Shionogi Study Title:	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
Shionogi Study Number:	1601T0831
ClinicalTrials.gov registration No.	NCT02954354
Study Document	Protocol (Version 3 dated 31October 2016)

History of Protocol Amendments

Version 1 (Original):	05 August 2016
This version of the protocol was not submitted to regulatory authorities	
Version 2 (Amendment 1):	16 September 2016
Version 3 (Amendment 2):	31 October 2016
The major change in protocol amendment 2 was: • Change in the threshold of body weight for 80-mg dose of S-033188 from ≥ 100 kg to ≥ 80 kg. This change required associated changes throughout the protocol in text, tables, and figures.	

Clinical Study Protocol: 1601T0831

Study Title:	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
Study Number:	1601T0831
Study Phase:	3
Product Name:	S-033188
IND Number:	126653
Sponsor* for Japan and other Asian countries:	Shionogi & Co., Ltd. 1-8, Doshomachi 3-chome, Chuo-ku, Osaka 541-0045, Japan
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Sponsor Contact:	[redacted]

Issue Date:

Version 1 (Original):	05 August 2016
Version 2 (Amendment 1):	16 September 2016
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*: The study sponsor may be one or more of the above companies. Throughout the protocol, the term "sponsor" represents the various legal entities identified in the "Sponsor List of the Study Administrative Structure" in the protocol. The above companies are referred to as Shionogi.

Confidentiality Statement

SYNOPSIS

Study Title:

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

Study Number:

1601T0831

Study Phase: 3

Primary Efficacy 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

Secondary Efficacy Objectives:

- 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

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

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

Pharmacokinetic Objective:

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

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

Study Design:

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 ≥ 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. Detailed study design and schedule are described in Sections 3.1 and 5.2.

Study Population:

Otherwise healthy male and female patients ≥ 12 and ≤ 64 years old with influenza A and/or B infection of developing influenza complications within 48 hours of symptom onset

Criteria for Inclusion and Exclusion:

Inclusion Criteria:

Patients who fulfill all of the following criteria will be included in the study:

1. Patients who are able to understand the study and comply with all study procedures, and willing to provide written informed consent/assent prior to the predose examinations appropriately. For adolescent patients, informed consent/assent of voluntary participation should be obtained in accordance with local requirements (see Section 7.1).
2. Male or female patients aged ≥ 12 to ≤ 64 years at the time of signing the informed consent/assent form.
3. Patients with a diagnosis of influenza confirmed by all of the following:
   a. Fever ≥ 38ºC (axillary) in the predose examinations or > 4 hours after dosing of antipyretics if they were taken
   b. At least one of the following general systemic symptoms associated with influenza are present with a severity of moderate or greater
      - Headache
      - Feverishness or chills
      - Muscle or joint pain
      - Fatigue
   c. At least one of the following respiratory symptoms associated with influenza are present with a severity of moderate or greater
      - Cough
      - Sore throat
      - Nasal congestion
4. The time interval between the onset of symptoms and the predose examinations (Screening) is 48 hours or less. The onset of symptoms is defined as either:
   a. Time of the first increase in body temperature (an increase of at least 1ºC from normal body temperature)

   b. Time when the patient experiences at least one general or respiratory symptom
5. Women of childbearing potential (WOCBP) who agree to use a highly effective method of contraception for 3 months after the first dose of S-033188 or oseltamivir (see Section 6.3.1 for approved contraceptive requirements).

Exclusion Criteria:

Patients who meet any of the following criteria will be excluded from the study:

1. Patients with severe influenza virus infection requiring inpatient treatment.
2. Patients aged ≥ 20 years with known allergy to oseltamivir (Tamiflu®).
3. Patients with any of the following risk factors*:
   - Women who are pregnant or within 2 weeks post-partum
   - Residents of long-term care facilities (eg, welfare facilities for the elderly, nursing homes)
   - Chronic respiratory diseases including bronchial asthma
   - Neurological and neurodevelopmental disorders including disorders of the brain, spinal cord, peripheral nerve, and muscle (eg, cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability, moderate to severe developmental delay, muscular dystrophy, or spinal cord injury)
   - Heart disease (such as congenital heart disease, congestive heart failure, or coronary artery disease), excluding hypertension without any other heart-related symptoms
   - American Indians and Alaskan natives
   - Blood disorders (such as sickle cell disease)
   - Endocrine disorders (including diabetes mellitus)
   - Kidney disorders
   - Liver disorders
   - Metabolic disorders
   - Compromised immune system (including patients receiving immunosuppressant therapy, or those with cancer or human immunodeficiency virus [HIV] infection)
   - Morbid obesity (body mass index [BMI] ≥ 40)

   * Based on the definitions of people at high risk by the Centers for Disease Control and Prevention (CDC). http://www.cdc.gov/flu/about/disease/high_risk.htm
4. Patients unable to swallow tablets or capsules.
5. Patients who have previously received S-033188.
6. Patients weighing < 40 kg
7. Patients who have been exposed to an investigational drug within 30 days prior to the predose examinations.
8. Women who are breastfeeding or have a positive pregnancy test in the predose examinations. The following female patients who have documentation of either a or b below do not need to undergo a pregnancy test in the predose examinations:
   a. Postmenopausal women (defined as cessation of regular menstrual periods for 2 years or more and confirmed by a follicle-stimulating hormone test)
   b. Women who are surgically sterile by hysterectomy, bilateral oophorectomy, or tubal ligation

9. Patients with concurrent infections requiring systemic antimicrobial and/or antiviral therapy at the predose examinations.
10. Patients who have received peramivir, laninamivir, oseltamivir, zanamivir, rimantadine, umifenovir or amantadine within 30 days prior to the predose examinations.
11. Patients who have received an investigational monoclonal antibody for a viral disease in the last year.
12. Patients with severe underlying diseases.
13. Patients with current creatinine clearance ≤ 60 mL/min (≤ 30 mL/min in Japan).
14. Patients who, in the opinion of the investigator, would be unlikely to comply with required study visits, self-assessments, and interventions.

Study Drug, Dose, and Mode of Administration:

Test Drug

- S-033188 20-mg tablets

Control Drugs

- Oseltamivir 75-mg capsules
- Placebo tablet matching S-033188 20-mg tablets
- Placebo capsule matching oseltamivir 75-mg capsules

All patients will receive the study drug provided for each group according to the result of allocation.

Patients aged ≥ 20 years

[S-033188 group]

Day 1: Two or four 20-mg S-033188 tablets (depending on weight) will be administered orally. One oseltamivir placebo capsule will be administered orally BID (morning and evening).

Days 2 to 5: One oseltamivir placebo capsule will be administered orally BID (morning and evening).

[Oseltamivir group]

Day 1: Two or four S-033188 placebo tablets (depending on weight) will be administered orally. One 75-mg oseltamivir capsule will be administered orally BID (morning and evening).

Days 2 to 5: One 75-mg oseltamivir capsule will be administered orally BID (morning and evening).

[Placebo group]

Day 1: Two or four S-033188 placebo tablets (depending on weight) will be administered orally. One oseltamivir placebo capsule will be administered orally BID (morning and evening).

Days 2 to 5: One oseltamivir placebo capsule will be administered orally BID (morning and evening).

