

<b>Shionogi Study Title:</b>	A Phase 3, Multicenter, Randomized, Double-blind Study of a Single Dose of S-033188 Compared with Placebo or Oseltamivir 75 mg Twice Daily for 5 Days in Patients with Influenza at High Risk of Influenza Complications
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## STATISTICAL ANALYSIS PLAN

<b>Study Title:</b>	A Phase 3, Multicenter, Randomized, Double-blind Study of a Single Dose of S-033188 Compared with Placebo or Oseltamivir 75 mg Twice Daily for 5 Days in Patients with Influenza at High Risk of Influenza Complications
<b>Study Number:</b>	1602T0832
<b>Study Phase:</b>	3
<b>Product Name:</b>	S-033188
<b>Sponsor:</b>	Shionogi & Co., Ltd./Shionogi Inc.

### Issue Date:

<b>Version 2.0</b>	19 June 2018
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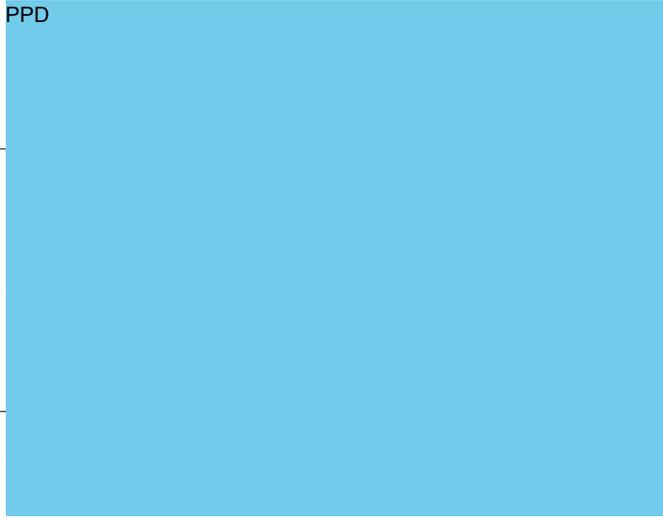
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## SIGNATURE PAGE

### Sponsor's Authors:

PPD



19 JUNE 2018

Date

19 JUNE 2018

Date

## RECORDS ON REVISIONS

Version	Date	Author	Remarks
Version 1.0	06 April 2018	PPD [REDACTED]	First version Collaborators: PPD [REDACTED]
Version 2.0	19 June 2018	PPD [REDACTED]	<ul style="list-style-type: none"><li>• Definition of ITTI population in <a href="#">Section 5.1</a> was updated.</li><li>• Allowance for EQ-5D-5L in <a href="#">Section 6.3</a> was updated.</li><li>• Definition of baseline for efficacy in <a href="#">Section 6.5.2</a> was updated.</li><li>• Supplemental analyses for efficacy assessment were added in <a href="#">Section 9.8</a>.</li><li>• <a href="#">Section 10.1 2)</a> was updated.</li><li>• <a href="#">Section 10.2 5)</a> was added.</li><li>• Supplemental analyses for safety assessment were added in <a href="#">Section 10.6</a>.</li></ul>

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## 1. INTRODUCTION

This document describes the statistical methods to be used in the summary and analysis of data from Protocol 1602T0832. All decisions regarding final analysis, as defined in this statistical analysis plan (SAP), have been made prior to unblinding/database lock of the study data. Table, listing, and figure (TLF) mock-ups are described in the TLF shell document prepared separately. Details of the analyses of pharmacokinetics and pharmacokinetics/pharmacodynamics will also be described in a separate document.

All the analyses described in the SAP will be performed in the Biometrics Department, Shionogi Inc. or Biostatistics Department, Shionogi & Co., Ltd.

The analyses of ‘Polymorphic and treatment-emergent amino acid substitutions in the PA gene of evaluable virus’ and ‘Drug susceptibility in patients with evaluable virus’ in [Section 9.3](#) will be reported in a separate document from the clinical study report (CSR).

## 2. OVERVIEW

This is a randomized, double-blind, multicenter, parallel-group, placebo- and active-controlled study enrolling 2157 patients diagnosed with influenza. Patients are randomly assigned in a ratio of 1:1:1 to receive a single dose of 40 or 80 mg of S-033188 according to their weight category, 75 mg twice daily (BID) of oseltamivir for 5 days, or placebo. With the aim to achieve a broadly comparable exposure, patients who weigh < 80 kg at Screening will receive 40 mg of S-033188, and patients who weigh  $\geq$  80 kg at Screening will receive 80 mg of S-033188.

For the schedule of this study, see [Appendix 1](#).

## 3. STUDY OBJECTIVES

### 3.1 Primary Objective

- To evaluate the efficacy of a single, oral dose of S-033188 compared with placebo by measuring the time to improvement of influenza symptoms in patients with influenza

### 3.2 Secondary Objectives

- To evaluate the efficacy of a single, oral dose of S-033188 compared with oseltamivir 75 mg BID for 5 days by measuring the time to improvement of influenza symptoms in patients with influenza
- To evaluate the efficacy of a single, oral dose of S-033188 compared with placebo by measuring the secondary endpoints in patients with influenza
- To evaluate the efficacy of a single, oral dose of S-033188 compared with oseltamivir 75 mg BID for 5 days by measuring the secondary endpoints in patients with influenza

### **3.3 Other Efficacy Objective**

- To evaluate the polymorphic and treatment-emergent amino acid substitutions in the polymerase acidic protein (PA) gene and drug susceptibility in patients with evaluable virus

### **3.4 Safety Objectives**

- To compare the safety and tolerability of a single dose of S-033188 with placebo
- To compare the safety and tolerability of a single dose of S-033188 with oseltamivir 75 mg BID for 5 days
- To compare the frequency of adverse events (AEs) in patients with influenza of a single dose of S-033188 with oseltamivir 75 mg BID for 5 days and with placebo

### **3.5 Pharmacokinetic Objective**

- To determine the pharmacokinetics (PK) of the active form of S-033188, ie, S-033447, in patients with uncomplicated influenza virus infection

### **3.6 Health Economic Outcomes Research Objective**

- To compare the total quality-of-life change by measuring the EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) and a work productivity (WP) questionnaire in patients treated with S-033188 compared with oseltamivir 75 mg BID for 5 days and placebo

## **4. OUTLINE OF STUDY DESIGN**

### **4.1 Study Blinding**

The study will be conducted in a double-blind, double-dummy fashion by using placebo matching S-033188 and oseltamivir in appearance, labeling, and packaging.

### **4.2 Allocation Procedure**

Patients are randomized on a 1:1:1 basis to S-033188 group, oseltamivir group or placebo group. An interactive response technology (IRT) is used to assign patients to numbers for which treatment is randomly assigned. The randomization is stratified by region (Asia, North America/Europe, Southern Hemisphere), body weight (< 80 kg, ≥ 80 kg), baseline composite symptom score ( $\leq 14$ ,  $\geq 15$ ), and preexisting and worsened symptom (Yes, No: if a patient has at least 1 of 3 symptoms [namely cough, muscle or joint pain, or fatigue] that is preexisting and worsened, the patient will be assigned to the 'Yes' category, otherwise 'No').

### **4.3 Target Sample Size**

The required sample size of the Intention-to-treat Infected (ITTI) Population will be 1185 (395 patients for each treatment group).

It is assumed that the reverse transcription polymerase chain reaction (RT-PCR) positive rate for influenza A or B virus will be 55%. Therefore, 2157 patients (719 patients for each treatment group) will be randomized to ensure an adequate number of patients in the ITTI Population. The number of randomized patients may change based on the percentage of patients who are RT-PCR positive during the study.

The primary analysis of the time to improvement of influenza symptoms is to compare between the S-033188 group and placebo group.

The median of the time to alleviation of symptoms in the placebo-controlled clinical trial of oseltamivir for high risk patients was estimated to be 161.0 hours (95% confidence interval [CI]: 117.3, 215.5) in the placebo group. Based on this result and the fact that the proposed study will use a modified primary endpoint, it was assumed that the median time to improvement of influenza symptoms in the placebo group will be 150 hours.

In the Japanese Phase 2 clinical trial in otherwise healthy patients, the median of the time to alleviation of symptoms was 49.5 hours (95% CI: 44.5, 64.4) in the 40-mg group versus 77.7 hours (95% CI: 67.6, 88.7) in the placebo group. Assuming the ratio of 0.64 (49.5/77.7) for the median time to alleviation of symptoms in the S-033188 group versus the placebo group is not different between otherwise healthy patients and high risk patients, it can further be assumed that the difference between the S-033188 and placebo groups is 54 hours (96 hours in the S-033188 group, 150 hours in the placebo group). In the past, placebo-controlled clinical trials of oseltamivir for the otherwise healthy and high risk patients, have demonstrated that the difference in the median time to alleviation of symptoms between the placebo group and the oseltamivir group for the otherwise healthy patients was larger than that in the studies of high risk patients. Therefore, it is speculated that the difference between the S-033188 group and the placebo group will be < 54 hours.

The required sample size will therefore be calculated based on the conservative assumption of a 36-hour difference (assuming that the median time to improvement of influenza symptoms in the placebo group and the S-033188 group was 150 and 114 hours, respectively) in the median time to improvement of influenza symptoms between the S-033188 group and the placebo group to ensure at least 90% power in the efficacy evaluation of S-033188.

Patients will be randomized on a 1:1 basis to either S-033188 or placebo and a follow-up period will be 336 hours (14 days). Assuming that the time follows an exponential distribution, the study will require 790 patients in the ITTI Population in order for the generalized Wilcoxon test to have 90% or more power with a 2-sided significance level of 5% (395 patients in the S-033188 group and placebo group, respectively).

Using a 1:1 randomization ratio between the S-033188 group and the oseltamivir group, the ITTI population of oseltamivir will be 395 patients. [Table 1](#) shows the statistical power to compare between the S-033188 group and the oseltamivir group under several sets of assumed time to improvement of influenza symptoms.

**Table 1**                      **Statistical Power to Compare between S-033188 and Oseltamivir**

Median time to alleviation of symptoms (S-033188 group, oseltamivir group)	Statistical power for comparison between the S-033188 group and the oseltamivir group by stratified generalized Wilcoxon test
(114 hours, 126 hours)	22.3%
(108 hours, 126 hours)	45.3%
(102 hours, 126 hours)	71.5%
(96 hours, 126 hours)	90.2%

## 5. ANALYSIS POPULATIONS

### 5.1 Efficacy and Safety Populations

The definitions of the Intention-to-treat-Infected (ITTI) Population and the Per-protocol Set (PPS) as efficacy populations, and Safety Population are provided below. In this study, the ITTI Population is the primary analysis population. The PPS is the secondary analysis population, and data from the PPS will be used to perform a sensitivity analysis for the primary analysis.

The following analysis populations will be analyzed for this study. The analysis populations will be determined before unblinding.

#### 1) Intention-to-treat-Infected Population

This population includes all patients who receive the study drug with a confirmed diagnosis of influenza virus infection and are enrolled at sites with good clinical practice (GCP) compliance. Confirmation of influenza virus infection will be based on the results of RT-PCR on Day 1. The population will be analyzed according to the treatment to which the patients are randomized.

#### 2) Per-protocol Set

This population includes all subjects included in the ITTI Population and did not meet any of the following conditions:

- Ineligible patients
- Patients with noncompliance of treatment
  - Treatment compliance rate is less than 60%. The definition of treatment compliance rate shown in [Section 8.1](#) will be used.
- Patients with inadequate Follow-up
  - Subjects have no symptom data after initial treatment
- Patients with prohibited medications
- Patients with incorrect treatment allocation
- Patients with severe protocol deviation

#### 3) Safety population

This population includes all randomized patients who receive at least 1 dose of the study drug. The population will be analyzed according to the initial treatment

that the patients actually received. If a subject takes S-033188 and oseltamivir as the initial treatment, the subject belongs to the S-033188 group.

## **6. HANDLING OF DATA IN ANALYSES**

### **6.1 Statistical Analysis**

Unless otherwise noted, continuous variables will be summarized by using the number of nonmissing observations, arithmetic mean, standard deviation, median, minimum, and maximum values as summary statistics; categorical variables will be summarized by using the frequency count and the percentage of subjects in each category as summary statistics.

Subject study data, including data not appearing in tables, will be presented in by-subject data listings. In general, all tables will be presented by treatment group. Individual subject data and any derived data will be presented by treatment and subject. All analyses and tabulations will be performed using SAS<sup>®</sup> Version 9.2 or higher.

### **6.2 Statistical Tests**

All statistical tests will be performed at the 0.05 significance level using 2-sided tests, unless otherwise noted.

