprotected subjects / Number of subjects evaluated for immunogenicity) × 100

- Seroconversion rate as measured by SRH antibody titer: Subjects with a 50% or more increase in SRH antibody titer from baseline (for those who have a baseline value of >4 mm^2) or with an SRH antibody titer ≥25 mm^2 (for those who have a baseline value of ≤4 mm^2) are defined as seroconverted subjects, and the proportion of seroconverted subjects will be calculated.

  Seroconversion rate (%) = (Number of seroconverted subjects / Number of subjects evaluated for immunogenicity) × 100

- Seroprotection rate as measured by MN antibody titer: Subjects with an MN antibody titer ≥20 are defined as seroprotected subjects, and the proportion of seroprotected subjects will be calculated.

  Seroprotection rate (%) = (Number of seroprotected subjects / Number of subjects evaluated for immunogenicity) × 100

- Seroconversion rate as measured by MN antibody titer: Subjects with 4-fold or more increase in MN antibody titer from baseline are defined as seroconverted subjects, and the proportion of seroconverted subjects will be calculated.

  Seroconversion rate (%) = (Number of seroconverted subjects / Number of subjects evaluated for immunogenicity) × 100

7.1.2 Definition of Study Days

- Study Day of the initial vaccination: The day before the initial vaccination will be Day -1, while the day of the initial vaccination will be Day 1.
- Study Day of the second vaccination: The day of the second vaccination will be Day 1.

7.1.3 Definition of Study Visit Windows

For each parameter of the testing, observations, and assessments, all evaluable data (i.e., non-missing data) will be handled according to the following rules.

For each visit, an observation that is evaluable and obtained in the corresponding time interval will be used. If more than one evaluable observation is available within the same visit window, the one obtained closest to the scheduled Study Day will be used. If there are two observations equidistant to the scheduled Study Day, the one obtained earlier will be used. The temporal distance from the scheduled Study Day will be determined based on the Study Day.

Table 7.a Visit Window of Antibody Titers of SRH and MN

Assessment Point	Scheduled Study Day		Time Interval (days)
			Study Day of Each Vaccination
Prevaccination	Study Day of the initial vaccination:	1	1
Day 22 of the initial vaccination (21 days after the initial vaccination)	Study Day of the initial vaccination:	22	15 to 28
Day 22 of the second vaccination (21 days after the second vaccination)	Study Day of the second vaccination:	22	15 to 28

Table 7.b Visit Window of Weight and BMI

Assessment Point	Scheduled Study Day		Time Interval (days)
			Study Day of Each Vaccination
Prevaccination	Study Day of the initial vaccination:	1	-28 to 1

Table 7.c Visit Window of Systolic/Diastolic Blood Pressure and Pulse Rate

Assessment Point	Scheduled Study Day		Time Interval (days)
			Study Day of Each Vaccination
Prevaccination	Study Day of the initial vaccination:	1	-28 to 1
30 minutes after the initial vaccination	Study Day of the initial vaccination:	1	1
Day 22 of the initial vaccination (before the second vaccination)	Study Day of the initial vaccination:	22	15 to 28
30 minutes after the second vaccination	Study Day of the second vaccination:	1	1
Day 22 of the second vaccination	Study Day of the second vaccination:	22	15 to 28

Table 7.d Visit Window of Body Temperature

Assessment Point	Scheduled Study Day		Time Interval (days)
			Study Day of Each Vaccination
Prevaccination	Study Day of the initial vaccination:	1	-28 to 1
Day 1 of the initial vaccination (after vaccination)	Study Day of the initial vaccination:	1	1
Day 2 of the initial vaccination	Study Day of the initial vaccination:	2	2
Day 3 of the initial vaccination	Study Day of the initial vaccination:	3	3
Day 4 of the initial vaccination	Study Day of the initial vaccination:	4	4
Day 5 of the initial vaccination	Study Day of the initial vaccination:	5	5
Day 6 of the initial vaccination	Study Day of the initial vaccination:	6	6
Day 7 of the initial vaccination	Study Day of the initial vaccination:	7	7
Day 22 of the initial vaccination (before the second vaccination)	Study Day of the initial vaccination:	22	15 to 28
Day 1 of the second vaccination (after vaccination)	Study Day of the second vaccination:	1	1
Day 2 of the second vaccination	Study Day of the second vaccination:	2	2
Day 3 of the second vaccination	Study Day of the second vaccination:	3	3
Day 4 of the second vaccination	Study Day of the second vaccination:	4	4
Day 5 of the second vaccination	Study Day of the second vaccination:	5	5
Day 6 of the second vaccination	Study Day of the second vaccination:	6	6
Day 7 of the second vaccination	Study Day of the second vaccination:	7	7
Day 22 of the second vaccination	Study Day of the second vaccination:	22	15 to 28