Patients aged 12 to 19 years

[S-033188 group]

Day 1: Two or four 20-mg S-033188 tablets (depending on weight) will be administered orally.

[Placebo group]

Day 1: Two or four S-033188 placebo tablets (depending on weight) will be administered orally.

Duration of Treatment:

Patients aged 20 to 64 years: 5 days

Patients aged 12 to 19 years: 1 day

Prohibited Concomitant Therapy:

The use of the following drugs and over-the-counter drugs with equivalent efficacy to them will be prohibited from Visit 1 (Day 1) until Visit 7 (Day 22) or early termination.

a. Systemic antiviral drugs
b. Antimicrobial* and antifungal drugs**
c. Antipyretics/analgesics except acetaminophen
d. Antitussives/expectorants
e. Combination cold remedies
f. Antihistamines**
g. Corticosteroids**
h. Immunosuppressants
i. Herbal medicines or complementary therapies indicated for influenza virus infection (eg, Maoutou)
j. Other investigational drugs

* Except for the treatment of complications of influenza suspected to be bacterial infection after Day 1.

** Dermal preparations will be permitted, but application to the eyes, nose or ears, or by inhalation will be prohibited.

Efficacy Assessments:

Primary endpoint:

Time to alleviation of symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue), defined as the time from the start of treatment to the time when all influenza symptoms are rated as absent or mild

Secondary endpoints:

- Proportion of patients positive for influenza virus titer and proportion of patients positive by RT-PCR at each time point
- Change from baseline in virus titer and in the amount of virus RNA (RT-PCR) at each time point
- Area under the curve adjusted by baseline in virus titer and in the amount of virus RNA (RT-PCR)
- Time to cessation of viral shedding by virus titer and by RT-PCR
- Proportion of patients whose symptoms has been alleviated at each time point
- Time to alleviation of the 4 systemic symptoms (headache, feverishness or chills, muscle or joint pain, and fatigue)

- Time to alleviation of the 3 respiratory symptoms (cough, sore throat and nasal congestion)
- Change from baseline in composite symptom score at each time point
- Time to resolution of fever
- Proportion of patients reporting normal temperature at each time point
- Body temperature at each time point
- Time to alleviation of individual symptoms
- Time to return to preinfluenza health status
- Incidence of influenza-related complications (hospitalization, death, sinusitis, bronchitis, otitis media, and radiologically confirmed pneumonia)
- Intrahousehold infection rate (for Japan only)

Other Assessments:

- Serum antibody titer
- Polymorphic and treatment-emergent amino acid substitutions in the PA gene
- Drug susceptibility in patients with evaluable virus
- Health economic outcomes
  - EQ-5D-5L
  - WP questionnaire

Safety Assessments:

Frequencies of AEs, serious AEs, vital sign measurements, electrocardiography (ECG), and clinical laboratory tests

Pharmacokinetic Assessments:

For the measurement of plasma S-033447 concentrations, blood samples will be collected at Visit 2 (Day 2) and 4 (Day 5). If circumstances permit, samples will also be collected at 0.5 to 4 hours postdose at Visit 1 (Day 1), Visit 3 (Day 3) and Visit 6 (Day 15).

Statistical Methods:

The intention-to-treat infected (ITTI, defined as RT-PCR positive for influenza) set will be the primary efficacy analysis population in the study. The per-protocol set (PPS) will be used as supportive evidence of the primary analyses for efficacy. All statistical testing will be performed at the two-sided significance level of 0.05 unless stated otherwise.

Primary efficacy analysis:

Comparison of the primary endpoint between S-033188 and placebo:

In the primary analysis, the time to alleviation of symptoms will be compared between the S-033188 group and the placebo group using the stratified generalized Wilcoxon test with composite symptoms score at baseline and region as stratification factors. Furthermore, the Kaplan-Meier curves will be plotted for each treatment group, and the median time to alleviation of symptoms and its 95% confidence interval (CI) will be calculated. The same analyses in PPS will be performed as a sensitivity analysis.

Secondary efficacy analysis for primary endpoint:

Comparison of the primary endpoint between adult stratum of S-033188 group and oseltamivir group:

Among patients aged 20 to 64 years, the time to alleviation of symptoms will be compared between the S-033188 group and the oseltamivir group using the stratified generalized Wilcoxon test with composite symptoms score at baseline and region as

stratification factors. Furthermore, the Kaplan-Meier curves will be plotted for each treatment group, and the median time to alleviation of symptoms and its 95% CI will be calculated.

Together with the primary efficacy analysis, this comparison will be conducted in a hierarchical manner so as to maintain control of overall Type I error. For Japan, control of overall Type I error is not required for the secondary efficacy analysis of primary endpoint.

Other secondary efficacy analyses:

The following analytical procedures will be applied to the various secondary efficacy variables: stratified generalized Wilcoxon test, analysis of covariance (ANCOVA), van Elteren test, Mantel-Haenszel test, and Fisher's exact test.

Safety analyses:

For AEs and treatment-related AEs, the numbers of events and patients with AEs/treatment-related AEs will be counted for each treatment group. The numbers of events and patients with AEs/treatment-related AEs will be counted by system organ class (SOC) and preferred term (PT) for each treatment group.

Descriptive statistics (number of patients, mean, standard deviation, minimum, median, and maximum) for quantitative data obtained at each time point will be calculated for each treatment group for vital sign measurements, ECG, and laboratory values. For qualitative data, the frequency of each category at each time point will be summarized.

Study Duration:

Study duration in individual patients: 22 days

Planned study duration for the study: [redacted]

Date of Original: 05 August 2016

Date of Latest Amendment: 31 October 2016 (Amendment 2)

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADL	Activities of Daily Living
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AR	adverse reaction
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-72}	area under the plasma concentration-time curve from time zero to 72 hours after dosing
AUC_{0-inf}	area under the plasma concentration-time curve extrapolated from time zero to infinity
AUC_{0-last}	area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration after dosing
BA	bioavailability
BCRP	breast cancer resistance protein
BID	twice daily
BLQ	below the limit of quantification
BMI	body mass index
C_{24}	plasma S-033447 concentration 24 hours post-dose
CDC	Centers for Disease Control and Prevention
CEN	cap-dependent endonuclease
CI	confidence interval
C_{max}	maximum plasma concentration
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CV%	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
ECG	electrocardiography
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
ePRO	electronic patient-reported outcome
EQ-5D-5L	EuroQol–5 Dimensions–5 Levels
FE	food effect
Feu_{0-72}	fraction of dose excreted in urine from time zero to 72 hours post-dose

GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBs	hepatitis B virus surface
h-CE	hepatic carboxylesterase
HCV	hepatitis C virus
hERG	human ether à go-go related gene
HIV	human immunodeficiency virus
IC_{50}	half maximal inhibitory concentration
IB	investigator's brochure
IEC	institutional ethics committee
IRB	institutional review board
IRT	interactive response technology
ITTI	intention to treat infected
IUD	intrauterine contraceptive device
LFT	liver function test
MATE	multidrug and toxin extrusion protein
Mean	arithmetic mean
MedDRA	Medical Dictionary for Regulatory Activities
NA	neuraminidase
NOAEL	no observed adverse effect level
NPAE	neuropsychiatric adverse event
OATP	organic anion transporting polypeptide
PA	polymerase acidic protein
PD	pharmacodynamic(s)
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PPS	Per-protocol set
PT	preferred term
QOL	quality of life
QTcF	QT interval corrected for heart rate by Fridericia's correction
RIDT	rapid influenza diagnostic test
RT-PCR	reverse transcription polymerase chain reaction
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SmPC	Summary of Product Characteristics
SOC	system organ class