The primary endpoint will first be compared between the S-033188 and placebo groups (primary analysis). Together with the primary efficacy analysis, the comparison between the S-033188 and the oseltamivir groups (secondary analysis) will be conducted. For the submission to countries other than Japan the secondary analysis will only be performed if a statistically significant difference is observed in the primary analysis, in order to maintain control of overall type I error.

### **6.3 Acceptable Time Windows for Investigations, Observations, and Examinations**

The acceptable time windows shown in [Table 2-1](#) will be used to collect data from the patient diary.

**Table 2-1 Acceptable Time Windows for Parameters of the Patient Diary**

<b>Time Point</b>	<b>Specified Assessment Time Point</b>	<b>Acceptable Time Window</b>
12 hours postdose	Time of first dosing + 12 hours	Between $\geq 6$ and $< 18$ hours after first dosing
24 hours postdose	Time of first dosing + 24 hours	Between $\geq 18$ and $< 30$ hours after first dosing
36 hours postdose	Time of first dosing + 36 hours	Between $\geq 30$ and $< 42$ hours after first dosing
48 hours postdose	Time of first dosing + 48 hours	Between $\geq 42$ and $< 54$ hours after first dosing
60 hours postdose	Time of first dosing + 60 hours	Between $\geq 54$ and $< 66$ hours after first dosing
72 hours postdose	Time of first dosing + 72 hours	Between $\geq 66$ and $< 78$ hours after first dosing
84 hours postdose	Time of first dosing + 84 hours	Between $\geq 78$ and $< 90$ hours after first dosing
96 hours postdose	Time of first dosing + 96 hours	Between $\geq 90$ and $< 102$ hours after first dosing
108 hours postdose	Time of first dosing + 108 hours	Between $\geq 102$ and $< 114$ hours after first dosing
120 hours postdose	Time of first dosing + 120 hours	Between $\geq 114$ and $< 126$ hours after first dosing
132 hours postdose	Time of first dosing + 132 hours	Between $\geq 126$ and $< 138$ hours after first dosing
144 hours postdose	Time of first dosing + 144 hours	Between $\geq 138$ and $< 150$ hours after first dosing
156 hours postdose	Time of first dosing + 156 hours	Between $\geq 150$ and $< 162$ hours after first dosing
168 hours postdose	Time of first dosing + 168 hours	Between $\geq 162$ and $< 174$ hours after first dosing
180 hours postdose	Time of first dosing + 180 hours	Between $\geq 174$ and $< 186$ hours after first dosing
192 hours postdose	Time of first dosing + 192 hours	Between $\geq 186$ and $< 198$ hours after first dosing
204 hours postdose	Time of first dosing + 204 hours	Between $\geq 198$ and $< 210$ hours after first dosing
216 hours postdose	Time of first dosing + 216 hours	Between $\geq 210$ and $< 222$ hours after first dosing
240 hours postdose	Time of first dosing + 240 hours	Between $\geq 228$ and $< 252$ hours after first dosing
264 hours postdose	Time of first dosing + 264 hours	Between $\geq 252$ and $< 276$ hours after first dosing
288 hours postdose	Time of first dosing + 288 hours	Between $\geq 276$ and $< 300$ hours after first dosing
312 hours postdose	Time of first dosing + 312 hours	Between $\geq 300$ and $< 324$ hours after first dosing
336 hours postdose	Time of first dosing + 336 hours	Between $\geq 324$ and $< 348$ hours after first dosing
360 hours postdose	Time of first dosing + 360 hours	Between $\geq 348$ and $< 372$ hours after first dosing
384 hours postdose	Time of first dosing + 384 hours	Between $\geq 372$ and $< 396$ hours after first dosing
408 hours postdose	Time of first dosing + 408 hours	Between $\geq 396$ and $< 420$ hours after first dosing
432 hours postdose	Time of first dosing + 432 hours	Between $\geq 420$ and $< 444$ hours after first dosing
456 hours postdose	Time of first dosing + 456 hours	Between $\geq 444$ and $< 468$ hours after first dosing
480 hours postdose	Time of first dosing + 480 hours	Between $\geq 468$ and $< 492$ hours after first dosing
504 hours postdose	Time of first dosing + 504 hours	Between $\geq 492$ and $< 516$ hours after first dosing
528 hours postdose	Time of first dosing + 528 hours	Between $\geq 516$ and $< 600$ hours after first dosing

Time points for EuroQol–5 Dimensions–5 Levels (EQ-5D-5L) and a visual analogue scale included in EQ-5D-5L will be not assigned separately.

The acceptable time windows shown in [Table 2-2](#) will be used for the assessment of items other than data from the patient diary.

**Table 2-2 Acceptable Time Windows for Parameters Other than Data from the Patient Diary**

<b>Time Point</b>	<b>Acceptable Time Window</b>
Predose at Visit 1 (Day 1: Day -2 to Day1)	Predose from Day -2 to Day 1 for safety assessment
Predose at Visit 1(Day 1)	Predose on Visit 1 for efficacy assessment
Postdose at Visit 1 (Day 1)	QOL assessment with EQ-5D-5L questionnaire: by 0.5 hour post-dose on Day 1 Other measurements: 0.5 to 4 hours post-dose on Day 1
Visit 2 (Day 2)	Day 2
Visit 3 (Day 3)	Between Days 3 and 4
Optional Visit 1 (Day 4)	Day 4
Visit 4 (Day 5)	Between Days 5 and 6
Optional Visit 2 (Day 6)	Day 6
Visit 5 (Day 9)	Between Days 7 and 11
Visit 6 (Day 15)	Between Days 12 and 18
Visit 7 (Day 22)	Between Days 19 and 25
Early Termination	Date of Early Termination + 3 days

Measurements collected within the acceptable time window for each scheduled assessment time point, including data obtained at the time of withdrawal, will be used for the analyses of all endpoints at each assessment time point. For all patients with multiple measurements within a visit window, the measurement obtained closest to the target time point will be used, except for EQ-5D-5L at 528 hours. If 2 measurements collected with the same time deviation exist before and after the target time point, the measurement obtained before the target time point will be adopted for analysis. Only for the assessment of EQ-5D-5L at 528 hours, data entered at the site is prioritized if multiple measurements collected within the window. The assessment time point having no measurements within the corresponding acceptable time window will be considered as missing.

In the patient diary, if there are multiple measurements which may be adopted for a scheduled assessment, even though the above rules have been strictly followed, the measurements of the earlier assessment date or the earlier assessment time of day will be adopted (with the priority given to morning, followed by afternoon, evening, and bedtime, in this order). If multiple measurements collected at the same time (date and time) for body temperature, the highest measurement will be adopted.

In the assessment of items from other than the patient diary, if there are multiple measurements that may be adopted for a scheduled assessment time point (even though the above rules have been strictly followed), the below rules will be applied:

1. The measurements at the time point entered in the case report form (CRF) will be adopted.
2. The measurements with the smallest specimen ID will be adopted if there are still more than one measurement after rule 1 is applied.

#### **6.4 Handling of Missing Data**

If the time of first dosing is missing and the dates of first dosing and assessment of influenza symptom before randomization are same, the time of assessment of influenza symptom before randomization will be imputed.

Other missing data will not be imputed.

- Patients who do not experience improvement of symptoms will be censored at the last observation time point, except for sensitivity analysis for the primary analysis.
  - If all symptoms were missing after baseline, the time to improvement of symptoms, the time to improvement of symptoms excluding cough, the time to improvement of the 4 systemic symptoms, the time to improvement of the 3 respiratory symptoms, and the time to improvement of individual symptoms will be handled as missing.
- The following rules will be applied to the assessment of the primary endpoint.
  - If at least 1 of 7 influenza symptom scores except for the preexisting symptoms judged as 'not worsened' and 'severe' at baseline is missing but the date and time of assessment are not missing, the missing values will conservatively be treated as failures at the corresponding date and time of assessment.
  - If influenza symptom scores are missing for the preexisting symptoms judged as 'not worsened' and 'severe' at baseline, these symptoms will not be evaluated for assessment of the primary endpoint.
- The following rule will be applied to the assessment of 'Time to alleviation of symptoms'.
  - If at least 1 of the 7 influenza symptom scores is missing but the date and time of assessment are recorded, this missing assessment will conservatively be treated as a moderate or severe symptom (as failures) at the corresponding date and time of assessment.
- The following rules will be applied to the assessment of 'Time to improvement of the 4 systemic symptoms'.
  - If at least 1 of 4 systemic symptom scores except for the preexisting symptoms judged as 'not worsened' and 'severe' at baseline is missing but the date and time of assessment are not missing, the missing values will conservatively be treated as having a moderate or severe symptom (as failures) at the corresponding date and time of assessment.

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- If influenza symptom scores are missing for the preexisting symptoms judged as ‘not worsened’ and ‘severe’ at baseline, these will not be evaluated for assessment.
  - The following rules will be applied to the assessment of ‘Time to improvement of the 3 respiratory symptoms’.
    - If at least 1 of 3 respiratory symptom scores except for the preexisting symptoms judged as ‘not worsened’ and ‘severe’ at baseline is missing but the date and time of assessment are not missing, the missing values will conservatively be treated as having a moderate or severe symptom (as failures) at the corresponding date and time of assessment.
    - If influenza symptom scores are missing for the preexisting symptoms judged as ‘not worsened’ and ‘severe’ at baseline, these will not be evaluated for assessment.
  - The following rule will be applied to the assessment of ‘Time to improvement of individual symptoms’.
    - If the symptom score is missing but the date and time of assessment are recorded, the missing assessment will conservatively be treated as not improved (as failures).
  - The following rule will be applied to the assessment of ‘Time to resolution of fever’.
    - If the value of body temperature is missing but the date and time of assessment are recorded, the missing assessment will conservatively be treated as more than 37°C (as failures).
  - The following rule will be applied to the assessment of ‘Time to return to preinfluenza health status’.
    - If the score of health status is missing but the date and time of assessment are recorded, the missing assessment will conservatively be treated as having less than the score of the preinfluenza health status.
  - For the sensitivity analysis for the primary endpoint, the patients who do not experience improvement of symptoms will be treated as follows.
    - For patients who discontinue from the study and still have influenza symptoms, the time to improvement of symptoms will be censored as 336 hours.
    - In consideration of treatment duration of the oseltamivir group.
      - For patients who discontinue up to Day 5 and still have influenza, the time to improvement of symptoms will be censored at the last observation time point.
      - If patients who discontinue after Day 5 and still have influenza, the time to improvement of symptoms will be censored as 336 hours.
    - In consideration of the reason of the discontinuation.

- For patients who discontinue due to AE or lack of efficacy, the time to improvement of symptoms will be censored as 336 hours.
- For patients who discontinue due to other reason, the time to improvement of symptoms will be censored at the last observation time point.

#### **6.4.1 Handling of Virology Test Data in Consideration of the Stability Window**

Sample processing time is defined as the time between the time of sample collecting and the time of sample aliquotting recorded in the shipment manifest from Eurofins. Any quantitative influenza virus titer and quantitative PCR samples processed within 96 hour as sample processing time will be included for analysis. The qualitative PCR before initial dosing is excluded from the 96 hour turn-around requirement. All qualitative PCRs before initial dosing will be considered evaluable regardless of sampling and aliquotting time. If the time of sample aliquotting is not recorded at Eurofins, sample processing time will be treated as missing and the sample will not be used for analysis.

### **6.5 Definition**

#### **6.5.1 Display of Days of Study**

The date of the first dose and the day before the first dose of the treatment will be designated as Day 1 and Day -1, respectively.

#### **6.5.2 Baseline**

For influenza symptom scores, the measurement entered in the CRF is defined as baseline. If there are influenza symptom scores entered in the e-Diary prior to the initial dosing, these measurements will not be used for analysis.

For body temperature, the measurement entered in the CRF as baseline is defined as baseline.

For assessment of health and EQ-5D-5L<sup>1</sup>, the measurement with the following 2 conditions is defined as baseline. If there are multiple measurements that may be adopted, the measurement obtained at the earliest time will be used, otherwise measurements prior to the initial dosing will not be used for analysis.

- Data observed when e-Diary is set up
- Data observed on the same date as the date of the first administration

For assessment of health prior to influenza symptoms, the measurement with the following condition is defined as health status prior to influenza symptoms. If there are

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<sup>1</sup> Baseline time point for EQ-5D-5L and a visual analogue scale included in EQ-5D-5L will be not assigned separately.

multiple measurements that may be adopted, the measurement obtained at the earliest time will be used.

- Data observed on the same date as the date of the first administration

For efficacy assessments other than above, baseline is defined as the measurement obtained at Visit 1 (predose).

For safety assessments other than above, baseline is defined as the last measurement obtained before the first administration.

