

<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 Otherwise Healthy Patients with Influenza
<b>Shionogi Study Number:</b>	1601T0831
<b>ClinicalTrials.gov registration No.</b>	NCT02954354
<b>Study Document</b>	Statistical Analysis Plan

## STATISTICAL ANALYSIS PLAN

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<b>Study Number:</b>	1601T0831
<b>Study Phase:</b>	3
<b>Product Name:</b>	S-033188
<b>Sponsor:</b>	Shionogi & Co., Ltd./Shionogi Inc.

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## RECORDS ON REVISIONS

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## 1. INTRODUCTION

This document describes the statistical methods to be used in the summary and analysis of data from Protocol 1601T0831. 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 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 Biostatistics Dept., Shionogi & Co., Ltd.

## 2. OVERVIEW

This is a randomized, double-blind, multicenter, parallel-group, placebo- and active controlled study enrolling approximately 1494 patients diagnosed with influenza. Approximately 1350 patients aged 20 to 64 years and 144 patients aged 12 to 19 years will be enrolled. Patients in 20 to 64 years age stratum will be randomly assigned in a ratio of 2:2:1 to receive a single dose of 40 or 80 mg of S-033188 according to their weight category, 75 mg 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. Patients in 12 to 19 years age stratum will be randomly assigned in a ratio of 2:1 to receive a single dose of 40 or 80 mg (depending on weight) S-033188 or placebo.

For the schedule of this study, see Appendix 1.

## 3. SUTDY 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 alleviation of symptoms in patients with uncomplicated influenza virus infection.

### 3.2 Secondary Objective

- To evaluate the efficacy of a single, oral dose of S-033188 compared with oseltamivir 75 mg twice daily (BID) for 5 days by measuring the time to alleviation of symptoms in patients aged 20 to 64 years with uncomplicated influenza virus infection
- To evaluate the efficacy of a single, oral dose of S-033188 compared with placebo by measuring the secondary endpoints in patients with uncomplicated influenza virus infection
- 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 uncomplicated influenza virus infection

### **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 Objectives**

- 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 in 20 to 64 years age stratum will be randomized on a 2:2:1 basis to S-033188 group, oseltamivir group, or placebo group. Patients in 12 to 19 years age stratum will be randomized on a 2:1 basis to either S-033188 group or placebo group. An interactive response technology (IRT) will be used to assign patients to numbers for which treatment has already been randomly assigned. The randomization will also be stratified by region

(Japan/Asia, Rest of the world), body weight ( $< 80$  kg,  $\geq 80$  kg) and baseline composite symptom score ( $\leq 11$ ,  $\geq 12$ ).

### **4.3 Target Sample Size**

The required sample size of the intention to treat infected (ITTI) Population will be 968 (93 patients in 12 to 19 years age stratum and 875 patients in 20 to 64 years age stratum).

It is assumed that the RT-PCR positive rate for influenza A or B virus will be 65%. Therefore, 1494 patients (144 patients in 12 to 19 years age stratum and 1350 patients in 20 to 64 years age stratum) will be randomized to ensure an adequate number of patients in the ITTI Population.

The primary analysis will be to compare time to alleviation of symptoms between the S-033188 group and the placebo group (both age strata combined). Based on the results of S-033188 Phase 2 study and the three placebo-controlled studies of oseltamivir, the difference between S-033188 and placebo will be assumed to be 28 hours. If the ratio of the median time to alleviation between the S-033188 group and the placebo group remains the same (i.e. 0.64: 49.5/77.7) in the proposed study, the difference can further be assumed to be 36 hours (64 hours in the S-033188 group, 100 hours in the placebo group). Patients will be randomized on a 2:1 basis to either S-033188 or placebo and the follow-up period will be 336 hours (14 days). Assuming that time to alleviation follows an exponential distribution, the study requires 618 patients in the ITTI Population in order for the stratified generalized Wilcoxon test to have 90% or more power with a two-sided significance level of 0.05. Assuming that the percentage of the number of patients in 12 to 19 years age stratum is 15%, the required breakdown will be 93 patients in 12 to 19 years age stratum (62 patients for the S-033188 group and 31 patients for the placebo group), 525 patients in 20 to 64 years age stratum (350 patients for the S-033188 group and 175 patients for the placebo group).

Using a 1:1 randomization ratio between the S-033188 and oseltamivir, ITTI Population of oseltamivir will be 350 patients to compare time to alleviation of symptoms between the S-033188 and the oseltamivir in 20 to 64 years age stratum. Table 1 shows the statistical power to compare between the S-033188 group and the oseltamivir group under several sets of difference in time to alleviation of symptoms.

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

<b>Median time to alleviation of symptoms (S-033188 group, oseltamivir group)</b>	<b>Statistical power for comparison between the S-033188 group and the oseltamivir group by stratified generalized Wilcoxon test</b>
(72 hours, 84 hours)	42.1%
(70 hours, 84 hours)	54.8%
(68 hours, 84 hours)	67.4%
(66 hours, 84 hours)	78.5%
(64 hours, 84 hours)	87.2%



## 5. ANALYSIS POPULATIONS

### 5.1 Efficacy Populations

The definitions of the Intention-To-Treat-Infected (ITTI) Population and the Per-Protocol Set (PPS) as efficacy populations 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 based on enrolled patients with GCP compliance:

1) ITTI Population

This population includes all patients who receive the study drug with a confirmed diagnosis of influenza virus infection. 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 were randomized.