SUSAR	suspected unexpected serious adverse reaction
$t_{1/2,z}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
T_{max}	time to maximum plasma concentration
UGT	UDP glucuronosyl transferase
ULN	upper limit of normal
VAS	visual analogue scale
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
WP	work productivity
ΔΔQTcF	placebo-subtracted changes from baseline in the QTcF interval
λ_z	terminal elimination rate constant

1. INTRODUCTION

Influenza is an acute respiratory infection caused by the influenza virus, which is transmitted primarily through airborne droplets. It is characterized by a sudden onset of clinical symptoms, such as fever, chills, headache, muscle pains, and loss of appetite, which start 1 to 4 days after infection, and it is especially remarkable in fever reaching 38ºC to 40ºC within 24 hours of the onset [1, 2]. Other symptoms include cough, sore throat, and nasal congestion; cough is very frequent and tends to be persistent. Although illness with influenza generally is self-limiting, severe disease with fatal outcome can occur in both the otherwise healthy and in those with underlying comorbidities. Fatal disease is also more often observed in children and in the elderly, although some influenza viruses with novel structures can lead to fatal disease at any age. Influenza is also considered to make some chronic health conditions worse, such as asthma and congestive heart failure. The Centers for Disease Control and Prevention (CDC) classifies people at high risk of developing flu related complications [3]. These characteristics make influenza a "potentially severe disease", which should be distinguished from the "common cold syndrome".

The following anti-influenza virus drugs are currently available (with geographic variability): the M2 ion channel inhibitor amantadine; the RNA polymerase inhibitor favipiravir; and the neuraminidase (NA) inhibitors oseltamivir, zanamivir, peramivir, and laninamivir. Since many cases of seasonal influenza A infection are resistant to amantadine, the CDC has recommended against the use of amantadine for the treatment and prophylaxis of influenza virus infection [4], and its use is limited in Japan. Favipiravir is only indicated for the treatment of novel or reemerging influenza virus infections with no or poor response to other anti-influenza drugs in Japan and cannot be manufactured or marketed unless requested by the Minister of Health, Labour, and Welfare. Thus, NA inhibitors are the mainstay of treatment for influenza infections, but their oral formulations need to be administered for 5 days, potentially resulting in poor patient compliance, and are associated with nausea, vomiting, headaches, and renal and psychiatric events. Inhalation formulations can only be used in patients who are able to inhale the drug and have been associated with bronchospasm in susceptible individuals. There is, therefore, an unmet medical need for anti-influenza virus drugs that are well tolerated and can be easily administered.

In addition, influenza viruses are known to mutate during replication, leading to drug resistance, and can evolve by reassortment into a strain to which most people are not immune, resulting in a pandemic, or into a strain resistant to existing anti-influenza virus drugs, which may be most prevalent in a seasonal epidemic. To protect against these situations, the development of an anti-influenza virus drug with a novel mechanism of action is needed.

S-033188 is a compound discovered by Shionogi & Co., Ltd. that exerts anti-influenza virus activity. S-033188 is a prodrug, which is converted to an active form (S-033447) through a metabolic process (hydrolysis). S-033447 acts on cap-dependent endonuclease (CEN), an enzyme specific to influenza viruses, and inhibits viral cap-snatching, thereby suppressing the growth of influenza viruses. The results from the completed nonclinical

and Phase 1 clinical studies are summarized below.

1.1 Nonclinical Studies

1.1.1 Pharmacology

[redacted]

1.1.2 Safety

[redacted]

[redacted]

[redacted]

1.1.3 Pharmacokinetics

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.2 Clinical Summary

[redacted]

1.2.1 Single-ascending Dose Study (Study 1510T0811)

[redacted]

[redacted]

1.2.2 Relative Bioavailability and Food Effect Study (Study 1512T0813)

[redacted]

1.2.3 Drug-drug Interaction Study with Midazolam (Study 1519T0814)

[redacted]

[redacted]

1.2.4 Drug-drug Interaction Study with Itraconazole (Study 1520T0815)

[redacted]

1.2.5 Thorough QT/QTc Study (Study 1527T0816)

[redacted]

[redacted]

1.2.6 A Phase 2 Proof of Concept and Dose Finding Study (Study 1518T0821)

[redacted]

1.3 Comparator Data

1.3.1 Clinical Data of Oseltamivir

1.3.1.1 Oseltamivir Efficacy

Oseltamivir (Tamiflu®) is a NA inhibitor indicated for the treatment of uncomplicated acute illness due to influenza infection in patients who have been symptomatic for no more than 2 days (please refer to local prescribing information for regional variations in indications). Oseltamivir phosphate is the prodrug of oseltamivir carboxylate, the effective form. Oseltamivir phosphate dissociates in the gastrointestinal tract to form oseltamivir, which is absorbed and metabolized into oseltamivir carboxylate by hepatic carboxylesterase

(h-CE).

Several large Phase 3 clinical studies have demonstrated that oseltamivir reduced time to alleviation of symptoms in otherwise healthy individuals with influenza presenting within 48 hours of symptom onset [5, 6]. Oseltamivir has also been shown to reduce the incidence of symptomatic influenza in contacts of individuals with influenza in prophylaxis trials [5]. The efficacy of oseltamivir to reduce complications of influenza is less clear with conflicting results across several studies [5, 6, 7, 8]. Oseltamivir has not been formally tested beyond 48 hours of symptom onset.

1.3.1.2 Oseltamivir Safety

Neuropsychiatric adverse events (NPAEs) have been reported during administration of oseltamivir in patients with influenza, especially in children and adolescents. Close monitoring is advised for behavioral changes, and the benefits and risks of continuing treatment should be carefully evaluated for each patient. These events may occur in the setting of encephalitis or encephalopathy but can occur without obvious severe disease and have been associated with fatal outcomes. A causal relationship between oseltamivir and these events has never been shown. Similar types and rates of NPAEs have been shown to occur in patients with influenza who did not receive oseltamivir.

In adults/adolescents, the most commonly reported adverse reactions (ARs) were nausea and vomiting in the treatment studies, and nausea in the prevention studies. The majority of these ARs were reported on a single occasion on either the first or second treatment day and resolved spontaneously within 1 to 2 days. In children, the most commonly AR was vomiting. In the majority of patients, these ARs did not lead to discontinuation of oseltamivir.

The following serious ARs have been rarely reported since oseltamivir has been marketed: anaphylactic and anaphylactoid reactions, hepatic disorders (fulminant hepatitis, hepatic function disorder, and jaundice), angioneurotic edema, Stevens-Johnson syndrome and toxic epidermal necrolysis, gastrointestinal bleeding, and neuropsychiatric disorders.