## **7. DEMOGRAPHIC VARIABLES AND OTHER BASELINE CHARACTERISTICS**

### **7.1 Subject Disposition**

- 1) Among all randomized subjects, the numbers of subjects who complete the study and subjects who discontinue the study will be tabulated by treatment group. For subjects who discontinue the study, reasons for withdrawal will also be tabulated by treatment group.
- 2) The number and percentage of subjects included in each of the ITTI and the PPS Populations among all randomized subjects will be calculated by treatment group. For the subjects excluded from each population, the reason for exclusion will be summarized. Fisher's exact test will be performed with a 2-sided significance level of 0.15 to check differences between the S-033188 group and the placebo or the oseltamivir group regarding the distribution of subjects in the ITTI and the PPS Populations.
- 3) The number and percentage of subjects included in the Safety population among all randomized subjects will be calculated by treatment group. For the subjects excluded from the Safety population, the reason for exclusion will be summarized. Patients who take at least 1 dose of the study drug will be included in the treatment group of the drug that they received. Patients who do not take any doses of study drug will be included in the treatment group that they were randomized to.

### **7.2 Demographic and Baseline Characteristics**

The following demographic and baseline characteristics among the ITTI and Safety Populations will be summarized using descriptive statistics for the S-033188 group, oseltamivir group and placebo group. For quantitative data, the descriptive statistics will be calculated. For qualitative data, the frequency of each category and the percentage of subjects in each category among all subjects included in the analysis population will be presented.

- Continuous variables  
Age, height, body weight, body mass index (BMI), composite symptom scores of influenza symptoms body temperature, influenza virus titer at baseline, amount of virus RNA at baseline
- Categorical variables  
Age, body weight, sex, region, race, ethnicity, prior drug, prior therapy, medical history, smoking habits, presence or absence of meal before initial study treatment, presence or absence of meal after initial study treatment, duration between meal and administration (hours) (definition: absolute value of “time of dosing on Day 1” minus “time of meal obtained closest to the time of dosing on Day 1”), composite symptom scores, time to treatment from flu onset, influenza virus subtype based on Rapid Influenza Diagnostic Test (RIDT), influenza virus subtype based on RT-PCR, presence or absence of flu vaccination.

If the mealtime before/after initial study treatment and the time of initial study treatment are not chronological, it will be assumed that the date is before/after the date of initial study treatment.

High risk factors (see [Table 8](#)) among the ITTI and Safety Populations will also be summarized by treatment groups.

The preexisting and worsened symptoms of ‘cough’, ‘muscle or joint pain’, and ‘fatigue’ will also be summarized by treatment groups for the ITTI Population. The categories for the summarization are ‘preexisting and worsened’, ‘preexisting and not worsened’ and ‘absent’. The percentage of patients with ‘preexisting and worsened’ will be calculated by treatment groups for the ITTI population also.

## 8. STUDY CONDUCT

### 8.1 Treatment Exposure and Compliance

The duration of treatment exposure will be summarized with descriptive statistics by the S-033188 group and oseltamivir group for the safety population.

The duration of treatment exposure [day] in the oseltamivir group is defined as the dosing period during which a subject takes medication as follows:

$$\{(\text{final dose date}) - (\text{initial dose date}) + 1\}$$

For the S-033188 group, duration of exposure is defined as 1 day if actual S-033188 tablets are dosed on Day 1.

The treatment compliance rate will be summarized with descriptive statistics by the treatment group for the Safety population. In addition, the frequency of each category (shown in [Table 8](#)) and the percentage of subjects in each category among all subjects included in the analysis population will be presented.

The treatment compliance rate [%] in the oseltamivir group is defined as:

$$100 \times \left\{ \frac{\text{actual frequency of treatment exposure}}{\text{expected frequency of treatment exposure by early discontinuation of treatment}} \right\}$$

For S-033188 group, treatment compliance is defined as 100% if actual S-033188 tablets are dosed on Day 1.

## 8.2 Medical History

Prior and concomitant medical histories will be coded using the MedDRA Version 19.1. Medical history (concurrent and previous disease) will be presented by treatment groups for the Safety population.

## 8.3 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. Medication consists of drug and therapy. Prior medication is defined as all medications taken before Day 1 of study administration. Concomitant medication is defined as all medications taken on Day 1 or later. The drug and therapy can also be classified as both prior and concomitant if the medication starts before study administration and is still ongoing after study administration.

For Safety population, the number of subjects who took prior medication and concomitant medication, and corresponding proportion will be summarized by WHO class and Preferred Term for each treatment group. For Safety population, the number of subjects who had prior therapy and concomitant therapy, and corresponding proportion will be summarized for each treatment group.

For ITTI Population, the frequency of acetaminophen use collected in the eDiary will be summarized by treatment groups. If the date or time of acetaminophen use is missing, but the record is available, the record is counted as the information that the patient uses acetaminophen. The Wilcoxon rank sum test will be used to compare the frequencies between the S-033188 group and the placebo or the oseltamivir group. The 2-sided significance level will be set at 0.15 in these analyses.

## 9. EFFICACY ANALYSIS

In the ITTI Population that is the primary analysis population, the primary endpoint and all secondary endpoints will be analyzed. For the PPS that is a secondary analysis population, only the primary endpoint will be analyzed. [Table 3](#) summarizes the primary endpoint, secondary endpoints, other endpoints and statistical methods used to analyze these endpoints. The detailed statistical methods are described in later sections.

The analysis of each efficacy endpoint will consist of comparison between the S-033188 group (40 mg and 80 mg combined) and the placebo group, and comparison between the S-033188 group (40 mg and 80 mg combined) and the oseltamivir group.

**Table 3 Statistical Methods Used to Analyze Each Endpoint**

Endpoint Analysis		Statistical Method
Primary Endpoint	Time to improvement of symptoms	1, 2, 9, 10, 11
Secondary Endpoints	Proportion of patients positive for influenza virus titer	3, 13
	Proportion of patients positive by RT-PCR	3, 13
	Change from baseline in influenza virus titer	4, 12
	Change from baseline in the amount of virus RNA (RT-PCR)	4, 12
	Area under the curve adjusted by baseline in influenza virus titer	4, 12
	Area under the curve adjusted by baseline in the amount of virus RNA (RT-PCR)	4, 12
	Time to cessation of viral shedding by influenza virus titer	1, 9, 10, 11
	Time to cessation of viral shedding by RT-PCR	1, 9, 10, 11
	Proportion of patients whose symptoms has been improved	3, 13
	Time to alleviation of symptoms	1, 9, 10, 11*
	Time to improvement in the 4 systemic symptoms	1, 9, 10, 11*
	Time to improvement in the 3 respiratory symptoms	1, 9, 10, 11*
	Time to resolution of fever	1, 9, 10, 11
	Proportion of patients reporting normal temperature	3, 13
	Body temperature	6, 12
	Time to improvement of individual symptoms	1, 9, 10, 11*
	Time to return to preinfluenza health status	1, 9, 10, 11*
Other Endpoints	Requirement for systemic antibiotics for infections secondary to influenza infection	5, 13
	Incidence of influenza-related complications	5, 13
	Serum influenza antibody titer	7, 13, 14
	Polymorphic and treatment-emergent amino acid substitutions in the PA gene of evaluable virus	13
	Drug susceptibility in patients with evaluable virus	12
	EQ-5D-5L and EQ VAS	12
	Work productivity questionnaire	12
Intrahousehold infection rate	8	

EQ-5D-5L = EuroQol-5 Dimensions-5 Levels; EQ VAS = Euro Qol visual analog scale

\* Confidence interval of difference in median time between treatment groups will not be calculated.

[Statistical test methods]

1. Stratified Peto-Prentice's generalized Wilcoxon test
2. Stratified log rank test
3. Mantel-Haenszel test
4. van Elteren test
5. Fisher's exact test

6. Analysis of covariance (ANCOVA)
  7. Wilcoxon rank sum test
  8. Poisson regression model
- [Summarization methods]
9. Kaplan-Meier curve
  10. Median time and its 95% confidence interval
  11. Treatment group difference in median time and its 95% confidence interval (Bootstrap method)
  12. Summary statistics (continuous variables)
  13. Summary statistics (categorical variables)
  14. Geometric mean

## 9.1 Primary Endpoint

The primary efficacy endpoint will be the time to improvement of influenza symptoms (with modification for preexisting symptoms):

- Preexisting symptoms (i.e., cough, fatigue, or muscle/joint pain that existed prior to developing influenza) that were judged by the patient to be worse at baseline (i.e., the predose examinations) must improve from baseline severity
  - Improvement in baseline severity is as follows:
    - Severe → moderate, mild, or absent
    - Moderate → mild or absent
    - Mild → mild or absent
    - Absent → mild or absent
  - Note: At baseline (i.e., the predose examinations), patients will only be asked if preexisting symptoms existed (within the last 30 days) and if they were worsened by influenza. Patients will be asked to rate the severity at baseline that needs to improve. To avoid recall bias, patients will not be asked to rate the severity of preexisting symptoms prior to influenza.
- Preexisting symptoms (i.e., cough, fatigue, or muscle/joint pain that existed prior to developing influenza) that were judged by the patient to NOT be worse at baseline (i.e., the predose examinations) must have their baseline severity maintained
  - Maintenance of baseline severity is as follows:
    - Severe → severe or less than severe
    - Moderate → moderate or less than moderate
    - Mild → mild or absent
    - Absent → mild or absent
- For new symptoms at baseline (i.e., the predose examinations), alleviation of symptoms assessment must be achieved
  - Alleviation of symptoms is as follows:
    - Severe → mild or absent
    - Moderate → mild or absent

- Mild → mild or absent
- Absent → mild or absent

Time to improvement of influenza symptoms is defined as the time from the initiation of the study treatment to the improvement of influenza symptoms. Once all of a patient's influenza symptoms are alleviated, maintained, or improved (hereafter all will be called 'improvement') as defined above, the endpoint for that patient will be reached, for a duration of at least 21.5 hours (24 hours –10%).

Patients who do not experience improvement of symptoms will be censored at the last observation time point.

## 9.1.1 Analyses of Primary Endpoint

### 9.1.1.1 Primary Analysis

The time to improvement of influenza symptoms will be compared between the S-033188 group and the placebo group or the oseltamivir group using the stratified Peto-Prentice's generalized Wilcoxon test with composite symptom score, i.e, sum of 7 influenza symptoms, at baseline ( $\leq 14$  or  $\geq 15$ ), preexisting and worsened symptom (Yes or No: if a patient has at least 1 of 3 symptoms [namely cough, muscle or joint pain, or fatigue] that is preexisting and worsened, the patient will be assigned to the 'Yes' category, otherwise 'No'), and region (Asia, North America/Europe, Southern Hemisphere) as stratification factors.

[Comparison between the S-033188 group and the placebo group]

```
proc lifetest data = analysisdata;  
  where TRTP in ("S-033188", "Placebo");  
  time TIME * CENSOR (0);  
  strata SCOREC PREEX REGION / group = TRTP test = PETO ;  
run;quit;
```

- TRTP: Treatment group
- TIME: Time to alleviation of symptoms
- SCOREC: Category of baseline composite symptom score ( $\leq 14$  or  $\geq 15$ )
- PREEX: Category of preexisting and worsened (Yes or No)
- REGION: Category of region (Asia, North America/Europe, Southern Hemisphere)

The same analysis in PPS will be performed as a sensitivity analysis.

### 9.1.1.2 Other Analysis

The Kaplan-Meier survival curve will be plotted for each treatment group, and the median time to improvement of influenza symptoms and its 95% CI will be calculated. The Greenwood method will be used in the calculation of the CIs. In addition, the treatment group difference in median time and its 95% CI will be estimated.

The 95% CI of treatment group difference in median time will be obtained by the bootstrap percentile method. The 10,000 bootstrap samples will be generated using the following SAS code. A random seed of 16010831 and 16010832 will be used for comparison between the S-033188 and the placebo or the oseltamivir, respectively. Then, the treatment group difference in median time will be calculated in each bootstrapped sample and its 95% CI will be constructed using percentiles of the bootstrap distribution.

```
proc surveyselect data = analysisdata seed = 16010831 out = bootstap method = urs  
  rate = 1.0 rep = 10000 outhits;  
  strata TRTP;  
run;quit;
```

- TRTP: Treatment group

The same analysis in PPS will be performed as a sensitivity analysis.

### 9.1.1.3 Sensitivity Analysis

- 1) Time to improvement of influenza symptoms will be compared between the S-033188 group and the placebo group using the stratified log-rank test with composite symptom score at baseline ( $\leq 14$  or  $\geq 15$ ), preexisting and worsened symptom (Yes or No), and region (Asia, North America/Europe, Southern Hemisphere) as stratification factors. Patients who do not experience improvement of influenza symptoms will be censored at the last observation time point. The same analysis will be applied to compare the S-033188 group with the oseltamivir group.
- 2) Patients who discontinue from the study and still do not achieve the improvement of influenza symptoms will be treated as follows in the similar analysis described in [Sections 9.1.1.1](#), [9.1.1.2](#) and [9.1.1.3](#) (excluding analyses of PPS population and 95% CI for the treatment group difference in the median time).
  - If a patient discontinues from the study and still does not achieve improvement of influenza symptoms, the time to improvement of influenza symptoms will be treated as censored at 336 hours.
  - In consideration of treatment duration of the oseltamivir group.
    - For patients who discontinue up to Day 5 and still do not achieve improvement of influenza symptoms, the time to improvement of influenza symptoms will be treated as censored at the last observation time point.