Table 7.e Visit Window of Respiratory Rate

Assessment Point	Scheduled Study Day		Time Interval (days)
			Study Day of Each Vaccination
Prevaccination	Study Day of the initial vaccination:	1	-28 to 1
30 minutes after the initial vaccination	Study Day of the initial vaccination:	1	1
Day 22 of the initial vaccination (21 days after the initial vaccination)	Study Day of the initial vaccination:	22	15 to 28
30 minutes after the second vaccination	Study Day of the second vaccination:	1	1

7.1.4 Significance Level and Confidence Coefficient

Confidence coefficient: 95% (two-sided estimation)

7.1.5 Conventions for Missing Adverse Event Dates

Not applicable.

7.1.6 Conventions for Missing Concomitant Medication Dates

Not applicable.

7.2 Analysis Sets

- Full analysis set (FAS): All subjects who received at least one dose of the study drug.
- Safety analysis set: All subjects who received at least one dose of the study drug.

7.3 Disposition of Subjects

7.3.1 Study Information

Analysis set: All subjects who signed the informed consent form

Analysis variable(s): Date first subject signed the informed consent form

Date of last subject's last visit/testing or last contact, whichever later

MedDRA version

WHO Drug version

SAS version used for creating the datasets

Analysis methods: The following analyses will be performed on the above variables.

(1) Display of analysis variables

7.3.2 Screen Failures

Analysis set: All subjects who did not receive any doses of the study drug

Analysis variable(s): Categories in square brackets (the same applies hereinafter)

Age (years)

Gender [Male, Female]

Analysis methods: The following analyses will be performed on the above variables.

(1) Frequency tabulations for categorical variables and summary statistics for continuous variables

7.3.3 Subject Eligibility

Analysis set: All subjects who signed the informed consent form

Analysis variable(s):

Status of the subject in terms of vaccination with the study drug	[Vaccinated, Not vaccinated]
Reason for discontinuation/withdrawal before the initial vaccination with the study drug	[Death, Adverse event, Screen failure (failure to meet inclusion criteria or meeting exclusion criteria), Protocol deviation, Lost to follow-up, Withdrawal by the subject, Study termination by sponsor, Pregnancy, Sufficient sample size, Other]

Analysis methods: The following analyses will be performed on the above variables.

The percentages of reasons for discontinuation/withdrawal before the initial vaccination with the study drug will be calculated using the number of subjects who discontinued/was withdrawn before the start of vaccination as the denominator.

(1) Frequency tabulation

7.3.4 Disposition of Subjects

Analysis set:	All Subjects who received vaccination with the study drug	
Analysis variable(s):	Study completion status	[Completed, Not completed]
	Reason for not completing the study	[Death, Adverse event, Protocol deviation, Lost to follow-up, Withdrawal by the subject, Study termination by sponsor, Pregnancy, Other]
Analysis methods:	The following analyses will be performed on the above variables. The percentages of reasons for not completing the study will be calculated using the number of subjects who did not complete the study as the denominator.	
	(1) Frequency tabulation	

7.3.5 Protocol Deviations and Analysis Sets

7.3.5.1 Protocol Deviations

Analysis set:	All Subjects who received vaccination with the study drug	
Analysis variable(s):	Protocol deviation	[Entry criteria violation, Concomitant medication/therapy violation, Protocol noncompliance, Treatment regimen/dosage violation, Discontinuation criteria violation, Major GCP violation]
Analysis methods:	The following analyses will be performed on the above variables.	
	The number of subjects with a protocol deviation will be obtained, and frequency distribution provided for each deviation category. A subject who has several deviations will be counted once in each appropriate category (repeated count).	
	(1) Frequency tabulation	

7.3.5.2 Analysis Sets

Analysis set:	All Subjects who received vaccination with the study drug	
Analysis variable(s):	Handling of subjects in analysis sets	[Categories are based on those specified in the List of Subject Evaluability Assignments.]
	Inclusion/Exclusion of analysis sets	
	Full analysis set	[Included]

	Safety analysis set	[Included]

Analysis methods: The following analyses will be performed on the above variables.