2) Per-Protocol Set (PPS)

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

- Ineligible subjects
- Subjects with non-compliance of treatment
  - Treatment compliance rate is less than 60%. The definition of treatment compliance rate shown in 8.1 will be used.
- Subjects with inadequate follow-up
  - Subjects have no symptom data after initial treatment
- Subjects with prohibited medication
- Subjects with incorrect treatment allocation

3) Safety population

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

## 6. HANDLING OF DATA IN ANALYSES

### 6.1 Statistical Analysis

Unless otherwise noted, continuous variables will be summarized by using the number of non-missing observations, arithmetic mean, standard deviation (SD), 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 by using the SAS Version 9.2 or higher.

## 6.2 Statistical Tests

All statistical tests will be performed at the 0.05 significance level using two-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, comparison between the S-033188 and the oseltamivir groups (secondary analysis) will be conducted. For the submission to countries other than Japan, only if statistically significant difference will be observed in primary analysis, secondary analysis will be performed 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 and 2-2. 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**

Time Point	Specified Assessment Time Point	Acceptable Time Window
12 hours post-dose	Time of first dosing + 12 hours	Between $\geq 6$ and $< 18$ hours after first dosing
24 hours post-dose	Time of first dosing + 24 hours	Between $\geq 18$ and $< 30$ hours after first dosing
36 hours post-dose	Time of first dosing + 36 hours	Between $\geq 30$ and $< 42$ hours after first dosing
48 hours post-dose	Time of first dosing + 48 hours	Between $\geq 42$ and $< 54$ hours after first dosing
60 hours post-dose	Time of first dosing + 60 hours	Between $\geq 54$ and $< 66$ hours after first dosing
72 hours post-dose	Time of first dosing + 72 hours	Between $\geq 66$ and $< 78$ hours after first dosing
84 hours post-dose	Time of first dosing + 84 hours	Between $\geq 78$ and $< 90$ hours after first dosing
96 hours post-dose	Time of first dosing + 96 hours	Between $\geq 90$ and $< 102$ hours after first dosing
108 hours post-dose	Time of first dosing + 108 hours	Between $\geq 102$ and $< 114$ hours after first dosing
120 hours post-dose	Time of first dosing + 120 hours	Between $\geq 114$ and $< 126$ hours after first dosing
132 hours post-dose	Time of first dosing + 132 hours	Between $\geq 126$ and $< 138$ hours after first dosing
144 hours post-dose	Time of first dosing + 144 hours	Between $\geq 138$ and $< 150$ hours after first dosing
156 hours post-dose	Time of first dosing + 156 hours	Between $\geq 150$ and $< 162$ hours after first dosing
168 hours post-dose	Time of first dosing + 168 hours	Between $\geq 162$ and $< 174$ hours after first dosing
180 hours post-dose	Time of first dosing + 180 hours	Between $\geq 174$ and $< 186$ hours after first dosing
192 hours post-dose	Time of first dosing + 192 hours	Between $\geq 186$ and $< 198$ hours after first dosing
204 hours post-dose	Time of first dosing + 204 hours	Between $\geq 198$ and $< 210$ hours after first dosing
216 hours post-dose	Time of first dosing + 216 hours	Between $\geq 210$ and $< 222$ hours after first dosing
240 hours postdose	Time of dosing + 240 hours	Between $\geq 228$ and $< 252$ hours after dosing
264 hours postdose	Time of dosing + 264 hours	Between $\geq 252$ and $< 276$ hours after dosing
288 hours postdose	Time of dosing + 288 hours	Between $\geq 276$ and $< 300$ hours after dosing

Time Point	Specified Assessment Time Point	Acceptable Time Window
312 hours postdose	Time of dosing + 312 hours	Between $\geq 300$ and $< 324$ hours after dosing
336 hours postdose	Time of dosing + 336 hours	Between $\geq 324$ and $< 348$ hours after dosing
528 hours postdose	Time of dosing + 528 hours	Between $\geq 456$ and $< 600$ hours after dosing

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**

Time Point	Acceptable Time Window
Pre-dose at Visit 1 (Day 1: Day -2 to Day1)	Predose from Day -2 to Day 1 for safety assessment
Pre-dose at Visit 1 (Day 1)	Predose on Day 1 for efficacy assessment
Post-dose 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 Day 3 and Day 4
Optional-Visit 1 (Day 4)	Day 4
Visit 4 (Day 5)	Between Day 5 and Day 6
Optional Visit 2 (Day 6)	Day 6
Visit 5 (Day 9)	Between Day 7 and Day 11
Visit 6 (Day 15)	Between Day 12 and Day 18
Visit 7 (Day 22)	Between Day 19 and Day 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. If two 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. 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 with the same time (date and hour) 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 which may be adopted for a scheduled assessment time point (even though the above rules have been strictly followed), the measurements at the time point entered in the CRF will be adopted.

## 6.4 Handling of Missing Data

Missing data will not be imputed.

- Patients who do not experience alleviation of symptoms will be censored at the last observation time point, except in the case of sensitive analysis for primary analysis.
- If all symptoms were missing after baseline, time to alleviation of symptoms, time to alleviation of symptoms excluded cough, time to alleviation of the 4 systemic symptoms, time to alleviation of the 3 respiratory symptoms and time to alleviation of individual symptoms will be handled as missing.
- For the sensitive analysis for primary endpoint, the patients who do not experience alleviation of symptoms will be treated as follows.
  - If patients who discontinue from the study and still have influenza symptoms, time to alleviation of symptoms will be censored as 14 days.
  - In consideration of treatment duration of the oseltamivir group.
    - If patients who discontinue until Day 5 and still have influenza, time to alleviation of symptoms will be censored at the last observation time point.
    - If patients who discontinue after Day 5 and still have influenza, time to alleviation of symptoms will be censored as 14 days.
  - In consideration of the reason of the discontinuation.
    - If patients discontinue due to AE or lack of efficacy, time to alleviation of symptoms will be censored as 14 days.
    - If patients discontinue due to other reason, time to alleviation of symptoms of the patients 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 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.