- For patients who discontinue after Day 5 and still do not achieve the improvement of influenza symptoms, the time to improvement of influenza symptoms will be treated as censored at 336 hours.
  - In consideration of the reason of the discontinuation.
    - If a patient discontinues due to an AE or lack of efficacy, the time to improvement of influenza symptoms will be treated as censored at 336 hours.
    - If a patient discontinues due to other reasons, the time to improvement of influenza symptoms of the patients will be censored at the last observation time point.
- 3) Time to improvement of symptoms excluding the cough symptom will be compared between the S-033188 group and the placebo group using the same analysis method as that for the sensitivity analysis in [Section 9.1.1.3 2](#)). The same analysis will be applied to compare the S-033188 group with the oseltamivir group.

## 9.2 Secondary Endpoints

- 1) Proportion of patients positive for influenza virus titer (unit: %)  
Proportion of patients positive for influenza virus titer is defined as the percentage of patients whose influenza virus titer is not less than the lower limit of quantification ( $0.7 \log_{10} \text{TCID}_{50}/\text{mL}$ ) or positive among those assessed for influenza virus titer on Days 2, 3, 4, 5, 6, and 9. Patients with a positive influenza virus titer on Day 1 will be included in this analysis.
- 2) Proportion of patients positive by RT-PCR (unit: %)  
Proportion of patients positive by RT-PCR is defined as the percentage of patients with detectable virus RNA (2.05 for flu A and 2.83 for flu B  $\log_{10} \text{vp}/\text{mL}$ ) among those assessed by RT-PCR on Days 2, 3, 4, 5, 6, and 9.  
Patients with a positive by RT-PCR on Day 1 will be included in this analysis.
- 3) Change from baseline in influenza virus titer (unit:  $\log_{10} \text{TCID}_{50}/\text{mL}$ )  
Change from baseline in influenza virus titer is defined as the change from baseline in influenza virus titer on Days 2, 3, 4, 5, 6, and 9. If influenza virus titer is less than the lower limit of quantification, the virus titer will be imputed 0.7 ( $\log_{10} \text{TCID}_{50}/\text{mL}$ ).  
Patients with a positive virus titer on Day 1 will be included in this analysis.
- 4) Change from baseline in the amount of virus RNA (RT-PCR) (unit:  $\log_{10}$  virus particles/mL)  
Change from baseline in the amount of virus RNA is defined as the change from baseline in the amount of virus RNA on Days 2, 3, 4, 5, 6, and 9. If the amount of virus RNA is less than the lower limit of quantification and greater than or equal to the lower limit of detection, the amount of virus RNA will be imputed 2.18 for flu A and 2.93 for flu B ( $\log_{10}$  virus particles/mL). If the amount of virus RNA is

less than the lower limit of detection, the amount of virus RNA will be imputed 2.05 for flu A and 2.83 for flu B ( $\log_{10}$  vp/mL). If the result is reported as 'POS' but the amount of virus RNA is not reported, the record will not be used for analysis. If a patient is infected with 1 virus type, the amount of virus RNA for infected virus type will be used for analysis. If a patient is infected with multiple virus types, the sum of those amounts of virus RNA  $[\log_{10}(10^{\log_{10}(\text{amount for flu A})} + 10^{\log_{10}(\text{amount for flu B})})]$  will be used for analysis. If the amount of virus RNA is missing for at least 1 of the multiple infected virus types collected on the same date, the amount of multiple virus RNA will be handled as missing at the corresponding date of assessment.

Patients with a positive by RT-PCR on Day 1 will be included in this analysis.

- 5) Area under the curve adjusted by baseline in influenza virus titer  
(unit:  $\log_{10}\text{TCID}_{50}/\text{mL} \times \text{hours}$ )

This endpoint is defined as AUC of change from baseline in influenza virus titer from Day 1 to Day 9. Area under the curve is calculated using the trapezoidal method. Area under the curve of change from time 0 ( $t_0$ ) to time  $K$  ( $t_K$ ) is given by the formula

$$\sum_{k=1}^K \frac{(y_k + y_{k-1} - 2y_0)(t_k - t_{k-1})}{2}$$

where  $t_k$  (hours) represents the time of the  $k^{\text{th}}$  viral titer assessment ( $k = 0, \dots, K$ ) and  $y_k$  represents the  $\log_{10}$  value of the  $k^{\text{th}}$  viral titer assessment ( $\log_{10}\text{TCID}_{50}/\text{mL}$ ). The lower limit is defined as 0.7 ( $\log_{10}\text{TCID}_{50}/\text{mL}$ ). One day is equal to 24-hours.

Patients with a positive influenza virus titer on Day 1 and available sample on Day 9 will be included in this analysis.

All measurements collected within acceptable time windows from Day 1 to Day 9 will be used to calculate the endpoint. If more than one measurement is collected on the same date, the measurement with smallest specimen ID will be used.

- 6) Area under the curve adjusted by baseline in the amount of virus RNA (RT-PCR)  
(unit:  $\log_{10}$  virus particles/mL  $\times$  hours)

This endpoint is defined as AUC of change from baseline in the amount of virus RNA (RT-PCR) from Day 1 to Day 9. The AUC is calculated using the same formula described in 'Area under the curve adjusted by baseline in influenza virus titer'. The lower limit of quantification and greater than or equal to the lower limit of detection is defined as 2.18 for flu A and 2.93 for flu B ( $\log_{10}$  virus particles/mL). The amount of virus RNA is less than the lower limit of detection, the amount of virus RNA will be imputed 2.05 for flu A and 2.83 for flu B ( $\log_{10}$  vp/mL). If a patient is infected with one virus type, the amount of virus RNA for infected virus type will be used for analysis. If a patient is infected with multiple virus types, the sum of those amounts of virus RNA will be used for analysis. If the amount of virus RNA is missing for at least one of the multiple infected virus

types collected on the same date, the amount of multiple virus RNA will be handled as missing at the corresponding date of assessment.

Patients with a positive by RT-PCR on Day 1 and available sample on Day 9 will be included in this analysis.

All measurements collected within acceptable time windows from Day 1 to Day 9 will be used to calculate the endpoint. If more than one measurement is collected on the same date, the measurement with smallest specimen ID will be used.

7) Time to cessation of viral shedding by influenza virus titer (unit: hours)

This endpoint is defined as the time between the initiation of the study treatment and first time when the influenza virus titer is below the limit of detection ( $0.7 \log_{10} \text{TCID}_{50}/\text{mL}$ ) or negative. Patients whose virus titers have not reached the limit by the last observation time point will be treated as censored at that time point. One day is converted into 24 hours.

Patients with a positive virus titer on Day 1 will be included in this analysis.

8) Time to cessation of viral shedding by RT-PCR (unit: hours)

This endpoint is defined as the time between the initiation of the study treatment and first time when the virus RNA by RT-PCR is below the limit of detection. Patients whose virus RNA have not reached the limit by the last observation time point will be treated as censored at that time point. For the patients with multiple virus types, this endpoint is defined as the time between the initiation of the study treatment and first time when the virus RNA by RT-PCR is below the limit of detection for all virus types. One day is converted into 24 hours.

Patients with a positive virus RNA on Day 1 will be included in this analysis.

9) Proportion of patients whose symptoms have been improved (unit: %)

This endpoint is defined as the percentage of patients whose symptoms have been improved at 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, and 216 hours after the initial of study treatment. The improvement of influenza symptom is defined in the [Section 9.1](#).

10) Time to alleviation of symptoms (unit: hours)

This endpoint is defined as the time between the initiation of the study treatment and the alleviation of influenza symptoms. The alleviation of symptoms is defined as the time when all of 7 influenza symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue) have been assessed by the patient as 0 (None) or 1 (Mild) in the patient eDiary, for a duration of at least 21.5 hours (24 hours –10%). Patients, who do not experience alleviation of symptoms, will be censored at the last observation time point.

11) Time to improvement of the 4 systemic symptoms (unit: hours)

The endpoint is defined as the time between the initiation of the study treatment and the improvement of the all 4 systemic symptoms (headache, feverishness or chills, muscle or joint pain, and fatigue). The improvement of influenza symptom is defined in the [Section 9.1](#). Once all 4 of a patient's influenza symptoms are

alleviated, maintained, or improved as defined, the endpoint for that patient will be reached, for a duration of at least 21.5 hours (24 hours –10%).

Patients who do not experience improvement of 4 systemic symptoms will be censored at the last observation time point.

12) Time to improvement of the 3 respiratory symptoms (unit: hours)

The endpoint is defined as the time between the initiation of the study treatment and the improvement of the all 3 respiratory symptoms (cough, sore throat, and nasal congestion). The improvement of influenza symptom is defined in the [Section 9.1](#). Once all 3 of a patient's influenza symptoms are alleviated, maintained, or improved as defined, the endpoint for that patient will be reached, for a duration of at least 21.5 hours (24 hours –10%).

Patients who do not experience improvement of 3 respiratory symptoms will be censored at the last observation time point.

13) Time to resolution of fever (unit: hours)

Time to resolution of fever is defined as the time between the initiation of the study treatment and the resolution of fever. The resolution of fever is defined as the time when the patient's self-measured axillary temperature becomes less than 37°C and is maintained at less than 37°C for at least 12 hours. Patients who do not experience resolution of fever by the last observation time point will be censored at that time point. Patients whose body temperatures at baseline are less than 37°C or not collected will be excluded from the analysis. Body temperature obtained when e-diary is set up after initial dosing will not be used for analysis. Because these data may be observed due to e-dairy system's incorrect setting.

14) Proportion of patients reporting normal temperature (unit: %)

Proportion of patients reporting normal temperature is defined as the percentage of patients whose axillary body temperature drops to less than 37°C after the initiation of the study treatment at 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, and 216 hours. Body temperature obtained when e-diary is set up after initial dosing will not be used for analysis.

Patients whose body temperatures at baseline are less than 37°C or not collected will be excluded from the analysis.

15) Body temperature (unit: degree)

Body temperature is defined as measured axillary body temperature at 12, 24, 36, 48, 72, 96, and 120 hours. Body temperature obtained when e-diary is set up after initial dosing will not be used for analysis.

Patients whose body temperatures at baseline are not collected will be excluded from the analysis.

16) Time to improvement of individual symptoms (unit: hours)

Time to improvement of cough symptom is defined as the time between the initiation of the study treatment and the improvement of cough. The improvement cough is defined as a patient's cough symptom is improved as defined in the

section 9.1, the endpoint for that patient will be reached, for a duration of at least 21.5 hours (24 hours –10%).

Patients who do not experience the improvement of cough symptom by the last observation time point will be censored at that time point.

Patients, whose symptoms at baseline are assessed as 0 (None), 1 (Mild), 2 (Moderate) but preexisting and not worsened, or 3 (Severe) but preexisting and not worsened, will be excluded from the analysis.

The following endpoints are defined in a similar way.

- Time to improvement of sore throat symptom
- Time to improvement of headache symptom
- Time to improvement of nasal congestion symptom
- Time to improvement of feeling feverish or having chills symptom
- Time to improvement of aches and pains of the muscle or joints symptom
- Time to improvement of fatigue symptom

For analyses of ‘sore throat’, ‘headache’, ‘nasal congestin’ and ‘feeling feverish or having chills’, patients, whose symptoms at baseline are assessed as 0 (None), 1 (Mild), will be excluded from the analysis population.

17) Time to return to preinfluenza health status (unit: hours)

Time to return to preinfluenza health status is defined as the time from the initiation of the study treatment to the first time when health status score is equal to or higher than the preinfluenza health status score. Patients who have the smaller score than the score as preinfluenza health status by the last observation time point will be censored at that time point.

Patients whose health status scores at baseline are equal to or higher than the score as preinfluenza health status will be excluded from the analysis. The health status score obtained when e-diary is set up after initial dosing will not be used for analysis.

18) Requirement for systemic antibiotics for infections secondary to influenza infection (unit: %)

This endpoint is defined as the percentage of patients who take antibiotics for any of the predefined complications (sinusitis, otitis media, bronchitis and pneumonia). The records will be identified with the following criteria, which is an example for sinusitis, in the form of ‘Incidence of influenza-related complication’.