Very common ARs listed in the prescribing information and Summary of Product Characteristics (SmPC) include headache and nausea. Common ARs include vomiting, abdominal pain, dyspepsia, insomnia, pain, dizziness, fatigue, pyrexia, bronchitis, cough, sore throat, rhinorrhea, herpes simplex, nasopharyngitis, upper respiratory tract infections, and sinusitis. Uncommon ARs include hypersensitivity reactions, altered level of consciousness, cardiac arrhythmia, elevated liver enzymes, eczema, dermatitis, rash, and urticaria. Rare ARs include visual disturbance, thrombocytopenia, anaphylactic/anaphylactoid reactions, agitation, abnormal behavior, anxiety, confusion, delusions, delirium, hallucinations, nightmares, and self-injury.

1.3.1.3 Clinical Studies

1.3.1.3.1 Treatment of Influenza Infection in Adults and Adolescents

A total of 1355 patients were included in two Phase 3 multicenter, placebo-controlled

trials in naturally acquired influenza conducted in the United States, Europe, etc. (Studies WV15670 & WV15671). Time to alleviation of symptoms, the primary efficacy endpoint, was significantly reduced by up to 30 hours in the patients received 75 mg of oseltamivir twice daily compared with placebo. Significant improvements in the secondary efficacy endpoints, such as the median total symptom score AUC and the time to return to an afebrile state, were also observed [5, 9].

The Phase 3 study conducted in Japan (Study JV15824) included 316 patients with influenza. As with the Phase 3 studies noted above, significant improvements in the time to alleviation of symptoms, the median total symptom score AUC and the time to return to an afebrile state were observed in Japanese patients [10].

1.3.1.4 Oseltamivir Dosing

The recommended oral dose of oseltamivir for adolescents/adults ≥ 13 years of age is 75 mg BID for 5 days in the United States. For adolescents 12 years of age, the recommended oral dose is 75 mg BID for 5 days if the individual weighs > 40 kg.

In Japan, the recommended oral dose for treatment of influenza in adolescent patients weighing ≥ 37.5 kg and adult patients is 75 mg BID for 5 days.

1.3.1.5 Oseltamivir Dosing and Renal Impairment

Oseltamivir 75 mg BID is recommended for individuals with a creatinine clearance of > 60 mL/min (≥ 30 mL/min in Japan), and dose adjustment is required for lower creatinine clearance. If patients are enrolled in the study and found to have a creatinine clearance ≤ 60 mL/min (≤ 30 mL/min in Japan), investigators should contact the study Medical Monitor to discuss patient management regarding continuation of oseltamivir/oseltamivir placebo. Creatinine clearance should be calculated as soon as the Screening creatinine result is available by using the following online calculator: http://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation.

1.4 Rationale for the Study

This randomized, double-blind, placebo- and active-controlled study will be conducted to investigate the superiority of S-033188 over placebo in efficacy in otherwise healthy patients with influenza virus infection receiving 40 or 80 mg of S-033188. The dose to be tested in this confirmatory study was selected based on the results of the Phase 2 dose-finding study, in which the statistically significant efficacy outcome and no notable safety concerns were observed in patients who received single 40 mg doses of S-033188 orally. This study will be conducted with an appropriate study design to confirm the superiority of S-033188 to placebo in otherwise healthy patients with influenza virus infection in sufficient consideration of the safety of study participants.

Since oseltamivir is to be avoided in adolescents except high risk patients in consideration of reports associated with anomalous behavior (per the Japanese label), subjects who are 12 to 19 years of age (approximately 15% of overall study population) will be randomized to either S-033188, 40 or 80 mg, or placebo only in this study. Thus, the superiority of S-033188 to oseltamivir in time to alleviation of symptom will be

confirmed only in the patients ≥ 20 years of age under control of overall Type I error (except for Japan).

2. STUDY OBJECTIVES

2.1 Primary Efficacy Objective

The primary objective of this study is:

- The primary efficacy objective of this study is 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.

2.2 Secondary Efficacy Objectives

The secondary efficacy objectives of this study are:

- 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 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

2.3 Other Efficacy Objective

The other efficacy objective of this study is:

- 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

2.4 Safety Objectives

Safety objectives of this study are:

- 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 AEs in patients with influenza of a single dose of S-033188 with oseltamivir 75 mg BID for 5 days and with placebo

2.5 Pharmacokinetic Objective

The PK objective of this study is:

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

2.6 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 of S-033188 compared with oseltamivir 75 mg BID for 5 days and placebo

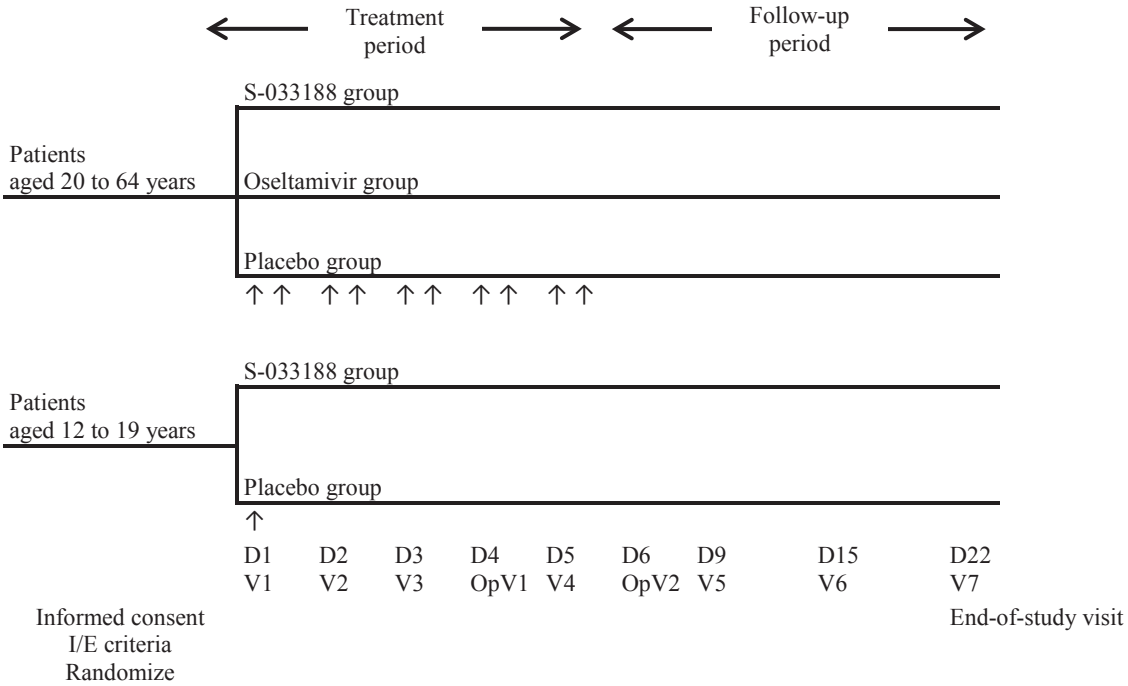
3. INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This study is a randomized, double-blind, multicenter, parallel-group, placebo- and active-controlled study designed to evaluate the efficacy and safety of single dose of S-033188 in otherwise healthy adult and adolescent patients with influenza virus infection.