## **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 S-033188/Placebo will be designated as Day 1 and Day -1, respectively.

### **6.5.2 Baseline**

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

For body temperature, assessment of health and EQ-5D-5L, the measurement with the following two conditions is defined as baseline. If there are multiple measurements which 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 when first administration and sending are occurred on the same day

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

- Data observed when first administration and sending are occurred on the same day

For efficacy assessments other than above, baseline is defined as the measurement obtained before the first administration 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 for the S-033188 group and Placebo group. For the subjects excluded from each population, the

reason for exclusion will be summarized. Fisher's exact test will be performed with a two-sided significance level of 0.15 to check differences among the treatment groups regarding the distribution of subjects in the ITTI and the PPS Populations. For the patients aged 20 to 64 years, the similar analyses will be applied in the S-033188 group and Oseltamivir group.

- 3) The number and percentage of subjects included in the Safety population among all randomized subjects will be calculated by prescribed treatment group. For the subjects excluded from the Safety population, the reason for exclusion will be summarized. For patients who receive at least one dose of the study drug, the treatment that the patients actually received will be defined as prescribed treatment. For patients who don't receive one dose of the study drug, the treatment to which the patients were randomized will be defined as prescribed treatment.

## **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.

For the patients aged 20 to 64 years in the ITTI Population, the following demographic and baseline characteristics will be summarized in the same manner.

- Continuous variable  
Age, height, body weight, BMI, total score of influenza symptoms and body temperature
- Categorical variable  
Age, body weight, sex, region, race, ethnicity, time to treatment from flu onset, presence or absence of flu vaccination, prior drug, prior therapy, medical history, smoking habits, presence or absence of meal before 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, presence or absence of meal after initial study treatment, influenza virus subtype based on RT-PCR and influenza virus subtype based on RIDT (Rapid Influenza Diagnostic Test).

## **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] is defined as the dosing period during which a subject took medication as follows;

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

If a patient does not take any study drug, the duration of treatment exposure will be defined as 0.

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 and the percentage of subjects in each category among all subjects included in the analysis population will be presented.

The treatment compliance rate [%] is defined as;

$$100 \times \{(\text{actual frequency of treatment exposure}) / (\text{expected frequency of treatment exposure by early discontinuation of treatment})\}$$

## 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 group for the Safety population.

## 8.3 Prior and Concomitant Medication

Prior and concomitant drugs 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 be also classified as both prior and concomitant.

For Safety population, the number of subjects who took prior drug and concomitant drug, and corresponding proportion will be summarized by WHO class and preferred term for each treatment group. For Safety population, the number of subjects who took prior therapy and concomitant therapy, and corresponding proportion will be summarized for each treatment group.

For ITTI Population, frequency of acetaminophen use will be summarized for each treatment group. Even though the date or time of acetaminophen use is missing, the frequency is counted. Wilcoxon rank sum test will be used to compare in frequency between the S-033188 group and the placebo or the Oseltamivir group. The two-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 using data of the two age strata pooled (i.e., 12 to 64 years age), and comparison between the S-033188 group (40 mg and 80 mg combined) and the oseltamivir group using data of 20 to 64 years age stratum.

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

	Endpoint Analysis	Statistical Method
Primary Endpoint	Time to alleviation 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 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 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 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 alleviated	3, 13
	Time to alleviation of the 4 systemic symptoms	1, 9, 10, 11*
	Time to alleviation of the 3 respiratory symptoms	1, 9, 10, 11*
	Change from baseline in composite symptom score	6, 12
	Time to resolution of fever	1, 9, 10, 11
	Proportion of patients reporting normal temperature	3, 13
	Body temperature	6, 12
	Time to alleviation of individual symptoms	1, 9, 10, 11*
	Time to return to preinfluenza health status	1, 9, 10, 11*
	Incidence of influenza-related complications	5, 13
Other Endpoints	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

\* Treatment group difference in median time

[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% CI
11. Treatment group difference in median time and its 95% CI (Bootstrap method)
12. Summary statistics (continuous variables)
13. Summary statistics (categorical variables)
14. Geometric mean

## 9.1 Primary Endpoint

The primary efficacy endpoint is the time to alleviation of symptoms (unit: hours), which 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%).

### 9.1.1 Analyses of Primary Endpoint

#### 9.1.1.1 Primary Analysis

Time to alleviation of symptoms will be compared between the S-033188 group and the placebo group using the stratified Peto-Prentice's generalized Wilcoxon test with composite symptoms score at baseline ( $\leq 11$  or  $\geq 12$ ) and region (Japan/Asia or Rest of the world) as stratification factors. Patients who do not experience alleviation of symptoms will be censored at the last observation time point. If at least one of the 7 influenza symptom scores is missing at date and time of assessment that patients have, missing assessments of influenza symptoms conservatively will be treated as having moderate or severe symptoms (as failures) at the corresponding date and time of assessment.

[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 REGION / group = TRTP test = PETO ;  
run;quit;
```

- TRTP: Treatment group
- TIME: Time to alleviation of symptoms

- SCOREC: Category of baseline composite symptom score ( $\leq 11$  or  $\geq 12$ )
- REGION: Category of region (Japan/Asia or Rest of the world)

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

#### **9.1.1.2 Secondary Analysis**

Time to alleviation of symptoms will be compared between the S-033188 group and the Oseltamivir group using the stratified Peto-Prentice's generalized Wilcoxon test with composite symptoms score at baseline ( $\leq 11$  or  $\geq 12$ ) and region (Japan/Asia or Rest of the world) as stratification factors. Patients who do not experience alleviation of symptoms will be censored at the last observation time point. If at least one of the 7 influenza symptom scores is missing at date and time of assessment that patients have, missing assessments of influenza symptoms conservatively will be treated as having moderate or severe symptoms (as failures) at the corresponding date and time of assessment.

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

#### **9.1.1.3 Other Analysis**

The Kaplan-Meier survival curve will be plotted for each treatment group, and the median time to alleviation of 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 difference of median time will be obtained by the bootstrap percentile method. The 10,000 bootstrap samples will be generated by 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 by each bootstrapped sample and its 95% CI will be constructed using percentiles of the bootstrap distribution.