- ‘Did these symptoms start after the influenza treatment was given on Day 1?’ is ‘Yes’.
- And ‘Have antibiotics been given to treat the sinusitis?’ is ‘Yes’

19) Incidence of influenza-related complications (unit: %)

This endpoint is defined as the percentage of patients who experience each influenza-related complication (any influenza-related complications,

hospitalization, death, sinusitis, otitis media, bronchitis, and radiologically confirmed pneumonia). The complications of hospitalization and death will be identified from the information of the serious AEs captured in the eCRF. Other complications will be identified from the information of specific complication eCRFs with the following diagnostic criteria.

- Sinusitis
  - ‘Sinusitis’ in the ‘Form Incidence of influenza-related complications’ is ‘Yes’
  - And ‘Did these symptoms start after the influenza treatment was given on Day 1?’ in the ‘Form Sinusitis’ is ‘Yes’
  - And ‘Does the patient have a purulent nasal discharge?’ in the ‘Form Sinusitis’ is ‘Yes’
  - And ‘Does the patient have facial pain, pressure sensation, or sensation of fullness?’ in the ‘Form Sinusitis’ is ‘Yes’
  - And ‘Does the patient have nasal obstruction, congestion or stuffiness?’ in the ‘Form Sinusitis’ is ‘Yes’
- Otitis media
  - ‘Otitis media’ in the ‘Form Incidence of influenza-related complications’ is ‘Yes’
  - And ‘Did these symptoms start after the influenza treatment was given on Day 1?’ in the ‘Form Otitis Media’ is ‘Yes’
  - And ‘Does the patient have pain or fullness in one or more ears?’ in the ‘Form Otitis Media’ is ‘Yes’
  - And ‘Does the patient have tympanic membrane bulging or fullness on otoscopy?’ in the ‘Form Otitis Media’ is ‘Yes’
- Bronchitis
  - ‘Bronchitis’ in the ‘Form Incidence of influenza-related complications’ is ‘Yes’
  - And ‘Did these symptoms start after the influenza treatment was given on Day 1?’ in the ‘Form Bronchitis’ is ‘Yes’
  - And ‘Does the subject have a productive cough that has got worse after Day 1?’ in the ‘Form Bronchitis’ is ‘Yes’
- Pneumonia
  - ‘Pneumonia’ in the ‘Form Incidence of influenza-related complications’ is ‘Yes’
  - And ‘Did these symptoms start after the influenza treatment was given on Day 1?’ in the ‘Form Pneumonia’ is ‘Yes’
  - And ‘Does a Chest X Ray confirm pneumonia i.e. consolidation?’ in the ‘Form Pneumonia’ is ‘Yes’

### 9.3 Other Endpoints

1) Serum influenza antibody titer

This endpoint is defined as the ratio of value on Day 22 to that on Day 1.

2) Polymorphic and treatment-emergent amino acid substitutions in the PA gene of evaluable virus

This endpoint is defined as follows:

- The percentage of samples which have polymorphic amino acid substitutions on Day 1 compared to the reference sequence
- The percentage of samples which have treatment-emergent amino acid substitutions between Day 1 and the RT-PCR positive time point

For treatment-emergent amino acid substitutions in the PA gene, sequencing data obtained at the baseline (Day 1) and the last RT-PCR positive time point will be compared for treatment-emergent amino acid substitutions in the PA gene in the S-033188 group and placebo group, respectively.

For polymorphic amino acid substitutions in the PA gene, sequencing data obtained at the baseline (Day 1) will be compared to that of the reference sequence in the S-033188 group and the placebo group, respectively.

The patients who have sequencing data will be included in this analysis.

3) Drug susceptibility in patients with evaluable virus (unit: EC<sub>50</sub> nM, IC<sub>50</sub> nM)

This endpoint is defined as follows:

- EC<sub>50</sub> for S-033447 at baseline
- IC<sub>50</sub> for oseltamivir at baseline
- The ratio of EC<sub>50</sub> for S-033447 relative to EC<sub>50</sub> for reference stain
- The ratio of IC<sub>50</sub> for oseltamivir relative to IC<sub>50</sub> for reference stain

If the EC<sub>50</sub> is less than the lower limit, the EC<sub>50</sub> will be imputed as the lower limit value (0.03 nM). If the EC<sub>50</sub> is greater than upper limit, the EC<sub>50</sub> will be imputed as the value of upper limit (1000 nM).

If the IC<sub>50</sub> is less than the detection limit, the IC<sub>50</sub> will be imputed as detection limit value (0.01 nM). If the IC<sub>50</sub> is greater than upper limit, the IC<sub>50</sub> will be imputed as the value of upper limit (10000 nM).

The patients with a detected value at baseline will be included in this analysis. However, the patients infected with multiple virus types will be excluded from the analysis.

4) EQ-5D-5L and EQ VAS

These endpoints consist of the change from baseline in the index value calculated from the EQ-5D-5L questionnaire and that in EQ VAS score at 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 240, 264, 288, 312, 336, 360, 384, 408, 432, 456, 480, 504, and 528 hours. A conversion table

proposed by Ikeda et al. [1] will be used to convert EQ-5D-5L status to index value.

The EQ-5D-5L and EQ VAS data obtained when e-diary is set up after initial administration will not be used for analysis. Because these data may be observed due to e-dairy system's incorrect setting.

5) Work productivity questionnaire

The WP questionnaire consists of 4 questions regarding employment, hours worked, productivity while at work, and requirement for personal assistance. The following 2 endpoints are derived from Q1 to Q3 questions. If a subject reported the Q1 as 0, the 'percentage of absenteeism due to influenza illness' and 'percentage of work productivity loss due to influenza illness' will not be calculated.

The percentage of absenteeism due to influenza illness is defined as follows;

$100 \times (\text{duration unable to work due to influenza illness: Q2}) / (\text{duration of working per 21 days: } Q1 \times 21 \text{ days} / 7 \text{ days})$  (unit: %)

The patients whose Q1 and Q2 were observed with the same unit will be included in this analysis.

The percentage of work productivity loss due to influenza illness is defined as follows;

$100 \times \{(\text{duration unable to work due to influenza illness: Q2}) + (\text{duration of working below normal standard: Q3})\} / (\text{duration of working per 21 days: } Q1 \times 21 \text{ days} / 7 \text{ days})$  (unit: %)

The patients whose Q1, Q2 and Q3 were observed with the same unit will be included in this analysis.

6) Intrahousehold infection rate (for Japan site only)

Intrahousehold infection rate in each patient is defined as follows;

$100 \times (\text{the number of household members infected between Day 1 and Day 15}) / \{(\text{the number of household members, excluding the patient himself/herself}) - (\text{the number of household members infected by Day 1})\}$  (unit: %).

The patients who have no household members or whose all household members have already been infected by Day 1 will be excluded from the analysis population.

When a part of the date of influenza diagnosis is observed for a household member, he/she is defined as an influenza case in household. If any part of the date of his/her influenza diagnosis is missing, it will be assumed that he/she is diagnosed on Day 1.

For each of the following time periods, definition of this endpoint will be defined as below.

- $100 \times (\text{the number of household members infected between Day 1 and Day 3}) / \{(\text{the number of household members, excluding the patient him/herself}) - (\text{the number of household members infected by Day 1})\}$  (unit: %)
- $100 \times (\text{the number of household members infected between Day 1 and Day 4}) / \{(\text{the number of household members, excluding the patient him/herself}) - (\text{the number of household members infected by Day 1})\}$  (unit: %)
- $100 \times (\text{the number of household members infected between Day 1 and Day 6}) / \{(\text{the number of household members, excluding the patient him/herself}) - (\text{the number of household members infected by Day 1})\}$  (unit: %)
- $100 \times (\text{the number of household members infected between Day 1 and Day 11}) / \{(\text{the number of household members, excluding the patient him/herself}) - (\text{the number of household members infected by Day 1})\}$  (unit: %)

#### 9.4 Analyses of the Secondary Endpoints

The analysis population for the following analyses will be the ITTI Population unless otherwise specified.

- 1) Proportion of patients positive for influenza virus titer and virus RNA by RT-PCR
  - The proportion of patients positive for influenza virus titer/virus RNA (RT-PCR) at each scheduled time point will be calculated. The corresponding 95% CIs will be calculated by the Clopper-Pearson method.
  - The Mantel-Haenszel test with baseline composite symptom score ( $\leq 14$  or  $\geq 15$ ), preexisting and worsened symptom (Yes or No) and region (Asia, North America/Europe, Southern Hemisphere) as stratification factors will be used to compare these endpoints between two groups at each scheduled time point.
- 2) Change from baseline in influenza virus titer and in the amount of virus RNA (RT-PCR)
  - The summary statistics for the change from baseline in influenza virus titer and in the amount of virus RNA (RT-PCR) will be presented by treatment group at each scheduled time point.
  - The van Elteren test with baseline composite symptom score ( $\leq 14$  or  $\geq 15$ ), preexisting and worsened symptom (Yes or No) and region (Asia, North America/Europe, Southern Hemisphere) as stratification factors will be used to compare these endpoints between two groups at each scheduled time point. The p-value for the van Elteren test is derived using the below SAS code and identified as the p-value for “Row Mean Scores Differ” in the “Alternative Hypothesis of Cochran-Mantel-Haenszel Statistics” on the output window.

[Example: Comparison between the S-033188 group and the placebo group]  
proc freq data= analysisdata;  
table PRE\*REGION\*SCOREC\*TRTP\*VARIABLE / cmh2 scores=modridit  
noprint;  
where TRTP in ("S-033188", "Placebo");  
run;

- PRE: Preexisting and worsened symptom
- REGION: Region
- SCOREC: Category of Baseline composite symptom score
- TRTP: Treatment group
- VARIABLE: Response variable

- 3) Area under the curve adjusted by baseline in influenza virus titer and in the amount of virus RNA (RT-PCR)
  - The same analysis methods as for ‘the change from baseline in influenza virus titer and the amount of virus RNA’ will be applied.
- 4) Time to cessation of viral shedding by influenza virus titer/by virus RNA
  - This endpoint will be compared between the S-033188 group and the placebo group or the Oseltamivir group using the stratified Peto-Prentice’s generalized Wilcoxon test with composite symptom score ( $\leq 14$  or  $\geq 15$ ), preexisting and worsened symptom (Yes, No), and region (Asia, North America/Europe, Southern Hemisphere) as stratification factors.
  - The Kaplan-Meier survival curve will be plotted for each treatment group, and the median time to improvement of influenza symptoms and its 95% CI will be calculated. In addition, the treatment group difference in median time and its 95% CI will be estimated. The 95% CI of difference of median time will be obtained using the method described in the [Section 9.1.1.2](#). Random seeds will be set as 16010833 and 16010834 for comparison between the S-033188 and the placebo or the oseltamivir for influenza virus titer, 16010835 and 16010836 for comparison between the S-033188 and the placebo or the oseltamivir for virus RNA.
- 5) Proportion of patients whose symptoms has been improved
  - The same analysis methods as for the ‘proportion of patients positive for influenza virus titer’ will be applied.
- 6) Time to alleviation of symptoms
  - This endpoint will be compared between the S-033188 group and the placebo group or the oseltamivir group using the stratified Peto-Prentice’s generalized Wilcoxon test with composite symptom score ( $\leq 14$  or  $\geq 15$ ), preexisting and worsened symptom (Yes or No), and region (Asia, North America/Europe, Southern Hemisphere) as stratification factors.

- The Kaplan-Meier survival curve will be plotted for each treatment group, and the median time and its 95% CI will be calculated. In addition, the treatment group difference in median time will be estimated.
- 7) Time to improvement of the 4 systemic symptoms/3 respiratory symptoms
- The same analysis methods as for the ‘time to alleviation of symptoms’ will be applied.
- 8) Time to resolution of fever
- The same analysis methods as for the ‘time to cessation of viral shedding by influenza virus titer/by virus RNA’ will be applied. Random seeds will be set as 16010837 and 16010838 for comparison between the S-033188 and the Placebo or the oseltamivir, respectively.
- 9) Proportion of patients reporting normal temperature
- The same analysis methods as for the ‘proportion of patients positive for influenza virus titer’ will be applied.
- 10) Body temperature
- The summary statistics for the body temperature will be presented by treatment group at each scheduled time point.
  - Analysis of covariance (ANCOVA) with baseline composite symptom score, preexisting and worsened symptom (Yes or No), region (Asia, North America/Europe, Southern Hemisphere) and body temperature at baseline as covariates will be used to compare the endpoint between 2 groups and calculate least squares means, the corresponding standard errors and the corresponding 95% CI.
- [Example: Comparison between the S-033188 group and the placebo group]
- ```
proc mixed data= analysisdata;  
  class REGION TRTP PRE;  
  model VARIABLE = TRTP PRE REGION bSCORE BASE /cl;  
  lsmeans TRTP;  
  estimate "S-033188 vs Placebo" TRTP 1 -1 0/cl;  
  estimate "S-033188 vs Oseltamivir" TRTP 1 0 -1/cl;  
run;
```
- PRE: Preexisting and worsened symptom
  - REGION: Region
  - bSCORE: Baseline composite symptom score
  - BASE: Body temperature at baseline
  - TRTP: Treatment group
  - VARIABLE: Response variable
- 11) Time to improvement of individual symptoms
- The same analysis methods as for the ‘time to alleviation of symptoms’ will be applied.