Prior to the initiation of the study treatment on Day 1, patients will be assessed for eligibility for participation in the study. Patients aged 20 to 64 years who are determined to be eligible will be randomly assigned in a ratio of 2:2:1 to receive a single dose of S-033188 (either 40 mg or 80 mg according to weight), 75 mg BID of oseltamivir for 5 days, or placebo. Patients aged 12 to 19 years who are determined to be eligible will be randomly assigned in a ratio of 2:1 to receive a single dose of either 40 or 80 mg of S-033188 or placebo. Patients who weigh < 80 kg at Screening will receive 40 mg of S-033188, and patients who weigh ≥ 80 kg at Screening will receive 80 mg of S-033188. The study drug will be administered orally at the study center on Day 1 (initial dose). Patients aged 20 to 64 years will receive study drug twice daily for 5 days in total. For patients aged 12 to 19 years, a single dose of study drug will be tested. There is a maximum of 9 visits including 2 optional visits during a period to assess the efficacy and safety: 14 days for efficacy and 22 days for safety. The study schematic is shown in Figure 3-1. The time and events schedule is provided in Appendix 1.

Figure 3-1 Study Schematic



D = day; I/E = inclusion/exclusion; OpV1 = optional Visit 1; OpV2 = optional Visit 2; V = visit
Up arrows demonstrate the administrations of study drug.

This study will be conducted in compliance with this protocol, International Conference on Harmonisation-Good Clinical Practices (ICH-GCPs), and all applicable requirements.

3.2 Rationale for Study Design and Control Group

3.2.1 Rationale for Study Design

A multicenter, randomized, double-blind design will be used to evaluate the efficacy of a single, oral dose of S-033188 compared with oseltamivir 75 mg BID for 5 days and placebo in patients with influenza virus infection.

3.2.2 Selection of the Dose of S-033188

[redacted]

Figure 3-2 [redacted]

3.2.3 Selection of the Dose of Oseltamivir

The dose of oseltamivir to be used in this study was set in accordance with the approved dosage and administration of oseltamivir (Tamiflu®) capsules for oral use.

3.3 Study Duration

3.3.1 Study Duration in Individual Patients

Study duration in individual patients is 22 days.

3.3.2 Planned Study Duration for the Study

The planned study duration is from [redacted]

3.3.3 End of Study

The End of the Study is defined as the last patient's last visit..

4. STUDY POPULATION SELECTION

4.1 Study Population

Patients will be male and female adolescents and adults (age 12 to 64 years) with influenza A and/or B virus infection, with typical systemic and respiratory symptoms of influenza, whose new symptoms were first noticed ≤ 48 hours prior to the predose examinations.

Approximately 1494 patients will be enrolled. Patients with confirmed influenza with symptom onset ≤ 48 hours who satisfy the following eligibility criteria will be randomized.

4.2 Inclusion Criteria

Patients who fulfill all of the following criteria will be included in the study:

1. Patients who are able to understand the study and comply with all study procedures, and willing to provide written informed consent/assent prior to the predose examinations appropriately. As for adolescent patients, informed consent/assent of voluntary participation should be obtained in accordance with local requirements (see Section 7.1).
2. Male or female patients aged ≥ 12 to ≤ 64 years at the time of signing the informed consent/assent form.
3. Patients with a diagnosis of influenza virus infection confirmed by all of the following:
   a. Fever ≥ 38ºC (axillary) in the predose examinations or > 4 hours after dosing of antipyretics if they were taken
   b. At least one of the following general systemic symptoms associated with influenza are present with a severity of moderate or greater
      - Headache
      - Feverishness or chills
      - Muscle or joint pain
      - Fatigue
   c. At least one of the following respiratory symptoms associated with influenza are present with a severity of moderate or greater
      - Cough
      - Sore throat
      - Nasal congestion
4. The time interval between the onset of symptoms and the predose examinations (Screening) is 48 hours or less. The onset of symptoms is defined as either:
   a. Time of the first increase in body temperature (an increase of at least 1ºC from normal body temperature)
   b. Time when the patient experiences at least one general or respiratory symptom
5. Women of childbearing potential (WOCBP) who agree to use a highly effective method of contraception for 3 months after the first dose of study drug (see Section

6.3.1 for approved contraceptive requirements).

4.3 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study:

1. Patients with severe influenza virus infection requiring inpatient treatment.
2. Patients aged ≥ 20 years with known allergy to oseltamivir (Tamiflu®).
3. Patients with any of the following risk factors*:
   a. Women who are pregnant or within 2 weeks post-partum
   b. Residents of long-term care facilities (eg, welfare facilities for the elderly, nursing homes)
   c. Chronic respiratory diseases including bronchial asthma
   d. Neurological and neurodevelopmental disorders including disorders of the brain, spinal cord, peripheral nerve, and muscle (eg, cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability, moderate to severe developmental delay, muscular dystrophy, or spinal cord injury)
   e. Heart disease (such as congenital heart disease, congestive heart failure, or coronary artery disease), excluding hypertension without any other heart-related symptoms)
   f. American Indians and Alaskan natives
   g. Blood disorders (such as sickle cell disease)
   h. Endocrine disorders (including diabetes mellitus)
   i. Kidney disorders
   j. Liver disorders
   k. Metabolic disorders
   l. Compromised immune system (including patients receiving immunosuppressant therapy, or those with cancer or human immunodeficiency virus [HIV] infection)
   m. Morbid obesity (body mass index [BMI] ≥ 40)

   * Based on the definitions of people at high risk by the Centers for Disease Control and Prevention (CDC). http://www.cdc.gov/flu/about/disease/high_risk.htm
4. Patients unable to swallow tablets or capsules.
5. Patients who have previously received S-033188.
6. Patients weighing < 40 kg
7. Patients who have been exposed to an investigational drug within 30 days prior to the predose examinations.
8. Women who are breastfeeding or have a positive pregnancy test in the predose examinations. The following female patients who have documentation of either a or b below do not need to undergo a pregnancy test in the predose examinations:
   a. Postmenopausal (defined as cessation of regular menstrual periods for 2 years or more and confirmed by a follicle-stimulating hormone test) women
   b. Women who are surgically sterile by hysterectomy, bilateral oophorectomy, or tubal ligation
9. Patients with concurrent infections requiring systemic antimicrobial and/or antiviral therapy at the predose examinations.

10. Patients who have received peramivir, laninamivir, oseltamivir, zanamivir, rimantadine, umifenovir or amantadine within 30 days prior to the predose examinations.
11. Patients who have received an investigational monoclonal antibody for a viral disease in the last year.
12. Patients with severe underlying diseases.
13. Patients with current creatinine clearance ≤ 60 mL/min (≤ 30 mL/min in Japan).
14. Patients who, in the opinion of the investigator, would be unlikely to comply with required study visits, self-assessments, and interventions.

4.4 Screen Failures

Screen failures are defined as patients who consented to participate in the study but were not subsequently randomized/administered the study drug. Minimal information will include informed consent date, baseline patient characteristics, all of eligibility criteria violated, reasons for screen failure, nasopharyngeal/pharyngeal swab influenza RT-PCR result, AEs that led to screen failure, and any SAEs and will be entered in the electronic case report form (eCRF). Rescreening will be permitted, but patients who do not meet the clinical criteria for participation in the study within 48 hours (screen failure) may not be rescreened.