For (1), a subject who corresponds to several categories will be counted once in each appropriate category (repeated count).

(1) Frequency tabulation concerning the handling of subject in each analysis set

(2) Frequency tabulation concerning the number of subjects included in each analysis set

7.4 Demographic and Other Baseline Characteristics

Analysis set: Full analysis set

Analysis variable(s):	Age (years)	[Min≤ - <30, 30≤ - <40, 40≤ - ≤Max]
	Gender	[Male, Female]
	Height (cm)	
	Weight (kg)	
	BMI (kg/m^2)	
	SRH antibody titer (prevaccination)	[Min≤ - <25, 25≤ - ≤Max]
	History of influenza infection within 1 year	[Yes, No]

Analysis methods: The following analyses will be performed on the above variables.

(1) Frequency tabulations for categorical variables and summary statistics for continuous variables

7.5 Medical History and Concurrent Medical Conditions

Analysis set: Safety analysis set

Analysis variable(s): Medical history

Present illness

Analysis methods: The following analyses will be performed on the above variables.

The analysis variables will be coded using the MedDRA and summarized by SOC and PT. SOC will be sorted alphabetically and PT in decreasing frequency.

(1) Frequency tabulation of medical history by SOC and PT

(2) Frequency tabulation of present illness by SOC and PT

Frequency tabulation will be provided according to the rules below.

[Number of subjects]

A subject with multiple occurrences of medical history or present illness within a SOC will be counted only once in that SOC. A subject with multiple occurrences of medical history or present illness within a PT will be counted only once in that PT.

7.6 Medication History and Concomitant Medications

Analysis set: Safety analysis set

Analysis variable(s): Prior medications (other than the influenza vaccination)

Prior medications (influenza vaccination within 1 year)

Concomitant medications

Analysis methods: The following analyses will be performed on the above variables.

The analysis variables will be coded using the WHO Drug and summarized by Preferred Name. Preferred Name will be sorted in decreasing frequency.

If a subject received more than one medication with the same Preferred Name, the subject will be counted only once for that medication (Preferred Name).

(1) Frequency tabulation of prior medications (other than influenza vaccination)

(2) Frequency tabulation of prior medications (influenza vaccination within 1 year)

(3) Frequency tabulation of concomitant medications started before the initial vaccination with the study drug and continued throughout the Treatment Period, and those started after the initial vaccination

7.7 Study Drug Exposure and Compliance

Analysis set: Safety analysis set

Analysis variable(s):	Number of vaccinations with the study drug	[1, 2]
	Time (days) from the initial vaccination to blood collection for antibody titer determination after the initial vaccination	[Min≤ - ≤21, 22≤ - ≤24, 25≤ - ≤Max]
	Time (days) from the second	[Min≤ - ≤19, 20≤ - ≤24, 25≤ - ≤Max]

vaccination to blood collection for antibody titer determination after the second vaccination

Analysis methods: The following analyses will be performed on the above variables.

(1) Frequency tabulation

7.8 Efficacy Analysis

7.8.1 Primary Efficacy Endpoint(s)

Analysis set: Full analysis set

Analysis variable(s):

(i) Seroprotection rate as measured by the SRH antibody titer for the vaccine strain 21 days after the second vaccination

(ii) Seroconversion rate as measured by the SRH antibody titer for the vaccine strain 21 days after the second vaccination

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

Assessment point: Analysis variable (i): Prevaccination, Day 22 of the second vaccination (21 days after the second vaccination)

Analysis variables (ii) and (iii): Day 22 of the second vaccination (21 days after the second vaccination)

Analysis methods: The following analyses will be performed on the "full analysis set."

(1) For analysis variable (i), frequency tabulations, point estimates, and two-sided 95% confidence intervals will be calculated. For reference, the same calculations will also be performed on prevaccination data.

(2) For analysis variable (ii), frequency tabulations, point estimates, and two-sided 95% confidence intervals will be calculated.