- 12) Time to return to preinfluenza health status
  - The same analysis methods as for the ‘time to alleviation of symptoms’ will be applied.
- 13) Requirement for systemic antibiotics for infections secondary to influenza infection
  - The proportion and the corresponding 95% CI will be calculated by treatment group. The 95% CIs will be calculated by the Clopper-Pearson method.
  - The Fisher’s exact test will be used will be used to compare the proportion between the S-033188 and both the Placebo and oseltamivir groups.
- 14) Incidence of influenza-related complications
  - The same analysis method as for the ‘requirement for systemic antibiotics for infections secondary to influenza infection’ will be applied.

## 9.5 Analyses of the Other Endpoints

- 1) Serum influenza antibody titer
  - Serum antibody titers measured on Day 1 and Day 22 will be categorized, and the frequency of each category and the corresponding percentage will be summarized by influenza virus subtype based on RT-PCR and treatment group.
  - The ratio of value at Day 22 to that at Day 1 will be categorized, and the frequency of each category and the corresponding percentage will be tabulated by influenza virus subtype based on RT-PCR and treatment group.

If serum antibody titer is observed as  $< 10$  and  $> 1280$ , the ratio of value at Day 22 to that at Day 1 will be calculated using 10 and 1280, respectively.

- The categorized serum antibody titer at Day 1 and at Day 22 will be cross-tabulated.
- The geometric mean value of the ratio of value at Day 22 to that at Day 1 will be calculated, and the Wilcoxon rank sum test will be used to compare the ratio between the S-033188 and the placebo or the oseltamivir.

If serum antibody titer is observed as  $< 40$  due to haemolytic serum sample, the observation will be handled as missing data for the above analyses.

- 2) Polymorphic and treatment-emergent amino acid substitutions in the PA gene of evaluable virus

The patients who have sequencing performed will be included in the following analysis.

- For the S-033188 group and the placebo group, amino acid substitutions data at the Day 1 and at the last RT-PCR positive time point will be cross-tabulated by each amino acid position in PA, influenza virus type and subtype of sequence sample and treatment group, in consideration of the reference sequence.

- 3) Drug susceptibility of evaluable virus
- The summary statistics for EC<sub>50</sub> and IC<sub>50</sub> at baseline will be presented by influenza virus type and subtype based on RT-PCR and treatment group (including overall group).
  - The summary statistics for the ratio of EC<sub>50</sub> at baseline relative to EC<sub>50</sub> for reference stain and the ratio of IC<sub>50</sub> at baseline relative to IC<sub>50</sub> for reference stain will be presented by influenza virus type and subtype based on RT-PCR and treatment group (including overall group). For the patients infected with influenza A virus (A/H1N1pdm or A/H3), EC<sub>50</sub> of reference strain A/Victoria/361/2011 and IC<sub>50</sub> of reference strain A/PuertoRico/8/34 will be used. For the patients infected with influenza B virus, EC<sub>50</sub> of reference stain B/Wisconsin/1/2010 and IC<sub>50</sub> of reference strain B/Lee/40 will be used.
- 4) Change in EQ-5D-5L and EQ VAS
- The summary statistics for change in the index value and change in visual analog scale (VAS) score will be presented by treatment group at each scheduled time point. As a reference, the summary statistics at baseline will also be presented.
- 5) Work productivity questionnaire
- The summary statistics for the percentage of absenteeism due to influenza illness and the percentage of work productivity loss due to influenza illness will be presented by treatment group.
  - For Question 4 in Work Productivity (WP) Questionnaire, the summary statistics for the number of days required for personal assistance will be presented by treatment group. One day is equal to 24 hours.
- 6) Intrahousehold infection rate

Let  $K$  be the total number of patients included in this analysis,  $y_k$  be the number of  $k^{\text{th}}$  patient's household members infected between Day 1 and Day 15, and  $n_k$  be the number of  $k^{\text{th}}$  patient's household members uninfected by Day 1 ( $k = 1, \dots, K$ ). Under the assumption that  $y_k$  is distributed according to Poisson distribution with mean  $\mu_k$ , the following Poisson regression model will be applied;

$$\log(\mu_k) = \log(n_k) + \beta_0 + \beta_1 x_k$$

$$\text{Var}(y_k) = \phi \mu_k \quad (\phi: \text{dispersion parameter})$$

In the model,  $x_k$  is a group indicator variable for the  $k^{\text{th}}$  patient, i.e.,  $x_k = 1$  for the S-033188 group,  $x_k = 0$  for the control group (the placebo group or the oseltamivir group). The  $\beta_0$  is an intercept parameter,  $\beta_1$  is a regression parameter. Intrahousehold infection rates for the S-033188 group and the control group are given by  $\exp(\beta_0 + \beta_1)$  and  $\exp(\beta_0)$ , respectively.

The dispersion parameter  $\phi$  will be estimated as Pearson's chi-square divided by its degrees of freedom.

Estimate and 95% CI of intrahousehold infection rate of each treatment group and comparison between two treatment groups will be carried out using the following SAS code. In addition, a risk ratio of the S-033188 group to the control group and the corresponding 95% CI will be estimated by the above Poisson regression model.

```
Data analysisdata;  
set analysisdata;  
lnum=log(NUM);  
run;
```

[Comparison between the S-033188 group and the placebo group or oseltamivir group]

```
proc genmod data = analysisdata;  
class TRTP;  
model RES = TRTP / dist = poisson link = log offset = lnum scale = pearson;  
lsmeans TRTP / cl exp;  
estimate "S-033188 vs Placebo" TRTP 1 -1 0 / exp;  
estimate "S-033188 vs Oseltamivir" TRTP 1 0 -1 / exp;  
run;
```

- NUM: Number of household members uninfected by Day 1
- TRTP: Treatment group (1:S-033188, 2:Placebo, 3: Oseltamivir)
- RES: Number of household members infected between Day 1 and Day 15

The similar Poisson regression model will be applied using the number of household members  $y_k$  infected during each of the following time periods as a response variable;

- From Day1 to Day 3
- From Day 1 to Day 4
- From Day1 to Day 6
- From Day 1 to Day 11

## 9.6 Subgroup Analyses for Primary and Secondary Endpoint

### Time to improvement of symptoms

Analyses of time to improvement of symptoms (Kaplan-Meier curve, the median time and its 95% CI, deference in median times and stratified Peto-Prentice's generalized Wilcoxon test described in [Section 9.1.1.1](#), [9.1.1.2](#)) will be presented for the following subgroup 1), 2), 3), 4), 5), 6), 7) and 8).

Subgroup analyses will be performed for the ITTI Population in the following subgroups. No multiplicity adjustment will be applied.

1) Total score of influenza symptoms at baseline

- $\leq 14$  points
- $\geq 15$  points

The stratified Peto-Prentice's generalized Wilcoxon test with preexisting and worsened symptom (Yes or No) and region as stratification factors will be applied.

2) Region

- Asia
- North America/Europe
- Southern hemisphere

Stratified Peto-Prentice's generalized Wilcoxon test with composite symptom score at baseline ( $\leq 14$  or  $\geq 15$ ) and preexisting and worsened symptom (Yes or No) as stratification factors will be applied.

3) Preexisting and worsened symptom

- Yes
- No

Stratified Peto-Prentice's generalized Wilcoxon test with composite symptom score at baseline ( $\leq 14$  or  $\geq 15$ ) and region as stratification factors will be applied.

4) Individual high risk categories grouped as follows (12 factors: Categories = Yes or No)

- Asthma or chronic lung disease, Endocrine disorders, Residents of long-term care facilities, Compromised immune system, Neurological and neurodevelopmental disorders, Heart disease, Adults  $\geq 65$  years of age, American Indians and Alaskan Natives, Blood disorders, Metabolic disorders, Morbid obesity (BMI  $\geq 40$ ), Women who are within 2 weeks postpartum and are not breastfeeding

This analysis will only be assessed for subgroups representing more than or equal to 10% of the whole population.

5) Age  $\geq 65$  years and other high risk factors

- Age factor ( $\geq 65$  years) and other high risk factors
- Only age factor ( $\geq 65$  years)
- Other

If a patient is equal to or greater than 65 years and suffered from other high risk factors, the patient is categorized in 'Age factor ( $\geq 65$  years) and other high risk factors'.

If a patient is equal to or greater than 65 years and suffered from no other factors, the patient is categorized in 'Only age factor ( $\geq 65$  years)'.

If a patient is less than 65 years, the patient is categorized in 'Other'.

- 6) Body weight
  - < 80 kg
  - $\geq 80$  kg
- 7) Influenza virus type based on RT-PCR
  - A/H1pdm
  - A/H3
  - B
- 8) Time to treatment from flu onset
  - 0 hours  $\leq$  to  $\leq$  12 hours
  - 12 hours  $\leq$  to  $\leq$  24 hours
  - 24 hours < to  $\leq$  36 hours
  - 36 hours < to  $\leq$  48 hours

Analyses of time to improvement of symptoms (the median time and its 95% CI, deference in median times and stratified generalized Wilcoxon test described in [Section 9.1.1.1](#), [9.1.1.2](#)) will be presented for the following subgroup 9 and 10.

- 9) Meals before and after dosing
  - Dosing > 4 hours before or > 4 hours after food intake
  - Dosing within 2 to 4 hours before or 2 to 4 hours after food intake
  - Dosing < 2 hours before or < 2 after food intake

If a subject has had meals both before and after dosing, the priority will be given to a category closer to the time of dosing. If multiple applicable categories exist even under this condition, data obtained before dosing will be adopted.

- 10) Age
  - < 18 years
  - 18 years  $\leq$  64 years
  - 65 years  $\leq$  74 years
  - $\geq 75$  years

#### Time to improvement of the three respiratory symptoms

Analysis of this endpoint will be presented for the subgroup 4) 'Individual high risk categories', but the Kaplan-Meier curve will not be created. Only for subgroups of which percentage is more than or equal to 10% of the whole population will be analyzed.

#### Time to improvement of cough symptom

Analysis of this endpoint will be presented for the subgroup 4) 'Individual high risk categories', but the Kaplan-Meier curve will not be created. Only for subgroups of which percentage is more than or equal to 10% of the whole population will be analyzed.

#### Complications

Analysis of complications will be presented for the subgroup 4) 'Individual high risk categories'. Only for subgroups of which percentage is more than or equal to 10% of the whole population will be analyzed.

#### Time cessation of viral shedding by virus to titer/RT-PCR

Analysis of the time cessation of viral shedding by virus to titer/RT-PCR will be presented for the subgroup 4) 'Individual high risk categories', but the Kaplan-Meier curve will not be created. The analysis results only for subgroups of which percentage is more than or equal to 10% of the whole population will be shown.

For these endpoints, the subgroup analysis for the subgroup 7) 'Influenza virus type based on RT-PCR' will also be performed (the Kaplan-Meier curve will be created).

#### Proportion of patients positive for influenza virus titer/RT-PCR

For these endpoints, the subgroup analysis for the subgroup 7) 'Influenza virus type based on RT-PCR' will also be performed. Only for the proportion of patients positive for influenza virus titer, the subgroup analysis for '8) Time to treatment from flu onset' will be performed.

#### Change from baseline in influenza virus titer/amount of virus RNA (RT-PCR)

For these endpoints, the subgroup analysis for the subgroup 7) 'Influenza virus type based on RT-PCR' will also be performed. Only for the change from baseline in influenza virus titer, the subgroup analysis for '8) Time to treatment from flu onset' will be performed.

#### Area under the curve adjusted by baseline in influenza virus titer/RT-PCR

For these endpoints, the subgroup analysis for the subgroup 7) 'Influenza virus type based on RT-PCR' will also be performed.

#### Intrahousehold infection rate

For these endpoints, the subgroup analysis for the subgroup 7) 'Influenza virus type based on RT-PCR' will also be performed.

## 9.7 Analyses for Health Technology Assessment

### 9.7.1 Comparison of Treatment Groups

For health technology assessment, the primary endpoint and the change from baseline in influenza virus titer will be analyzed for specific subgroups.

- Vaccination = Yes
- Vaccination = No

For analysis of the health technology assessment endpoint, the analysis methods described in Sections 9.1.1.1 and 9.1.1.2 will be applied.

For analysis of the change from baseline in influenza virus titer, the analysis method described in Section 9.4 2) will be applied.