5. STUDY TREATMENTS

5.1 Description of Treatments

5.1.1 Test Drug

- S-033188 20-mg tablets: White to light yellow, oblong shaped film-coated tablets containing 20 mg of S-033188, manufactured by Shionogi & Co., Ltd.

5.1.2 Placebo

- S-033188 placebo tablets: white to light yellow, oblong-shaped, film-coated placebo tablets matching the S-033188 20-mg tablets but without active drug substance
- Oseltamivir placebo capsules: matching placebo for oseltamivir 75-mg capsules

5.1.3 Active Control

- Oseltamivir 75-mg capsules: Oseltamivir phosphate (Tamiflu® Roche) capsules.

5.2 Treatments to be Administered

5.2.1 Patients Aged 20 to 64 Years

Patients who are qualified for entry will be randomly assigned in a ratio of 2:2:1 to receive S-033188, oseltamivir, or placebo according to the assignment procedures specified in Section 5.4. Patients will receive S-033188 or placebo once on Day 1. Oseltamivir or placebo should be dosed 12 hours apart from Day 1 through Day 5. The details of administration are shown in Table 5-1. Study drugs can be taken without regard to food (although food may improve tolerability of oseltamivir).

Patients should be instructed that in the case of missed doses of oseltamivir/placebo they should take the missed dose as soon as they remember, unless it is 2 hours or less before the next dose. They should then continue to take oseltamivir/placebo at the usual times. Patients should not take 2 doses at a time to make up for a missed dose.

Table 5-1 Study Drug Administration (Patients Aged ≥ 20 Years)

Treatment Group	Day 1	Day 2	Day 3	Day 4	Day 5*
S-033188					
Oseltamivir placebo	2 capsules	2 capsules	2 capsules	2 capsules	2 capsules
S-033188 40 mg (weight < 80 kg)	2 tablets				
S-033188 80 mg (weight ≥ 80 kg)	4 tablets				
Oseltamivir					
Oseltamivir 75 mg	2 capsules	2 capsules	2 capsules	2 capsules	2 capsules
S-033188 placebo (weight < 80 kg)	2 tablets				
S-033188 placebo (weight ≥ 80 kg)	4 tablets				
Placebo					
Oseltamivir placebo	2 capsules	2 capsules	2 capsules	2 capsules	2 capsules
S-033188 placebo (weight < 80 kg)	2 tablets				
S-033188 placebo (weight ≥ 80 kg)	4 tablets				

* If only 1 dose of oseltamivir or placebo is taken on Day 1 due to the patient being randomized after 17:00, dosing will be completed on Day 6.

5.2.2 Patients Aged 12 to 19 Years

Patients who are qualified for entry will be randomly assigned in a ratio of 2:1 to receive S-033188 or placebo according to the assignment procedures specified in Section 5.4. Patients will receive two or four S-033188 20-mg tablets or two or four matching placebo tablets (depending on weight at Screening) on Day 1. Study drugs can be taken without regard to food.

5.3 Selection and Timing of Dose for Each Patient

The patient will be randomly assigned to one of the treatment groups, and the dosage assigned will be maintained until the end of the study. The initial single oral dose of study medication (S-033188, oseltamivir or placebo) will be taken by patients at the study site. Patients who weigh less than 80 kg at Screening will receive 40 mg of S-033188, and patients who weigh ≥ 80 kg at Screening will receive 80 mg of S-033188.

5.4 Method of Assigning Patients to Treatment Groups

This study will be primarily conducted in Japan, but other Asian countries and the US are also expected to participate. Because of the recommendation in Japan not to use oseltamivir in patients aged < 20 years due to previously reported neuropsychiatric AEs and suicidality in Japan, assignment of patients to treatment groups will be proceeded in each of two age strata, ie, 12 to 19 years age stratum and 20 to 64 years age stratum, separately. Approximately 15% of the whole population to be enrolled in this study will

be patients in 12 to 19 years age stratum.

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), patients weight (< 80 kg, ≥ 80 kg) and baseline composite symptom score (≤ 11, ≥ 12).

5.5 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. An IRT will be used for central patient randomization and study drug assignment. IRT will assign drug identifiers according to a randomization schedule. Only unblinded staff members of contract research organization (CRO) or designee will have the authority to assign the drug identifiers. All patients, investigators, study personnel and data analysts will be blinded to the treatment assigned at randomization until database lock. The randomization schedule will be kept confidential and will not be accessible to anyone until unblinding, except for Drug Supply Management staff, IRT clinical coordinators, IRT vendor staff, the unblinded statistician and Drug Safety personnel for reporting suspected unexpected serious adverse reactions (SUSARs) as required by local regulations.

Unblinding by request of an investigator should occur only in the event of an emergency, pregnancy of the patient or the patient's partner, or AEs for which it is necessary to know the study treatment to determine an appropriate course of therapy for the patient. Should the investigator decide that the treatment assignment of an individual patient needs to be disclosed, the investigator or qualified designee is to call the IRT.

Prior to unblinding, and if the situation allows it, the investigator should try to contact the sponsor or CRO designee within 24 hours. If this is impractical, the investigator must notify the sponsor as soon as possible, without revealing the treatment assignment of the unblinded patient. The investigator must document the patient identification, the date and time for breaking the blind and must clearly explain the reasons for breaking the code. This information must be documented and submitted to the sponsor in a form specified by the sponsor. Procedures for emergency unblinding will be detailed in a separate document.

Plasma drug concentrations may reveal the treatment assignment and will therefore be reported to the sponsor after the database is locked.

5.6 Packaging and Labeling

The study drugs will be supplied in wallet card(s) containing 2 S-033188 active 20-mg tablets or its matching placebo with/without the 10 oseltamivir capsules or their matching placebo, or only placebo. The wallet card will be labelled with an identification number, protocol number, contents, direction for use, storage condition at a minimum, as well as other pertinent information according to local regulations. The expiry or use-by date will be stored in the IRT or on the label according to local regulations. Study drug should not be used after the expiry or use-by date. All packaged and labelled supplies will be formally released in accordance with both Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) guidelines.

5.7 Storage and Accountability

The study drug will be stored at room temperature (15°C to 25°C [59°F to 77°F]). The temperature of the drug storage area will be recorded every working day.

The sponsor will supply the study drug to the person responsible for study drug handling, who is a designee of the head of the study center, under the study contract between the sponsor and the study center. The person responsible for study drug handling will handle the study drug according to procedures for method of storage and drug accountability record as specified in a separate document.

The investigator or person responsible for study drug handling will ensure that all study drugs are stored and dispensed in accordance with local regulations concerning the storage and administration of investigational drugs. All drug supplies must be kept in a secure locked area with access limited to those authorized by the investigator.

The investigator or pharmacist will maintain accurate records on the information: receipt and condition of all study drugs, date of the receipt, when and how much study drug is dispensed and used by each patient in the study, and any reasons for departure from the protocol-dispensing regimen. The drug accountability records will be available for verification by sponsor's monitor (or designee) at each monitoring visit. At the completion of the study, a final reconciliation of all study drugs will be performed. Study drug must not be used for any purpose other than the present study. Further details on drug procedures and accountability are described in a separate written procedure.