```
proc surveyselect data = analysisdata seed = 16010831 out = bootstrap 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.

#### **9.1.1.4 Sensitivity Analysis**

- 1) Time to alleviation of symptoms will be compared between the S-033188 group and the placebo group using the stratified log rank test with composite symptoms score at baseline ( $\leq 11$  or  $\geq 12$ ) and region (Japan/Asia or Rest of the world) as stratification factors. Patients who do not experience alleviation of 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) If patients who discontinue from the study and still have influenza symptoms, they will be treated as follows in the similar analysis at section 9.1.1.1, 9.1.1.2 and 9.1.1.3 (excluding analyses of PPS population and 95% CI for group difference in median time).
- If patients who discontinue from the study and still have influenza symptoms, time to alleviation of symptoms will be censored as 14 days.
  - In consideration of treatment duration of the Oseltamivir group.
    - If patients who discontinue until Day 5 and still have influenza, time to alleviation of symptoms will be censored at the last observation time point.
    - If patients who discontinue after Day 5 and still have influenza, time to alleviation of symptoms will be censored as 14 days.
  - In consideration of the reason of the discontinuation.
    - If patients discontinue due to AE or lack of efficacy, time to alleviation of symptoms will be censored as 14 days.
    - If patients discontinue due to other reason, time to alleviation of symptoms of the patients will be censored at the last observation time point.
- 3) Time to alleviation of symptoms excluding cough will be compared between the S-033188 group and the placebo group using the stratified Peto-Prentice's generalized Wilcoxon test with composite symptoms score at baseline ( $\leq 11$  or  $\geq 12$ ) and region (Japan/Asia or Rest of the world) as stratification factors. Patients who do not experience alleviation of symptoms will be censored at the last observation time point. If at least one of the 6 influenza symptom scores is missing at date and time of assessment that patients have, missing assessments of influenza symptoms conservatively will be treated as having moderate or severe symptoms (as failures) at the corresponding date and time of assessment. The same analysis will be applied to compare the S-033188 group with the Oseltamivir group. This alleviation of symptoms excluding cough is defined as the time when all of 6 influenza symptoms (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%).

## 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 virus titer is not less than the lower limit of quantification ( $0.7 \log_{10} \text{TCID}_{50}/\text{mL}$ ) among those assessed for virus titer on Days 2, 3, 4, 5, 6 and 9. Patients with a positive 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<sub>10</sub> vp/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 virus titer (unit: log<sub>10</sub> TCID<sub>50</sub>/mL)

Change from baseline in virus titer is defined as the change from baseline in virus titer on Days 2, 3, 4, 5, 6 and 9. If virus titer is less than the lower limit of quantification, the virus titer will be imputed 0.7 (TCID<sub>50</sub>/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<sub>10</sub> 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<sub>10</sub> 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<sub>10</sub> 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 amount 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 will be included in this analysis.

5) Area under the curve adjusted by baseline in virus titer

(unit: log<sub>10</sub> TCID<sub>50</sub>/mL×hours)

This endpoint is defined as AUC of change from baseline in virus titer from Day 1 to Day 9. AUC is calculated using the trapezoidal method. AUC 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 date of the  $k^{\text{th}}$  viral titer assessment ( $k = 0, \dots, K$ ) and  $y_k$  represents the log<sub>10</sub> value of the  $k^{\text{th}}$  viral titer assessment (TCID<sub>50</sub>/mL). The lower limit is defined as 0.7 (TCID<sub>50</sub>/mL). One day is equal to 24-hours.

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

- 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 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 the amount 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.

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

This endpoint is defined as the time between the initiation of the study treatment and first time when the virus titer is below the limit of detection ( $0.7 \log_{10}$  TCID<sub>50</sub>/mL). Patients whose virus titer have not reached cessation by the last observation time point will 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 cessation by the last observation time point will 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 alleviated (unit: %)

This endpoint is defined as the percentage of patients whose symptoms have been alleviated at 12, 24, 36, 48, 72, 96, 120, 144, 168, 192 and 216 hours after the initial of study treatment. The alleviation of symptoms is defined as the time when all of 7 symptoms have been assessed by the patient as 0 (None) or 1 (Mild) in the patient eDiary.

- 10) Time to alleviation of the 4 systemic symptoms (unit: hours)

The endpoint is the time to alleviation of the 4 systemic symptoms (headache, feverishness or chills, muscle or joint pain, and fatigue), which is defined as the

time between the initiation of the study treatment and the alleviation of influenza symptoms. The alleviation of the 4 symptoms is defined as the time when all of the 4 systemic symptoms 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 by the last observation time point will be censored at that time point. If at least one of the 4 influenza symptom scores is missing at date and time of assessment that patients have, missing assessments of influenza symptoms conservatively will be treated as having moderate or severe symptoms (as failures) at the corresponding date and time of assessment.