### 9.7.2 Summary of Specific Conditions

For health technology assessment, summary statistics (the number of nonmissing observations, arithmetic mean, and standard deviation) for the EQ-5D-5L index will be calculated at each evaluation time point by 4 specific conditions in the Japanese population. Similarly, the summary statistics for the absenteeism and work productivity loss due to influenza illness and the time required for personal assistance at the end of follow-up time will be calculated by 4 specific conditions in the Japanese population. Note that these analyses are not for comparison of treatment arms. The definitions of 4 specific conditions are shown below.

| Conditions                                                        | Improvement of influenza symptoms [a] | Any influenza-related complications (death, hospitalization, sinusitis, otitis media, bronchitis, and radiologically confirmed pneumonia) | Any treatment-related AEs |
|-------------------------------------------------------------------|---------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| With flu symptoms, no complications, no treatment-related AE      | No                                    | No                                                                                                                                        | No                        |
| Without flu symptoms, no complications, no treatment-related AE   | Yes                                   | No                                                                                                                                        | No                        |
| With flu symptoms, no complications, with treatment-related AE    | No                                    | No                                                                                                                                        | Yes                       |
| Without flu symptoms, no complications, with treatment-related AE | Yes                                   | No                                                                                                                                        | Yes                       |

AE = adverse event; flu = influenza

[a] The patients whose time to improvement of influenza symptoms is censored or who have no observations of influenza symptom score after the start of treatment will be considered as 'No' at all evaluation time points. The patients whose all influenza symptoms at baseline are mild or absent will be considered as 'Yes' at all evaluation time points.

## 9.8 Supplemental Analyses

As supplemental analyses, the primary endpoint (time to improvement of influenza symptoms) and the time to cessation of viral shedding by influenza virus titer will be conducted including the subjects enrolled in Site PPD and PPD with a confirmed diagnosis of influenza virus infection.

## 10. SAFETY EVALUATION

The following analyses will be performed in the safety population.

### 10.1 Adverse Events

Adverse events will be classified by system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1. Adverse events reported after the initial dose of study drug will be used for safety analyses.

- 1) The number and proportion of patients who experienced at least 1 AE will be tabulated by treatment group. Their 95 % CIs will also be calculated with the Clopper-Pearson method. In addition, the proportion in the S-033188 group will be compared with the value in the placebo group or the oseltamivir group using the Fisher's exact test. The number of events will also be tabulated. Death, other serious AEs, AEs leading to withdrawal of the study drug, and treatment-related AEs will be summarized in the same manner as the overall summary of AEs. The definitions of death, other serious AEs, AEs leading to withdrawal, treatment-related AEs are shown below.

| Term                                               | Definition                                                              |
|----------------------------------------------------|-------------------------------------------------------------------------|
| Death                                              | AEs with "Fatal" in terms of outcome.                                   |
| Other serious AEs<br>(Serious AEs excluding death) | AEs with "Serious" in terms of seriousness excluding death              |
| AEs leading to withdrawal of the study drug        | AEs with "Drug withdrawn" in terms of the action taken for study drug.  |
| Treatment-related AEs                              | AEs with "Related" in terms of the causal relationship with study drug. |

AEs = adverse events

- 2) The number and proportion of patients who experienced AEs will be tabulated by System Organ Class (SOC) and Preferred Term (PT) for each treatment group. For these summaries, patients with multiple AEs will be counted only once within the SOC and PT. Serious AEs excluding death, AEs leading to withdrawal of the study drug, treatment-related AEs, serious treatment-related AEs excluding death, and treatment-related AEs leading to withdrawal of the study drug will be summarized in a similar manner. In addition, the AEs, of which proportions are equal to or higher than 2% in any treatment groups, will be tabulated by SOC and

PT.

- 3) The number and proportion of patients who experienced AEs in each category of the severity, the outcome, and the time-of-onset will be tabulated by SOC and PT in each treatment group.

Regarding summarization of the severity and the outcome, a patient with multiple AEs will be counted only once in the highest priority of the categories shown in Table 4, if the SOC or PTs are same.

The time-of-onset is categorized into Week 1 (1 to 7 days postdose), Week 2 (8 to 14 days postdose), and Week  $\geq 3$  ( $\geq 15$  days postdose). Each AE will be classified into a time-of-onset category based on the number of days that is calculated as (Date of AE onset – Date of dosing + 1). If a patient experiences multiple AEs of the same SOC or PT in different categories, the patient will be counted once in each category.

Treatment-related AEs will be summarized in a similar manner.

**Table 4 Priority of Categories**

| Priority | Category |                                  |
|----------|----------|----------------------------------|
|          | Severity | Outcome                          |
| 1        | Grade 5  | Fatal                            |
| 2        | Grade 4  | Recovered/Resolved with sequelae |
| 3        | Grade 3  | Not recovered/Not resolved       |
| 4        | Grade 2  | Recovering/Resolving             |
| 5        | Grade 1  | Recovered/Resolved               |
| 6        |          | Unknown                          |

- 4) Adverse events related to hepatic disorders (SMQ code = 20000006) and neuropsychiatric disorders (SOC = psychiatric disorders or nervous system disorders) will be listed.

## 10.2 Clinical Laboratory

If reported values include inequality signs (> or <), the values without inequality signs will be used for summarizing the results.

- 1) For each of the hematological and biochemical test parameter, summary statistics of observed values and changes from baseline at each time point will be presented by treatment group at each scheduled time point.
- 2) For each urinalysis parameter, the frequency of each category will be summarized by treatment group at each scheduled time point.
- 3) Each observed value will be classified into 3 categories: “within the normal range,” “higher than normal,” and “lower than normal.” The frequency of each category will be summarized by treatment group at each scheduled time point.
- 4) The number and proportion of patients who meet the prespecified criteria shown

- in [Table 5](#) will be presented by treatment group during the study (after first dosing). If a patient meet multiple criterion in all observed time points, the patient will be counted only once within the worst category.
- 5) The number and proportion of patients, whose each parameter is categorized into Grade 3 and 4 based on the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.1, will be summarised by treatment group at each scheduled time point.

**Table 5 Prespecified Criteria**

| Term                                               | Criteria                                                                                                                                                                                                                                                                     |
|----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ALT (U/L)                                          | $\leq 3 \times \text{ULN}$<br>$> 3 \text{ to } \leq 5 \times \text{ULN}$<br>$> 5 \text{ to } \leq 20 \times \text{ULN}$<br>$> 20 \times \text{ULN}$                                                                                                                          |
| AST (U/L)                                          | $\leq 3 \times \text{ULN}$<br>$> 3 \text{ to } \leq 5 \times \text{ULN}$<br>$> 5 \text{ to } \leq 20 \times \text{ULN}$<br>$> 20 \times \text{ULN}$                                                                                                                          |
| Total bilirubin (mg/dL)                            | $\leq 1.5 \times \text{ULN}$<br>$> 1.5 \text{ to } \leq 3 \times \text{ULN}$<br>$> 3 \text{ to } \leq 10 \times \text{ULN}$<br>$> 10 \times \text{ULN}$                                                                                                                      |
| AST (U/L) or ALT (U/L)                             | $\leq 3 \times \text{ULN}$<br>$> 3 \text{ to } \leq 5 \times \text{ULN}$<br>$> 5 \text{ to } \leq 20 \times \text{ULN}$<br>$> 20 \times \text{ULN}$                                                                                                                          |
| AST (U/L) or ALT (U/L) and Total bilirubin (mg/dL) | Meet all of the following criteria at the same time point: <ul style="list-style-type: none"> <li>• AST <math>&gt; 3 \times \text{ULN}</math> or ALT <math>&gt; 3 \times \text{ULN}</math></li> <li>• Total bilirubin value <math>&gt; 2 \times \text{ULN}</math></li> </ul> |

ULN = upper limit of normal.

### 10.3 Vital Signs

For each of the vital signs (diastolic blood pressure, systolic blood pressure, respiratory rate, and pulse rate), summary statistics of observation and the change from baseline will be presented by treatment group at each scheduled time point.

### 10.4 Electrocardiography

The frequency of each electrocardiography (ECG) finding will be summarized by treatment group at each scheduled time point. Each ECG finding will be classified into 3 categories: “normal,” “abnormal-not clinically significant,” and “abnormal-clinically significant.”

### 10.5 Subgroup Analyses for Safety Endpoint

Analyses of AEs [Sections 10.1](#) 1 and 2, except proportion of patients who experienced AEs of 2% or higher, will be presented for the following subgroups.

Subgroup analyses will be performed for the Safety population.

- 1) Body weight
  - < 80 kg
  - ≥ 80 kg
- 2) Age
  - < 18 years
  - 18 years ≤ 64 years
  - 65 years ≤ 74 years
  - ≥ 75 years
- 3) High risk factors (12 factors: Categories = Yes or No)
  - Asthma or chronic lung disease, Endocrine disorders, Residents of long-term care facilities, Compromised immune system, Neurological and neurodevelopmental disorders, Heart disease, Adults aged ≥ 65 years, American Indians and Alaskan Natives, Blood disorders, Metabolic disorders, Morbid obesity (BMI ≥ 40), Women who are within 2 weeks postpartum and are not breastfeeding

## 10.6 Supplemental Analyses

As supplemental analyses, the number and proportion of patients who experienced AEs, AEs of which proportions are equal to or higher than 2% in any treatment groups and treatment-related AEs will be tabulated by SOC and PT for each treatment group with patients enrolled excluding site PPD which had repeated deviations in protocol required procedures, will be performed.

## 11. INTERIM ANALYSES

No interim analysis for efficacy assessment is planned in this study.

## 12. PROGRAMMING SPECIFICATIONS

Unless otherwise specified, the following conventions will be used when the analysis TLFs are prepared:

- Every summary table and figure will clearly specify the analysis population being summarized. Listings will be prepared for all patients randomized.
- Treatment group of the S-033188 in the listings will be reported as following rules.
  - S-033188 40 mg: Kit number (1) was assigned and the S-033188 was administered
  - S-033188 80 mg: Both kit number (1) and (2) were assigned and the S-033188 was administered
- Number of digits to be displayed for calculated values

For the following endpoints, data will be rounded off to 8 decimal places, and the rounded values will be used for analysis. The digit displayed in analysis tables for each endpoint is shown in Table 6.

**Table 6 Summary of the Number of Digits Displayed for Endpoints**

| Endpoint                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Number of digits displayed<br>(after the decimal point) |                |          |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|----------------|----------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Minimum<br>Maximum                                      | Mean<br>Median | SD<br>CI |
| <ul style="list-style-type: none"> <li>• Time to improvement of symptoms</li> <li>• Time to cessation of viral shedding by influenza virus titer/RT-PCR</li> <li>• Time to improvement of the 4 systemic symptoms</li> <li>• Time to improvement of the 3 respiratory symptoms</li> <li>• Time to alleviation of symptoms</li> <li>• Time to resolution of fever</li> <li>• Time to improvement of individual symptoms</li> <li>• Time to return to preinfluenza health status</li> <li>• Area under the curve adjusted by baseline in influenza virus titer</li> <li>• Area under the curve adjusted by baseline in the amount of virus RNA (RT-PCR)</li> <li>• Time required for personal assistance due to influenza illness</li> </ul> | 1                                                       | 1              | 1        |
| Index value                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                         |                |          |
| Percentage of absenteeism due to influenza illness                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 3                                                       | 3              | 3        |
| Percentage of work productivity loss due to influenza illness                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                         |                |          |
| <ul style="list-style-type: none"> <li>• Change from baseline in influenza virus titer</li> <li>• Change from baseline in amount of virus RNA</li> <li>• Drug susceptibility in patients with evaluable virus: the ratio of EC<sub>50</sub>/IC<sub>50</sub> at baseline relative to EC<sub>50</sub>/IC<sub>50</sub> for reference</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                               | 2                                                       | 2              | 2        |
| Treatment compliance rate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 1                                                       | 2              | 2        |

CI = confidence interval; SD = standard deviation

Summary statistics will be displayed to the number of digits as shown in [Table 7](#).

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**Table 7**                      **Summary of the Number of Digits Displayed**

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|                                                | <b>No. of digits displayed</b>                                                                         |
|------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| p-value                                        | Round off to 4 decimal places<br>However, p value of < 0.0001 will be displayed as “< .0001”           |
| Number of subjects                             | Display as a whole number                                                                              |
| Mean, SD, median, adjusted mean,<br>SE, 95% CI | One decimal place beyond the number of decimal places<br>with which the original endpoint is presented |
| Minimum, maximum                               | Same number of digits of the observed data                                                             |
| Percentage (%)                                 | Round off to 1 decimal place                                                                           |

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CI = confidence interval; SD = standard deviation; SE = standard error

- Categories used for summarization

Basically, categories described in CRFs will be used. If data need to be categorized, the data will be categorized according to [Table 8](#) below.