(3) For analysis variable (iii), summary statistics, geometric means, and two-sided 95% confidence intervals of the geometric means will be calculated on the fold increase in the SRH antibody titer from baseline.

7.8.2 Secondary Efficacy Endpoint(s)

Analysis set: Full analysis set

Analysis variable(s):

(i) Seroprotection rate as measured by SRH antibody titer for the vaccine strain 21 days after the initial vaccination

(ii) Seroconversion rate as measured by SRH antibody titer for the vaccine strain 21 days after the initial vaccination

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

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

Assessment point:

Analysis variable (i): Prevaccination, Day 22 of the initial vaccination (21 days after the initial vaccination)

Analysis variables (ii) and (iii): Day 22 of the initial vaccination (21 days after the initial vaccination)

Analysis variable (iv): Prevaccination, Day 22 of the initial vaccination (before the second vaccination), Day 22 of the second vaccination (21 days after the second vaccination)

Analysis methods:

The following analyses will be performed on the "full analysis set."

(1) For analysis variable (i), frequency tabulations, point estimates, and two-sided 95% confidence intervals will be calculated. For reference, the same calculations will also be performed on prevaccination data.

(2) For analysis variable (ii), frequency tabulations, point estimates, and two-sided 95% confidence intervals will be calculated.

(3) For analysis variable (iii), summary statistics, geometric means, and two-sided 95% confidence intervals of the geometric means will be calculated on the fold increase in the SRH antibody titer from baseline.

(4) For analysis variable (iv), summary statistics, geometric means, and two-sided 95% confidence intervals of the geometric means will be calculated on the SRH antibody titer for the vaccine strain 21 days after each vaccination. For reference, the same calculations will also be performed on prevaccination data.

7.8.3 Additional Efficacy Endpoint(s)

Analysis set: Full analysis set

Analysis variable(s):

(i) Seroprotection rate as measured by the MN antibody titer for the vaccine strain 21 days after each vaccination

(ii) Seroconversion rate as measured by the MN antibody titer for the vaccine strain 21 days after each vaccination

(iii) GMFI in MN antibody titer from baseline for the vaccine strain 21 days after each vaccination

(iv) GMT of MN antibody titer for the vaccine strain 21 days after each vaccination

Assessment point: Analysis variables (ii) and (iii): Day 22 of the initial vaccination (21 days after the initial vaccination), Day 22 of the second vaccination (21 days after the second vaccination)

Analysis variables (i) and (iv): Prevaccination, Day 22 of the initial vaccination (before the second vaccination), Day 22 of the second vaccination (21 days after the second vaccination)

Analysis methods: The following analyses will be performed on the "full analysis set."

(1) For analysis variable (i), frequency tabulations, point estimates, and two-sided 95% confidence intervals will be calculated. For reference, the same calculations will also be performed on prevaccination data.

(2) For analysis variable (ii), frequency tabulations, point estimates, and two-sided 95% confidence intervals will be calculated.

(3) For analysis variable (iii), summary statistics, geometric means, and two-sided 95% confidence intervals of the geometric means will be calculated on the fold increase in the MN antibody titer from baseline.

(4) For analysis variable (iv), summary statistics, geometric means, and two-sided 95% confidence intervals of the geometric means will be calculated on the MN antibody titer for the vaccine strain 21 days after each vaccination. For reference, the same calculations will also be performed on prevaccination data.

7.8.4 Statistical/Analytical Issues

7.8.4.1 Adjustments for Covariates

Not applicable.

7.8.4.2 Handling of Dropouts or Missing Data

Missing test results and data determined to be non-evaluable according to this SAP will not be used for hypothesis testing and estimations. For the analysis of the SRH antibody titer, values below the lower reporting limit will be replaced with 4, whereas those above the upper reporting limit will be replaced with the upper reporting limit[1]. For the analysis of the MN antibody titer, values below the lower reporting limit will be replaced with 7.1, whereas those above the upper reporting limit will be replaced with the upper reporting limit.

7.8.4.3 Multicenter Studies

Since this is a single-arm study, treatment-by-site interaction will not be evaluated.

7.8.4.4 Multiple Comparison/Multiplicity

Not applicable.