5.8 Investigational Product Retention at Medical Institution

At the end of the study, all unused study drug and used wallet cards will be returned. The site monitor or designee responsible for study drug handling will record accurate amounts of used and unused drug supplies. Final reconciliation must be completed by the monitor prior to returning. All used and unused drug supplies in appropriate boxes will be returned as per Shionogi's written instructions with a copy of the overall drug accountability record and appropriate return form as described in a separate written procedure.

5.9 Treatment Compliance

The investigator or subinvestigator will administer the first dose of the study drugs and perform a mouth check of patients immediately after the drug is taken. The time of ingestion (co-administration of S-033188, oseltamivir, and placebo) will be recorded in the source documents and the eCRF. Patients must bring their wallet cards and any unused drug at all visits up to Visit 5 (Day 9), unless dosing was completed at Visit 4 (Day 5), whether or not the wallet card is empty. The investigator or subinvestigator will perform compliance checks of wallet cards to verify that the correct number of doses have been taken according to the actual time interval that has elapsed between clinic visits. A record of the supplies dispensed and returned will be documented. On the basis of compliance checks, if < 100% of the required study drug has been taken by a patient, the patient will be counseled by the site about the importance of taking study drug as directed.

6. RESTRICTIONS

6.1 Prior Therapy

Prior therapies are defined as therapies which were taken prior to the initiation of study treatment. All prior therapy (prescription drugs, over-the-counter drugs, procedures without any medication) taken by a patient within 14 days prior to the initiation of study treatment will be recorded in the eCRF and the information will include a name of used drug or used procedures, duration of treatment, and reason for use.

6.2 Concomitant Therapy during the Study

Concomitant therapies are defined as therapies taken at or after the initiation of study treatment. The investigator or subinvestigator will record the following information for all therapies (prescription drugs, over-the-counter drugs, procedures without any medication) used during the study (from Visit 1 [Day 1] to Visit 7 [Day 22] or early termination) in the eCRF.

- Name of used drug or used procedures
- Route of administration
- Duration of treatment
- Reason for use

6.2.1 Prohibited Concomitant Therapy

The use of the following drugs and over-the-counter drugs with equivalent efficacy to them will be prohibited from Visit 1 (Day 1) until Visit 7 (Day 22) or early termination.

- Systemic antiviral drugs
- Antimicrobial* and antifungal drugs**
- Antipyretics/analgesics except acetaminophen
- Antitussives/expectorants
- Combination cold remedies
- Antihistamines**
- Corticosteroids**
- Immunosuppressants

Herbal medicines or complementary therapies indicated for influenza virus infection (eg, Maoutou)

- Other investigational drugs

* Except for the treatment of complications of influenza suspected to be bacterial infection after Day 1.

** Dermal preparations will be permitted, but application to the eyes, nose or ears, or by inhalation will be prohibited.

6.2.2 Rescue Therapy (Noninvestigational Medicinal Product)

If influenza symptoms, such as fever, headache and muscle pain, are so severe that the patient needs rescue therapy between Visits 1 (Day 1) and 7 (Day 22), the use of acetaminophen at a dose of 3000 mg/day or less will be permitted only for the relief of fever or pain. The site can supply the acetaminophen tablets or the investigator can

prescribe the tablets then reimburse the patient; in either case, the country's commercial pack will be used, and the sponsor or designee will indirectly supply the tablets by reimbursing the site. If acetaminophen is used, the patient will record the date and time of each administration in the patient eDiary. The measurement of body temperature and assessment of influenza symptoms by the patient will occur immediately before the use of acetaminophen or more than 4 hours after acetaminophen administration.

6.3 Other Restrictions

6.3.1 Contraception

WOCBP should use one of the following highly effective methods of contraception as instructed by the investigator or subinvestigator for 3 months after the initiation of the study treatment (Visit 1, Day 1).

Highly effective methods of contraception are:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine contraceptive device (IUD)
- Intrauterine hormone-releasing system (IUS, ie, Mirena®)
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence (considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence will need to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.)

7. STUDY PROCEDURES AND METHODS OF ASSESSMENTS

The time and events schedule are referred to Appendix 1.

7.1 Informed Consent/Assent

For adult patients, the investigator or subinvestigator will fully explain the nature of the study to a patient using the institutional review board (IRB)/institutional ethics committee (IEC)-approved informed consent document. When the patient agrees to participate in the study, the patient must voluntarily sign a consent form prior to the initiation of any study procedures. A copy of the signed and dated informed consent document will be given to the patient. The signed and dated original consent form will be retained by the investigator. Informed consent will be obtained from all patients. A patient cannot be entered the study until he/she has signed and dated on the consent form.

For adolescent patients, the investigator or subinvestigator will fully explain the nature of the study to a patient and parent(s)/legally acceptable representative as required by age or local regulations of each patient by using the IRB/IEC-approved informed consent/assent document. Informed consent will be obtained from parent(s) or legally acceptable representative of each patient. The parent or the legally acceptable representative must sign a consent form prior to the initiation of any study procedures. Patients will be informed about the nature and duration of the study with written age-appropriate information, in language and terms they can understand and must sign an assent form. A copy of the signed and dated informed consent/assent document will be given to the patient and parent(s)/legally acceptable representative. The signed and dated original consent/assent form will be retained by the investigator. A patient cannot be entered the study until his/her parent(s)/legally acceptable representative has signed and dated the consent form. The informed consent/assent should be obtained in accordance with local requirements.

The investigator or subinvestigator is responsible for ensuring that the patient understands the risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing any new information in a timely manner that may be relevant to the patient's willingness to continue his/her participation in the study.

7.2 Baseline Patient Characteristic and Medical History

7.2.1 Baseline Patient Characteristic and Medical History

The following baseline patient characteristics will be obtained at Visit 1 (Day 1) if allowed per the country's requirement and entered in the eCRF:

Date of written informed consent by the patient/guardian
Date of birth
Sex
Ethnicity
Race
Current smoking status

Prior therapy
Presence or absence of influenza vaccination within the last 6 months
Duration of influenza symptoms
Medical history

Medical history will include any previous or concurrent significant medical condition such as hospitalization, all concurrent medical conditions, and surgical history within 12 months.

7.2.2 Rapid Influenza Diagnostic Test (RIDT)

Once a patient has been determined to be eligible based on body temperature and clinical symptoms, the investigator or subinvestigator will collect nasopharyngeal (a nasopharyngeal swab is preferred, but a pharyngeal swab will be acceptable if a nasopharyngeal swab cannot be performed) swabs for influenza A and/or B virus using a supplied commercial RIDT kit at the same time as performing the central lab PCR nasopharyngeal/pharyngeal swabs. The RIDT results will be recorded in the eCRF. The collection of specimens, operation of the kit, and interpretation of test results will be performed according to the instructions for use or package insert of the RIDT kit. The RIDT will be provided by the sponsor, and this will be the preferred test; however, if a site has performed a RIDT prior to consideration for the study, the local RIDT result will be entered into the eCRF. The patient will be informed of the RIDT result, and if the result is negative, the investigator will explain the low and unpredictable sensitivity of the RIDT and will confirm with the patient that they wish to continue in the study. This decision will be documented in the ICF addendum, and this will serve as source documentation.