**Table 8**                      **Category of Variable**

| Variable                                                           | Category                                                                                                                                                                                                                          |
|--------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Age                                                                | 12-19 years, 20-29 years, 30-39 years, 40-49 years, 50-59 years, 60-64 years                                                                                                                                                      |
| Body weight                                                        | < 80 kg, ≥ 80 kg                                                                                                                                                                                                                  |
| Timing of meal before and after dosing                             | < 2 hours, 2- 4 hours, > 4 hours                                                                                                                                                                                                  |
| Time of onset of influenza symptoms                                | 0-12 hours, 12-24 hours, 24-36 hours, 36-48 hours                                                                                                                                                                                 |
| Influenza virus subtype based on RIDT                              | A, B, A and B, Negative, Unknown                                                                                                                                                                                                  |
| Influenza virus subtype based on RT-PCR                            | A/H1N1pdm: A/H1N1pdm<br>A/H3: A/H3<br>B:B<br>Mixed infection: A/H1N1pdm and B, A/H3 and B, A/Unknown and B, A/ND and B, A/H1N1pdm and A/H3 and B, A/H1N1pdm and A/H3<br>Other: A/Unknown, A/ND, Unknown<br>Negative:<br>Not done: |
|                                                                    | The above virus subtype classification is derived from the following specification:<br>– A/H1N1pdm: H1_2009<br>– A/H3: H3<br>– A/H1N1pdm and A/H3: H1_2009/H3<br>– A/ND: ND<br>– A/Unknown: UNKNOWN                               |
| Virus subtype classification used for subgroup analysis            | A/H1N1pdm, A/H3, B                                                                                                                                                                                                                |
| Serum influenza antibody titer (Day 1, Day 22)                     | < 10, ≥ 10 to < 20, ≥ 20 to < 40, ≥ 40 to < 80, ≥ 80 to <160, ≥160                                                                                                                                                                |
| Serum influenza antibody titer (Ratio of Day 22 relative to Day 1) | <4, ≥ 4 to < 8, ≥ 8 to < 16, ≥ 16 to < 32, ≥ 32 to < 64, ≥ 64 to < 128, ≥ 128 to < 256, ≥ 256                                                                                                                                     |
| Composite symptom score at baseline                                | ≤ 14, ≥ 15                                                                                                                                                                                                                        |
| Treatment compliance rate                                          | < 80, ≥ 80                                                                                                                                                                                                                        |
| Acetaminophen use                                                  | 0, 1-2, 3-4, ≥ 5                                                                                                                                                                                                                  |
| Time of onset of AE                                                | Week 1 (≥ 1 to < 8 days), Week 2 (≥ 8 to < 15 days), Week ≥ 3 (≥ 15 days)                                                                                                                                                         |
| Urine protein                                                      | -, 1+, 2+, 3+, 4+, Unknown                                                                                                                                                                                                        |
| Urine glucose                                                      | -, 1+, 2+, 3+, 4+, Unknown                                                                                                                                                                                                        |
| Urobilinogen                                                       | -, 1+, 2+, 3+, 4+, Unknown                                                                                                                                                                                                        |
| Urine occult blood                                                 | -, 1+, 2+, 3+, 4+, Unknown                                                                                                                                                                                                        |

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| <b>Variable</b>  | <b>Category</b>                                                                                                                                                                                                                                                                                                                                                                                     |
|------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| High risk factor | Asthma or chronic lung disease, Endocrine disorders, Residents of long-term care facilities, Compromised immune system, Neurological and neurodevelopmental disorders, Heart disease, Adults $\geq 65$ years of age, American Indians and Alaskan natives, Blood disorders, Metabolic disorders, Morbid obesity (BMI $\geq 40$ ), Women who are within 2 weeks postpartum and are not breastfeeding |

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### **13. BLINDED REVIEW**

The PCR positive rate at baseline will be estimated during the study.

### **14. SUMMARY OF CHANGES FROM PROTOCOL SPECIFIED ANALYSIS**

- The definition of the Safety population was updated. The patients enrolled at sites with GCP noncompliance were not included in the population, originally. These patients will be included based on the updated definition.
- An additional condition for the viral samples was described in the [Section 6.4.1](#).
- It was planned in Section 9.11.1 that the summary for action taken with the study drug will be presented by system organ class and preferred term. Due to single dose of S-033188, this analysis is not performed.
- The frequency of each pair of laboratory tests at baseline and scheduled time points, which were described in Section 9.11.3 in the protocol, were not presented.

## **15. REFERENCES**

- [1] Ikeda S., et al. Developing a Japanese version of the EQ-5D-5L value set, *J. Natl. Inst. Public Health*, 64 (1): 2015 p.47-55

## Appendix 1 Time and Events Schedule

|                                                                                                     |                                                  | Treatment Period  |                                                                               |    |      |             | Follow-up Period |            |    |     |     |     |     |     |     |                |                   |
|-----------------------------------------------------------------------------------------------------|--------------------------------------------------|-------------------|-------------------------------------------------------------------------------|----|------|-------------|------------------|------------|----|-----|-----|-----|-----|-----|-----|----------------|-------------------|
|                                                                                                     |                                                  | D1                | D2                                                                            | D3 | D4   | D5          | D6               | D7         | D8 | D9  | D10 | D11 | D12 | D13 | D14 | D15            | D22/<br>ET        |
|                                                                                                     |                                                  | V1                | V2                                                                            | V3 | OpV1 | V4          | OpV2             |            |    | V5  |     |     |     |     |     | V6             | V7                |
| Visit Window (days)                                                                                 |                                                  | -                 | -                                                                             | +1 | -    | +1          | -                |            |    | ± 2 |     |     |     |     |     | ± 3            | ± 3               |
| Informed Consent/Assent                                                                             |                                                  | X                 |                                                                               |    |      |             |                  |            |    |     |     |     |     |     |     |                |                   |
| Inclusion/Exclusion Criteria                                                                        |                                                  | X                 |                                                                               |    |      |             |                  |            |    |     |     |     |     |     |     |                |                   |
| Demographics                                                                                        |                                                  | X                 |                                                                               |    |      |             |                  |            |    |     |     |     |     |     |     |                |                   |
| Medical History <sup>a</sup>                                                                        |                                                  | X                 |                                                                               |    |      |             |                  |            |    |     |     |     |     |     |     |                |                   |
| Rapid Influenza Diagnostic Test                                                                     |                                                  | X <sup>b</sup>    |                                                                               |    |      |             |                  |            |    |     |     |     |     |     |     |                |                   |
| Randomization                                                                                       |                                                  | X                 |                                                                               |    |      |             |                  |            |    |     |     |     |     |     |     |                |                   |
| Study Drug Dispensation                                                                             |                                                  | X                 |                                                                               |    |      |             |                  |            |    |     |     |     |     |     |     |                |                   |
| Study Drug Administration                                                                           |                                                  | X                 | X                                                                             | X  | X    | X           |                  |            |    |     |     |     |     |     |     |                |                   |
| Patient<br>eDiary <sup>c</sup>                                                                      | Body Temperature Measurement                     | X <sup>d</sup>    | 4 Times Daily                                                                 |    |      | Twice Daily |                  |            |    |     |     |     |     |     |     |                |                   |
|                                                                                                     | Assessment of Severity of Influenza Symptoms     | X <sup>d</sup>    | Twice Daily                                                                   |    |      |             |                  | Once Daily |    |     |     |     |     |     |     |                |                   |
|                                                                                                     | EQ-5D-5L                                         | X <sup>d</sup>    | Twice Daily                                                                   |    |      |             |                  | Once Daily |    |     |     |     |     |     |     |                |                   |
|                                                                                                     | Assessment of Health                             | X <sup>d</sup>    | Once Daily                                                                    |    |      |             |                  |            |    |     |     |     |     |     |     |                |                   |
|                                                                                                     | Assessment of Health Prior to Influenza Symptoms | X <sup>d</sup>    |                                                                               |    |      |             |                  |            |    |     |     |     |     |     |     |                |                   |
| WP Questionnaire                                                                                    |                                                  |                   | X (the earliest visit following the resolution of symptoms, at Day 22, or ET) |    |      |             |                  |            |    |     |     |     |     |     |     |                |                   |
| Assessment of Influenza-related Complications (sinusitis, bronchitis, otitis media, pneumonia)      |                                                  | X                 | X                                                                             | X  | X    | X           | X                |            |    | X   |     |     |     |     |     | X              | X                 |
| Full Physical Examination                                                                           |                                                  | X <sup>e, f</sup> |                                                                               |    |      |             |                  |            |    |     |     |     |     |     |     |                | X <sup>e</sup>    |
| Symptom-focused Physical Examination                                                                |                                                  |                   | X                                                                             | X  | X    | X           | X                |            |    | X   |     |     |     |     |     | X              |                   |
| Concomitant Therapies                                                                               |                                                  |                   | X                                                                             | X  | X    | X           | X                |            |    | X   |     |     |     |     |     | X              | X                 |
| Study Drug Accountability                                                                           |                                                  |                   | X                                                                             | X  | X    | X           | X                |            |    |     |     |     |     |     |     |                |                   |
| Urine Pregnancy Test (WOCBP) <sup>g</sup>                                                           |                                                  | X                 |                                                                               |    |      | X           |                  |            |    |     |     |     |     |     |     |                | X                 |
| Immunological Tests                                                                                 |                                                  | X <sup>h</sup>    |                                                                               |    |      |             |                  |            |    |     |     |     |     |     |     |                |                   |
| Routine Laboratory Tests (hematology and blood chemistry)                                           |                                                  | X                 |                                                                               |    |      | X           |                  |            |    |     |     |     |     |     |     | X              | X                 |
| Influenza Antibody Titer Test                                                                       |                                                  | X <sup>h</sup>    |                                                                               |    |      |             |                  |            |    |     |     |     |     |     |     |                | X                 |
| Nasopharyngeal (preferred)/pharyngeal (if nasopharyngeal cannot be collected) Swabs (Virology Test) |                                                  | X <sup>h</sup>    | X                                                                             | X  | X    | X           | X                |            |    | X   |     |     |     |     |     | X <sup>i</sup> | X <sup>i, j</sup> |

|                                                     |                |   |                |   |   |   |  |  |   |  |  |  |  |  |                |   |
|-----------------------------------------------------|----------------|---|----------------|---|---|---|--|--|---|--|--|--|--|--|----------------|---|
| Vital Sign Measurements                             | X              | X | X              | X | X | X |  |  | X |  |  |  |  |  | X              | X |
| Electrocardiography                                 | X              | X |                |   |   |   |  |  |   |  |  |  |  |  |                | X |
| Pharmacokinetic Blood Samples                       | X <sup>k</sup> | X | X <sup>k</sup> |   | X |   |  |  |   |  |  |  |  |  | X <sup>k</sup> |   |
| Adverse Event Assessments                           | X              | X | X              | X | X | X |  |  | X |  |  |  |  |  | X              | X |
| Record if Meal Eaten and Time                       | X              |   |                |   |   |   |  |  |   |  |  |  |  |  |                |   |
| Intrahousehold Infection Interview (for Japan only) | X              | X | X              |   | X |   |  |  | X |  |  |  |  |  | X              |   |

D = day; eDiary = electronic diary; EuroQol-5 Dimensions-5 Levels; ET = early termination; OpV= optional visit; V = visit; WOCBP = women of childbearing potential; WP = work productivity

- a Include a review of prior therapies.
- b Not necessary if a site has performed a Rapid Influenza Diagnostic Test (RIDT) prior to consideration for the study.
- c The patient will measure or assess and record in the patient eDiary, body temperature 4 times daily (morning, noon, evening, and bedtime) from Days 1 to 3 and twice daily (morning and evening) from Days 4 to 14; assessment of health once daily (evening) from Days 1 to 14; the severity of influenza symptoms twice daily (morning and evening) from Days 1 to 9 and once daily (evening) from Days 10 to 14; and the EQ-5D-5L twice daily (morning and evening) from Days 1 to 9 and once daily (evening) from Days 10 to 22. The WP questionnaire will be assessed at the earliest visit following the resolution of symptoms, at Day 22, or ET.
- d Predose; if the study treatment is initiated at 18:00 or later on Day 1, the patient will not need to perform the Day 1 evening assessments.
- e Including measurement of body weight.
- f Height and body mass index will be measured at the predose examinations only.
- g Urine pregnancy test will be performed only for females who are not diagnosed as postmenopausal.
- h Predose.
- i To be collected if the investigator determines that flu symptoms are persisting.
- j If the investigator determines that flu symptoms are persisting at ET.
- k Blood samples will be collected for the measurement of plasma drug concentrations once each at Visits 2 (Day 2) and 4 (Day 5). If circumstances permit, samples also will be collected postdose at Visit 1 (Day 1) within the period from 0.5 to 4 hours after the initial dose, at Visit 3 (Day 3), and at Visit 6 (Day 15).