11) Time to alleviation of the 3 respiratory symptoms (unit: hours)

The endpoint is the time to alleviation of the 3 respiratory symptoms (cough, sore throat, and nasal congestion), which is defined as the time between the initiation of the study treatment and the alleviation of influenza symptoms. The alleviation of the 3 symptoms is defined as the time when all of the 3 respiratory symptoms 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 by the last observation time point will be censored at that time point. If at least one of the 3 influenza symptom scores is missing at date and time of assessment that patients have, missing assessments of influenza symptoms conservatively will be treated as having moderate or severe symptoms (as failures) at the corresponding date and time of assessment.

12) Time to alleviation of individual symptoms (unit: hours)

Time to alleviation of cough symptom is defined as the time from the start of treatment to the start of the time period when cough symptom 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%). The following endpoints are defined in a similar way. Patients who do not experience alleviation of symptoms by the last observation time point will be censored at that time point. If symptom score is missing at date and time of assessment that patients have, missing assessment of influenza symptom conservatively will be treated as having moderate or severe symptoms (as failures) at the corresponding date and time of assessment.

Patients whose symptom at baseline is assessed as 0 (None) or 1 (Mild) will be excluded from the analysis.

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



13) Change from baseline in composite symptom score

This endpoint is defined as the change from baseline in the total score of 7 influenza symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue) as assessed by the patient in the patient eDiary at 12, 24, 36, 48, 72, 96, 120, 144, 168, 192 and 216 hours. “None”, “Mild”, “Moderate” and “Severe” will be scored as 0, 1, 2 and 3, respectively. If at least one of the 7 influenza symptom scores is missing at date and time of assessment that patients have, composite symptom score will be handled as missing at the corresponding date and time of assessment.

14) 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 duration of 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. If body temperature is missing at date and time of assessment that patients have, missing assessments of body temperature conservatively will be treated as having more than 37 °C (as failures) at the corresponding date and time of assessment. Patients whose body temperature at baseline is less than 37°C 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.

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

Proportion of patients reporting normal temperature is defined as the percentage of patients whose axillary 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. Because these data may be observed due to e-dairy system’s incorrect setting.

Patients whose body temperature at baseline is less than 37°C will be excluded from the analysis.

16) Body temperature (unit: degree)

Body temperature is defined as measured axillary 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. Because these data may be observed due to e-dairy system’s incorrect setting.

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

Patients will be asked to record their preinfluenza health status between 0 (worst possible health) and 10 (normal health [for someone your age and your health condition]). 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

smaller number on scale for preinfluenza health status by the last observation time point will be censored at that time point. If preinfluenza health status is missing at date and time of assessment that patients have, missing assessments of preinfluenza health status conservatively will be treated as having less than preinfluenza health status at the corresponding date and time of assessment.

Patients whose health status score at baseline is equal to or higher than the preinfluenza health status score will be excluded from the analysis. Health status score 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.

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

This endpoint is defined as the percentage of patients who experience each influenza-related complication (hospitalization, death, sinusitis, otitis media, bronchitis, and radiologically confirmed pneumonia) as an AE after the initiation of the study treatment. A specific complication eCRF with diagnostic criteria for the complications of sinusitis, otitis media, bronchitis and pneumonia will be provided as following rules.

- 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 the patient have worsening cough since starting study treatment?' 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 endpoints 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 time point when last positive RT-PCR is obtained

For treatment-emergent amino acid substitutions in the PA gene, sequencing data obtained at the baseline (Day 1) and last RT-PCR positive timepoint 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 performed 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 endpoints 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 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 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 this 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 on Day 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 and 22. The index value will be recorded twice daily (morning and evening) from Day 1 to Day 9, and once daily (evening) from Day 10 to 14, and Day 22. A conversion table proposed by Ikeda et al. (2015) [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. In addition, the EQ-5D-5L and EQ VAS data observed in the evening after Day 15 will be excluded from this analysis. Because these data may be observed at unplanned time point in the protocol due to e-dairy system's incorrect setting. Only if evening data observed on the last visit date but no data whose timepoint is 'Visit' are collected, the data will be included in the analysis.

#### 5) Work productivity (WP) 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.

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

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

The patients who have no household members or whose all household members has 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 a influenza case in household. If any part of the date of his/her influenza diagnosis is missing, he/she will be diagnosed between Day 1 and Day 15.

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 95% CIs will be calculated by the Clopper-Pearson method.
  - The Mantel-Haenszel test with baseline composite symptom score ( $\leq 11$  or  $\geq 12$ ) and region (Japan/Asia, Rest of the world) as stratification factors will be used to compare these endpoints between two groups at each scheduled time point.
- 2) Change from baseline in virus titer and in the amount of virus RNA (RT-PCR)
  - The summary statistics for the change from baseline in virus titer and in the amount of virus RNA (RT-PCR) will be presented by treatment group at each scheduled time point.

- Van Elteren test with baseline composite symptom score ( $\leq 11$  or  $\geq 12$ ) and region (Japan/Asia, Rest of the world) 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 defined as the p value for “Row Mean Scores Differ” in the “Alternative Hypothesis of Cochran-Mantel-Haenszel Statistics”, using the following SAS code.  
[Example: Comparison between the S-033188 group and the placebo group]  

```
proc freq data= analysisdata;  
  table REGION*SCOREC*TRTP*VARIABLE / cmh2 scores=modridit  
  noprint;  
  where TRTP in ("S-033188", "Placebo");  
run;
```