7.8.4.5 Use of an "Efficacy Subset" of Subjects

Not applicable.

7.8.4.6 Active-Control Studies Intended to Show Equivalence or Non-Inferiority

Not applicable.

7.8.4.7 Examination of Subgroups

Not applicable.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

Not applicable.

7.9.2 Pharmacodynamic Analysis

Not applicable.

7.10 Other Outcomes

Not applicable.

[1] Note for guidance on harmonisation of requirements for influenza vaccines(CPMP/BWP/214/96)

7.11 Safety Analysis

7.11.1 Adverse Events

7.11.1.1 Overview of Treatment-Emergent Adverse Events

Analysis set:	Safety analysis set	
Analysis variable(s):	TEAE	
Categories:	Relationship to study drug	[Related, Not related]
	Intensity	[Mild, Moderate, Severe]

Analysis methods: The following summaries will be provided on the above variables.

(1) Overview of TEAEs

1) All TEAEs (number of events, number and percentage of subjects)
2) Relationship of TEAEs to study drug (number of events, number and percentage of subjects)
3) Intensity of TEAEs (number of events, number and percentage of subjects)
4) TEAEs leading to study drug discontinuation (number of events, number and percentage of subjects)
5) Serious TEAEs (number of events, number and percentage of subjects)
6) Relationship of serious TEAEs to study drug (number of events, number and percentage of subjects)
7) Serious TEAEs leading to study drug discontinuation (number of events, number and percentage of subjects)
8) TEAEs resulting in death (number of events, number and percentage of subjects)

TEAEs will be counted according to the rules below.

[Number of subjects]

- Summaries for 2) and 6)
  A subject with occurrences of TEAE in both categories (i.e., “Related” and “Not related”) will be counted once in the “Related” category.
- Summary for 3)
  A subject with multiple occurrences of TEAE will be counted once for

the TEAE with maximum intensity.

- Summaries other than 2), 3), and 6)
  A subject with multiple occurrences of TEAE will be counted only once.

[Number of events]

For each summary, the total number of events will be calculated.

7.11.1.2 Displays of Treatment-Emergent Adverse events

Analysis set:	Safety analysis set	
Analysis variable(s):	TEAE	
Categories:	Intensity	[Mild, Moderate, Severe]
	Vaccination number	[Initial vaccination, Second vaccination]
	Timing of onset by vaccination number	[Day 1 of the initial vaccination ≤ - ≤ Day 7 of the initial vaccination, Day 8 of the initial vaccination ≤ - ≤ Before the second vaccination]
		[Day 1 of the second vaccination ≤ - ≤ Day 7 of the second vaccination, Day 8 of the second vaccination ≤ - ≤ Max]

Analysis methods: The following summaries will be provided for the above analysis variables using frequency tabulations.

TEAEs will be coded using the MedDRA and summarized by SOC and PT. SOC will be sorted alphabetically and PT in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by SOC only or PT only.

(1) TEAEs by SOC and PT

(2) TEAEs by SOC

(3) TEAEs by PT

(4) Drug-related TEAEs by SOC and PT

(5) Intensity of TEAEs by SOC and PT

(6) Intensity of drug-related TEAEs by SOC and PT

(7) TEAEs leading to study drug discontinuation by SOC and PT

(8) Serious TEAEs by SOC and PT

(9) Vaccination number of TEAEs by SOC and PT

(10) Vaccination number and timing of onset of TEAEs by SOC and PT

For each frequency tabulation, the number and percentage of subjects will be obtained according to the rules below.

[Number of subjects]

- Summaries other than (5), (6), (9), and (10)
  A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT. The percentage of subjects with TEAEs will be calculated using the number of subjects in the safety analysis set as the denominator.
- Summaries for (5) and (6)
  A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once for the TEAE with maximum intensity in that SOC or PT. The percentage of subjects with TEAEs will be calculated using the number of subjects in the safety analysis set as the denominator.
- Summary for (9)
  A subject with multiple occurrences of TEAE within a SOC or a PT will be counted once in each relevant category of vaccination number. For calculation of the percentage of subjects with TEAEs for each vaccination number, the denominator used will be the number of subjects "who received the study drug of the relevant vaccination number" in the safety analysis set.
- Summary for (10)
  A subject with multiple occurrences of TEAE within a SOC or a PT will be counted once in each relevant category of vaccination number and timing of onset. For calculation of the percentage of subjects with TEAEs for each timing of onset, the denominator used will be the number of subjects "who received the study drug of the relevant vaccination number" in the safety analysis set.