    - SCOREC: Category of Baseline composite symptom score ( $\leq 11$  or  $\geq 12$ )
    - TRTP: Treatment group
    - VARIABLE: Response variable
- 3) Area under the curve adjusted by baseline in virus titer and in the amount of virus RNA (RT-PCR)
- The similar analyses for the change from baseline in virus titer and the amount of virus RNA will be performed with the area under the curve adjusted by baseline as the response variable.
- 4) Time to cessation of viral shedding by virus titer/by virus RNA
- The patients with a positive virus titer/the amount of virus RNA on Day 1 (i.e., patients whose virus titer/the amount of virus RNA is equal to the lower limit of detection or higher) will be included in the following analysis.
- The similar analyses for the primary endpoint (Section 9.1.1.1, 9.1.1.2 and 9.1.1.3, excluding analyses of PPS population) will be performed with time to cessation of viral shedding by virus titer/RT-PCR. The seed of bootstrapping will be used 16010832.
- 5) Proportion of patients whose symptoms has been alleviated
- The proportion of patients whose symptoms has been alleviated at each scheduled time point will be calculated. The 95% CIs will be calculated by the Clopper-Pearson method.
  - The Mantel-Haenszel test with baseline composite symptom score ( $\leq 11$  or  $\geq 12$ ) and region (Japan/Asia, Rest of the world) as stratification factors will be used to compare these endpoints between two groups at each scheduled time point.
- 6) Time to alleviation of the 4 systemic symptoms/3 respiratory symptoms
- The similar analyses for the primary endpoint (Section 9.1.1.1, 9.1.1.2 and 9.1.1.3, excluding analyses of PPS population and 95% CI for group difference in median time) will be performed with time to alleviation of the 4 systemic symptoms/3 respiratory symptoms.

7) Change from baseline in composite symptom score

- The summary statistics for the change from baseline in composite symptom score will be presented by treatment group at each scheduled time point.
- Analysis of covariance (ANCOVA) with baseline composite symptom score and region (Japan/Asia, Rest of the world) as covariates will be used to compare the change from baseline in the composite symptoms score between two groups at each scheduled time point.
  - The least squares mean (LSM) change and its standard error of means (SE) in each group, the difference between two groups in LSM change, SE, and 95% CI, and p values will be calculated.

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

```
proc mixed data= analysisdata;  
class REGION TRTP;  
model CHG = TRTP bSCORE REGION /cl;  
lsmeans TRTP;  
estimate "S-033188 vs Placebo" TRTP 1 -1/cl;  
run;
```

- TRTP: Treatment group
- CHG: Change from baseline in the composite symptoms score
- bSCORE: Composite symptoms score at baseline

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

```
proc mixed data= analysisdata;  
class REGION TRTP;  
model CHG = TRTP bSCORE REGION /cl;  
lsmeans TRTP;  
estimate "S-033188 vs Oseltamivir" TRTP 1 -1/cl;  
run;
```

- TRTP: Treatment group
- CHG: Change from baseline in the composite symptoms score
- bSCORE: Composite symptoms score at baseline

8) Time to resolution of fever

- An analysis similar to that for the primary endpoint (Section 9.1.1.1, 9.1.1.2 and 9.1.1.3, excluding analyses of PPS population) will be performed with the time to resolution of fever as the response variable. The seed of bootstrapping will be used 16010833.

- 9) Proportion of patients reporting normal temperature
  - An analysis similar to that for the proportion of patients positive for influenza virus titer and by RT-PCR will be performed with the proportion of patients reporting normal temperature.
- 10) Body temperature by time point
  - An analysis similar to that for the change from baseline in composite symptom score will be performed with the body temperature. Body temperature at baseline will be added to the covariates in performing ANCOVA.
- 11) Time to alleviation of individual symptoms
  - The similar analyses for the primary endpoint (Section 9.1.1.1, 9.1.1.2 and 9.1.1.3, excluding analyses of PPS population and 95% CI for group difference in median time) will be performed with time to alleviation of individual symptoms.
- 12) Time to return to preinfluenza health status
  - The similar analyses for the primary endpoint (Section 9.1.1.1, 9.1.1.2 and 9.1.1.3, excluding analyses of PPS population and 95% CI for group difference in median time) will be performed with time to return to preinfluenza health status.
- 13) Incidence of influenza-related complications
  - The incidence of each complication (hospitalization, death, sinusitis, otitis media, bronchitis, and radiologically confirmed pneumonia) and its 95% CI will be calculated by treatment group. The 95% CIs will be calculated by the Clopper-Pearson method.
  - Fisher's exact test will be used will be used to compare incidence between two groups for each complication.

## 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 will be observed  $< 10$  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 titers 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 two groups.

If serum antibody titer will be observed  $< 40$  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 consiration of reference sequence.

3) Drug Susceptibility of Evaluable Virus

- The summary statistics for  $EC_{50}$  and  $IC_{50}$  at baseline will be presented by influenza virus type and subtype based on RT-PCR and treatment group.
- The summary statistics for the ratio of  $EC_{50}$  at baseline relative to  $EC_{50}$  for reference stain and the ratio of  $IC_{50}$  at baseline relative to  $IC_{50}$  for reference stain will be presented by influenza virus type and subtype based on RT-PCR and treatment group. For the patients infected with influenza A virus (A/H1N1pdm or A/H3),  $EC_{50}$  of reference strain A/Victoria/361/2011 and  $IC_{50}$  of reference strain A/Puerto/Rico/8/34 will be used. For the patients infected with influenza B virus,  $EC_{50}$  of reference stain B/Wisconsin/1/2010 and  $IC_{50}$  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 VAS score will be presented by treatment group at each scheduled time point.

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;



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

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. 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]

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

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

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

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

- NUM: Number of household members uninfected by Day 1
- TRTP: Treatment group (1:S-033188, 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

Analyses of time to alleviation of symptoms (Section 9.1.1.1, 9.1.1.2, Kaplan-Meier curve, the median time to alleviation of symptoms and its 95% CI) will be presented for the following subgroup 1), 2), 3) and 4).

Subgroup analyses will be performed for the ITTI Population in the following subgroups.

- 1) Total score of influenza symptoms at baseline
  - $\leq 11$  points
  - $\geq 12$  pointsStratified Peto-Prentice's generalized Wilcoxon test with region (Japan/Asia or Rest of the world) as stratification factors will be applied.
- 2) Region
  - Japan/Asia
  - Rest of the worldStratified Peto-Prentice's generalized Wilcoxon test with composite symptoms score at baseline ( $\leq 11$  or  $\geq 12$ ) as stratification factors will be applied.
- 3) Body weight
  - $< 80$  kg
  - $\geq 80$  kg
- 4) Influenza virus type based on RT-PCR
  - A/H1pdm
  - A/H3
  - B
- 5) Time to treatment from flu onset
  - 0 hours  $\leq$  to  $\leq 24$  hours
  - 24 hours  $<$  to  $\leq 48$  hours

Analyses of time to alleviation of symptoms (Section 9.1.1.1, 9.1.1.2, the median time to alleviation of symptoms and its 95% CI) will be presented for the following subgroup 5) and 6).

6) Meals before and after dosing

- Dosing > 4 hours before or > 4 hours after food taken
- Dosing within 2-4 hours before or 2-4 hours after food intaken
- Dosing < 2 hours before or < 2 after food intaken

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.

7) Age

- < 18 years
- ≥ 18 years

For the proportion of patients positive for influenza virus titer/RT-PCR, change from baseline in virus titer/amount of virus RNA (RT-PCR), area under the curve adjusted by baseline in virus titer/RT-PCR and time to cessation of viral shedding by virus titer/RT-PCR, these analyses will be presented for the following subgroup 8). Analyses of intrahouse infection rate will be presented for the following subgroup 8)

8) Influenza virus type and subtype based on RT-PCR

- A/H1pdm
- A/H3
- B

For the proportion of patients positive for influenza virus titer, change from baseline in virus titer for the following subgroup 9).

9) Influenza virus type and subtype based on RT-PCR

- A/H1pdm
- A/H3
- B

## 10. SAFETY EVALUATION

The following analyses will be performed in the safety population.

### 10.1 Adverse Events

AEs will be classified by system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1. Of reported AEs on the eCRF, AEs 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 Clopper-Pearson method. In addition, the proportion will be compared with placebo group or oseltamivir group by using Fisher's exact test will be calculated. 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 definition of death, serious AEs, AEs leading to withdrawal, other severe AEs, treatment-related AEs are shown below.

Term	Definition
Death	AEs with “Fatal” in terms of outcome.
Other serious AEs (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.

- 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 an SOC and PT. Serious AEs, Treatment-related AEs and serious treatment-related AEs will be summarized in a similar manner. In addition, proportion of patients who experienced AEs of 2% or higher in any the dose treatment groups will be tabulated by SOC and PT.
- 3) The number and proportion of patients who experienced AEs in each category of timing of onset, severity, and outcome will be tabulated by SOC and PT for each treatment group. For these summaries, patients with multiple AEs will be counted only once by the highest priority shown in Table 4 within an SOC and preferred term. Treatment-related AEs will be summarized in a similar manner. The time-of-onset categories include Week 1 (1 to 7 days post-dose), Week 2 (8 to 14 days post-dose), and Week ≥3 (≥15 days post-dose). Each AE will be classified into a time-of-onset category based on the number of days to onset which is calculated as (Date of AE onset – Date of dosing + 1). If a subject experienced multiple episodes of the same AE at different times of onset, the subject will be counted once each in the relevant time-of-onset categories.

**Table 4 Priority of Categories**

Priority	Category		
	Severity	Outcome	Timing of onset (day)
1	Grade 5	Fatal	≥1 to ≤7
2	Grade 4	Recovered/Resolved with sequelae	≥8 to ≤14
3	Grade 3	Not recovered/Not resolved	≥15
4	Grade 2	Recovering/Resolving	
5	Grade 1	Recovered/Resolved	
6		Unknown	

- 4) AEs related hepatic disorders (SMQ code=20000006) will be listed.

## 10.2 Clinical Laboratory

- 1) For each of the hematological and biochemical test parameters, 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 of the hematological and biochemical test parameters, the plot of the baseline value and last observation value is presented for all patients. Last observation value is defined as the value at the last time point in all observed time points within acceptable window and the time point of early termination within acceptable window.
- 3) For each urinalysis parameter, the frequency of each category will be summarized by treatment group at each scheduled time point.
- 4) Each observed value will be classified into three 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.
- 5) The number and proportion of patients who meet the pre-specified criteria shown in Table 5 will be presented by treatment group during the study. If a patient meet multiple criterion in all observed time points, the patient will be counted only once within the worst category.

**Table 5 Pre-specified Criteria**

Term	Criteria
ALT (U/L)	$\leq 3 \times \text{ULN}$ $>3 \text{ to } \leq 5 \times \text{ULN}$ $>5 \text{ to } \leq 20 \times \text{ULN}$ $>20 \times \text{ULN}$
AST (U/L)	$\leq 3 \times \text{ULN}$ $>3 \text{ to } \leq 5 \times \text{ULN}$ $>5 \text{ to } \leq 20 \times \text{ULN}$ $>20 \times \text{ULN}$
Total Bilirubin (mg/dL)	$<1.5 \times \text{ULN}$ $\geq 1.5 \text{ to } <3 \times \text{ULN}$ $>3 \text{ to } \leq 10 \times \text{ULN}$ $>10 \times \text{ULN}$
AST (U/L) or ALT (U/L)	$\leq 3 \times \text{ULN}$ $>3 \text{ to } \leq 5 \times \text{ULN}$ $>5 \text{ to } \leq 20 \times \text{ULN}$ $>20 \times \text{ULN}$
AST (U/L) or ALT (U/L) and Total bilirubin (mg/dL)	Meet all of the following criteria: <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 pressures, systolic blood pressures, 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. For each of the vital sign parameters, the plot of the baseline value and last observation value is presented for all patients in the safety population. Last observation value is defined as the value at the last time point in all observed time points within acceptable window and the time point of early termination within acceptable window.