7.11.1.3 Displays of Pretreatment Events

Analysis set:	All subjects who signed the informed consent form
Analysis variable(s):	PTE
Analysis methods:	The following summaries will be provided for the above analysis variables using frequency tabulations.

PTEs will be coded using the MedDRA and summarized by SOC and PT. SOC will be sorted alphabetically and PT in decreasing frequency.

(1) PTEs by SOC and PT

(2) Serious PTEs by SOC and PT

Frequency tabulation will be provided according to the rules below.

[Number of subjects]

A subject with multiple occurrences of PTE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of PTE within a PT will be counted only once in that PT.

[Number of events]

For each summary, the total number of events will be calculated.

7.11.1.4 Displays of Solicited Local and Systemic Adverse Events

Analysis set:	Safety analysis set	
Analysis variable(s):	Solicited local and systemic AEs to be recorded in the subject diary	
Categories:	Intensity	[Mild, Moderate, Severe]
	Vaccination number	[Initial vaccination, Second vaccination]
	Timing of onset by vaccination number	[Day 1 of the initial vaccination ≤ - ≤ Day 7 of the initial vaccination, Day 8 of the initial vaccination ≤ - ≤ Before the second vaccination]
		[Day 1 of the second vaccination ≤ - ≤ Day 7 of the second vaccination, Day 8 of the second vaccination ≤ - ≤ Max]

Analysis methods: The following summaries will be provided for the above analysis variables using frequency tabulations.

(1) Solicited local and systemic AEs recorded in the subject diary

(2) Solicited local and systemic AEs recorded in the subject diary by intensity

(3) Solicited local and systemic AEs recorded in the subject diary by vaccination number

(4) Solicited local and systemic AEs recorded in the subject diary by vaccination number and timing of onset

For each frequency tabulation, the number and percentage of subjects will be obtained according to the rules below.

[Number of subjects]

- Summary for (1)
  A subject with multiple occurrences of a solicited local or systemic AE recorded in the subject diary will be counted only once for that AE. The percentage of subjects with solicited local or systemic AEs recorded in the subject diary will be calculated using the number of subjects in the safety analysis set as the denominator.
- Summary for 2)
  A subject with multiple occurrences of a solicited local or systemic AE recorded in the subject diary will be counted only once for the AE with maximum intensity. The percentage of subjects with solicited local or systemic AEs recorded in the subject diary will be calculated using the number of subjects in the safety analysis set as the denominator.
- Summary for (3)
  A subject with multiple occurrences of a solicited local or systemic AE recorded in the subject diary will be counted once in each relevant category of vaccination number. For calculation of the percentage of subjects with solicited local or systemic AEs recorded in the subject diary for each vaccination number, the denominator used will be the number of subjects “who received the study drug of the relevant vaccination number” in the safety analysis set.
- Summary for (4)
  A subject with multiple occurrences of a solicited local or systemic AE recorded in the subject diary will be counted once in each relevant category of vaccination number and timing of onset. For calculation of the percentage of subjects with solicited local or systemic AEs recorded in the subject diary for each timing of onset, the denominator used will be

the number of subjects "who received the study drug of the relevant vaccination number" in the safety analysis set.

7.11.2 Clinical Laboratory Evaluations

Not applicable.

7.11.3 Vital Signs

Analysis set:	Safety analysis set
Analysis variable(s):	Systolic blood pressure Diastolic blood pressure Pulse rate Body temperature Respiratory rate
Assessment point:	Systolic blood pressure, diastolic blood pressure, pulse rate: Prevaccination, 30 minutes after the initial vaccination, Day 22 of the initial vaccination (before the second vaccination), 30 minutes after the second vaccination, Day 22 of the second vaccination Body temperature: Prevaccination; Days 1 (after vaccination), 2, 3, 4, 5, 6, 7, and 22 (before the second vaccination) of the initial vaccination; Days 1 (after vaccination), 2, 3, 4, 5, 6, 7, and 22 of the second vaccination Respiratory rate: Prevaccination, 30 minutes after the initial vaccination, Day 22 of the initial vaccination (before the second vaccination), 30 minutes after the second vaccination
Analysis methods:	For systolic/diastolic blood pressure, pulse rate and respiratory rate, analyses (1) and (3) below will be performed. For body temperature, analyses (2) and (3) below will be performed. (1) Summary statistics of measurement values and the changes in postvaccination values (postvaccination – prevaccination of each vaccination) at each assessment point (2) Summary statistics for measurement values at each assessment point (3) Case plots

7.11.4 12-Lead ECGs

Not applicable.