### 10.4 Electrocardiography (ECG)

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

### 10.5 Subgroup Analyses for Safety Endpoint

Analyses of adverse events (Section 10.1 1) and 2), except proportion of patients who experienced AEs of 2% or higher) will be presented for the following subgroup 1) and 2).

Subgroup analyses will be performed for the Safety population.

- 1) Body weight
  - < 80 kg
  - ≥ 80 kg
- 2) Age
  - < 18 years
  - ≥ 18 years

## 11. INTERIM ANALYSES

No interim analysis is planned in this study.

## 12. PROGRAMMING SPECIFICATIONS

Unless otherwise specified, the following conventions should be used when constructing the analysis tables, figures and listings are prepared:

- Every summary table and figure should 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. Table 6 is shown the summary of the number of digit displayed for each endpoint.

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

Endpoint	No. of digits displayed (after the decimal point)		
	Minimum Maximum	Mean Median	SD CI
Time to alleviation of symptoms			
Time to cessation of viral shedding by virus titer/ RT-PCR			
Time to alleviation of the 4 systemic symptoms			
Time to alleviation of the 3 respiratory symptoms			
Time to resolution of fever			
Time to alleviation of individual symptoms			
Time to return to preinfluenza health status			
Area under the curve adjusted by baseline in virus titer	1	1	1
Area under the curve adjusted by baseline in the amount of virus RNA (RT-PCR)			
Drug susceptibility in patients with evaluable virus: the ratio of EC50/IC50 at baseline relative to EC50/IC50 for reference			
Time Required for Personal Assistance Due to Influenza Illness			
Index value			
Percentage of absenteeism due to influenza illness	3	3	3
Percentage of work productivity loss due to influenza illness			
Change from baseline in influenza virus titer	2	2	2
Change from baseline in amount of virus RNA			
Treatment compliance rate	1	2	2

Summary statistics will be displayed to the number of digits as shown in Table 7.

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

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

- Categories used for summarization

Basically, categories described in CRFs will be used for summarization. If data need to be categorized, the data should 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 to 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 A/H3: A/H3 B:B 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 Other: A/Unknown, A/ND, Unknown Negative:
	The above virus subtype classification is derived from the following specification:
	– A/H1N1pdm: H1_2009
	– A/H3: H3
	– A/H1N1pdm and A/H3: H1_2009/H3
	– A/ND: ND
	– 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 symptoms score at baseline	≤11, ≥12
Treatment compliance rate	<80, ≥80
Acetaminophen use	0, 1-2, 3-4, ≥5
Time of onset of AE	Week 1 (≥1 day to <8 days), Week 2 (≥8 days to <15 days), Week ≥3 (≥15 days)
Urine protein	-, 1+, 2+, 3+, Unknown
Urine glucose	-, 1+, 2+, 3+, 4+, Unknown
Urobilinogen	-, 1+, 2+, 3+, 4+, Unknown
Urine occult blood	-, 1+, 2+, 3+, 4+, Unknown

### **13. BLINDED REVIEW**

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

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

In Protocol section 9.11.1, the following analysis will be changed.

- 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.



## **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 or ET	
		V1	V2	V3	OpV <sub>1</sub>	V4	OpV <sub>2</sub>			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 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								
	Assessment of Health	X <sup>d</sup>	Once Daily															
	Assessment of Health Prior to Influenza Symptoms	X <sup>d</sup>																
	EQ-5D-5L	X <sup>d</sup>	Twice Daily							Once Daily						X		
Work Productivity Questionnaire			X (following resolution of symptoms)															
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	

	Treatment Period					Follow-up Period										
	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D22 or ET
	V1	V2	V3	OpV <sub>1</sub>	V4	OpV <sub>2</sub>			V5						V6	V7
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	X				X										X	X
Influenza Antibody Titer Test	X <sup>h</sup>															X
Nasal/Throat 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 Assessment	X	X	X	X	X	X			X						X	X
Interview for Meal Consumption	X															
Intrahousehold Infection Interview (for Japan only)	X	X	X		X				X						X	

1. D = Day, ET = early termination, V = visit, OpV = optional visit.

- a Prior therapies will also be reviewed.
- b Not necessary if a site has performed a Rapid Influenza Diagnostic Test 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; severity of influenza symptoms twice daily (morning and evening) from Days 1 to 9 and once daily (evening) from Days 10 to 14; assessment of health once daily (evening) from Days 1 to 14; and EQ-5D-5L twice daily (morning and evening) from Days 1 to 9 and once daily (evening) from Days 10 to 14.
- d Predose; if the study treatment is initiated at 18:00 or later on Day 1, the patient will not need to perform Day 1 evening assessments.
- e Body weight will be measured.
- f Height will be measured in the predose examinations only.
- g Urine pregnancy test will be performed only for females who are not diagnosed as postmenopausal.
- h Predose.
- i Virology swabs will be collected if investigator determines that flu symptoms are persisting.
- j Virology swabs will be collected at the early termination.
- k Blood samples will be collected for the measurement of plasma drug concentrations at Visits 2 (Day 2) and 4 (Day 5). If circumstances permit, samples will also be collected at 0.5 to 4 hours post-dose at Visit 1 (Day 1), and at Visit 3 (Day 3) and Visit 6 (Day 15).