7.11.5 Other Observations Related to Safety

7.11.5.1 Summary of the Longest Diameter of Local Reactions

Analysis set:	Safety analysis set	
Analysis variable(s):	Maximum diameter (cm) of injection site reaction	[Min≤ - <2.5, 2.5≤ - <5.1, 5.1≤ - <10.1, 10.1≤ - ≤Max]
	Maximum diameter (cm) of injection site swelling	[Min≤ - <2.5, 2.5≤ - <5.1, 5.1≤ - <10.1, 10.1≤ - ≤Max]
	Maximum diameter (cm) of injection site induration	[Min≤ - <2.5, 2.5≤ - <5.1, 5.1≤ - <10.1, 10.1≤ - ≤Max]
Categories:	Vaccination number	[Initial vaccination, Second vaccination]
Analysis methods:	The following analyses will be performed on the above variables for each vaccination number. (1) Frequency tabulations for categorical variables and summary statistics for continuous variables	

7.11.5.2 Displays of Treatment-Emergent Adverse Events (Japanese)

Analysis set:	Safety analysis set
Analysis variable(s):	TEAE
Analysis methods:	TEAEs will be summarized in the same way as in Section 7.11.1.2. All summaries will be presented in Japanese.

7.12 Interim Analysis

No interim analysis is planned.

7.13 Changes in the Statistical Analysis Plan

Statistical Analysis Plan (Version 1: Created 7 May 2018 → Version 2: Created 3 Jul 2018)

Before change

Section 7.7: Study Drug Exposure and Compliance

Analysis variable(s): Time (days) from the initial vaccination to blood collection for antibody titer determination after the initial vaccination

[Min≤ - <22, 22≤ - <24, 24≤ - ≤Max]

Time (days) from the second vaccination to blood collection for antibody titer determination after the second vaccination

[Min≤ - <20, 20≤ - <24, 24≤ - ≤Max]

Section 7.11.5.1: Summary of the Longest Diameter of Local Reactions

Analysis variable(s): Maximum diameter (cm) of injection site reaction

[Min≤ - <2.5, 2.5≤ - <5.0, 5.0≤ - <10.0, 10.0≤ - ≤Max]

Maximum diameter (cm) of injection site swelling

[Min≤ - <2.5, 2.5≤ - <5.0, 5.0≤ - <10.0, 10.0≤ - ≤Max]

Maximum diameter (cm) of injection site induration

[Min≤ - <2.5, 2.5≤ - <5.0, 5.0≤ - <10.0, 10.0≤ - ≤Max]

After change

Section 7.7: Study Drug Exposure and Compliance

Analysis variable(s): Time (days) from the initial vaccination to blood collection for antibody titer determination after the initial vaccination

[Min≤ - <=21, 22≤ - <=24, 25≤ - ≤Max]

Time (days) from the second vaccination to blood collection for antibody titer determination after the second vaccination

[Min≤ - <=19, 20≤ - <=24, 25≤ - ≤Max]

Section 7.11.5.1: Summary of the Longest Diameter of Local Reactions

Analysis variable(s): Maximum diameter (cm) of injection site reaction

[Min≤ - <2.5, 2.5≤ - <5.1, 5.1≤ - <10.1, 10.1≤ - ≤Max]

Maximum diameter (cm) of injection site swelling

[Min≤ - <2.5, 2.5≤ - <5.1, 5.1≤ - <10.1, 10.1≤ - ≤Max]

Maximum diameter (cm) of injection site induration

[Min≤ - <2.5, 2.5≤ - <5.1, 5.1≤ - <10.1, 10.1≤ - ≤Max]

Reason for change

Discrepancies from the protocol are corrected.

8.0 REFERENCES

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