7.2.3 Meals

To collect information on meals before and after the initial study treatment (coadministration of S-033188/placebo and oseltamivir/placebo), whether the patient takes meals on Day 1 and the time of meal ingestion will be recorded in the eCRF.

7.3 Enrollment in the Study and Dispensing Study Drug

After a patient is determined to be eligible according to the inclusion/exclusion criteria, the investigator or subinvestigator will contact the IRT for an identification number or send the registration sheet with the required information filled in to the registration center. If the registration is accepted, the patient will be entered in the study. After the patient is entered in the study, the investigator, subinvestigator, or site pharmacist will dispense the study drug as specified in Section 5.

7.4 Efficacy Assessments

7.4.1 Patient Electronic Diary

The patient will self-measure/assess the following outcome measures and record the results in the patient electronic diary (eDiary). The patient eDiary will consist of electronic data entered by the patient into the electronic patient-reported outcome (ePRO) system via a mobile computer or other vendor-provided electronic devices.

The results of the measurements and assessments will be entered into the eDiary predose at Visit 1 (Day 1) once the device has been set up by the investigator or designee. After the initiation of the study treatment on Day 1, only the measurements and the assessments in the available time period of the day will be conducted. 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.

Prior to the initiation of the study treatment on Day 1, the investigator, subinvestigator, or study coordinator will instruct the patient on how to assess the outcome measures and then have him/her record the results of the initial assessments. The ePRO system will be personally delivered to the patient after enrollment.

7.4.1.1 Body Temperature Measurement

With an electronic thermometer, the patient will self-measure axillary temperature. The sweat should be wiped off the measurement site in advance. The patient will measure, and record in the patient eDiary, body temperature predose on Day 1, and then 4 times daily (morning, noon, evening and bedtime) until Day 3 and twice daily (morning and evening) from Days 4 to 14. The patient will measure body temperature during the time period described in Table 7-1 or at time point as near as possible. After the initiation of the study treatment, body temperature measurement will occur before taking acetaminophen or more than 4 hours after the last dose of acetaminophen.

The body temperature obtained at the study center prior to informed consent will be acceptable as an alternative to the predose value on Day 1 (provided that it is obtained on Day 1).

Table 7-1 Time Windows of Body Temperature Measurement as a Guide

Assessment period	Time period of a day	Time window as a guide
Day 1 - Day 3	Morning	- 9:59
	Noon	10:00 - 14:59
	Evening	15:00 - 19:59
	Bedtime	20:00 -
Day 4 - Day 14	Morning	- 11:59
	Evening	18:00 -

7.4.1.2 Assessment of Severity of Influenza Symptoms

The patient will self-assess 7 symptoms associated with influenza (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue) on a 4-point rating scale (0, None; 1, Mild; 2, Moderate; 3, Severe).

The patient will assess, and record on a paper questionnaire, influenza symptoms predose on Day 1; then subsequent influenza symptoms will be assessed and recorded in the patient eDiary twice daily (morning and evening) until Day 9 and once daily (evening) from Days 10 to 14. Table 7-2 provides the time windows of assessment as a guide.

Table 7-2 Time Windows of Assessment as a Guide: Assessment of Severity of Influenza Symptoms

Assessment period	Time period of a day	Time window as a guide
Day 1 - Day 9	Morning	- 11:59
	Evening	18:00 -
Day 10 - Day 14	Evening	18:00 -

7.4.1.3 Assessment of Health

The patient will self-assess his or her health on a scale of 0 (Worst possible health) to 10 (Normal health [for someone your age and condition]) and record in the patient eDiary, predose on Day 1 and then once daily (evening) until Day 14. Table 7-3 provides the time windows of assessment as a guide.

Table 7-3 Time Window of Assessment as a Guide: Assessment of Health

Assessment period	Time period of a day	Time window as a guide
Day 1 - Day 14	Evening	18:00 -

Assessment of health prior to influenza symptoms will be performed predose on Day 1 and recorded in either the eDiary or a paper diary (see Appendix 4).

7.4.1.4 EuroQol-5 Dimensions-5 Levels (EQ-5D-5L)

The EQ-5D-5L will be recorded in the patient eDiary. The details of the measurement are described in the Section 7.7.4.1.

7.4.2 Virology Test

Two nasopharyngeal/pharyngeal swabs (nasopharyngeal swabs are the preferred method of virology collection as they are the most accurate, but pharyngeal swabs will be acceptable if nasopharyngeal swabs cannot be performed) will be collected predose at Visit 1 (Day 1 at the same time as the RIDT), Visit 2 (Day 2), Visit 3 (Day 3), Visit 4 (Day 5) and Visit 5 (Day 9). If circumstances permit, specimens will also be collected at Optional Visit 1 (Day 4) and Optional Visit 2 (Day 6) and Visit 7 (Day 22). If the investigator or subinvestigator determines that influenza symptoms are ongoing, specimens will also be collected at Visit 6 (Day 15) and Visit 7 (Day 22) (or early termination). Specimens will be handled according to Section 7.6.4.5.

The virology testing facility (see Section 10.1) will perform virus typing and subtyping, determination of virus titer and viral RNA load according to procedures or a protocol specified in a separate document. Access to the virological endpoints will be limited. Specific details of who will have access to each endpoint will be specified in a separate document.

7.4.3 Intrahousehold Infection Rate

For sites in Japan only, patient will be interviewed predose at Visit 1 (Day 1) about their household size, the number of household members infected this season before the patient is enrolled the study and their diagnosis date (if the date is within 2 weeks) of influenza. From Day 1 to Day 15, the patient will be interviewed about the number of household members infected and their diagnosis date of influenza to evaluate the intrahousehold infection rate.

7.5 Pharmacokinetics Assessments

For the measurement of plasma S-033447 concentrations, blood samples will be collected at Visit 2 (Day 2) and Visit 4 (Day 5); if circumstances permit, samples will also be collected within the period from 0.5 to 4 hours after the initial dose at Visit 1 (Day 1), Visit 3 (Day 3) and Visit 6 (Day 15).

The actual time of each blood sample collection and the time of study drug ingestion will be recorded in the eCRF.

At each sample collection, blood will be drawn into a heparin sodium-containing tube, followed promptly by centrifugation to separate plasma. The resulting plasma will be stored at −20ºC or below. Detailed procedures for the sample collection, handling, and shipping to the bioanalytical laboratory (see Section 10.1) are specified in a separate document.

Plasma concentrations of S-033447 will be analyzed with a validated liquid chromatography-tandem mass spectrometry method.

7.6 Safety Assessments

7.6.1 Physical Examination

The full physical examination will be performed at Visit 1 (Day 1) and Visit 7 (Day 22) (or early termination) according to the normal practice of the clinical study center by the investigator or subinvestigator in order to check for any AEs (see Section 7.6.5.1). In addition, symptom-focused physical examination will be performed at Visit 2 (Day 2), Visit 3 (Day 3), optional Visit 1 (Day 4), Visit 4 (Day 5), optional Visit 2 (Day 6), Visit 5 (Day 9) and Visit 6 (Day 15). The patient will also be observed for any influenza-related complications (sinusitis, bronchitis, otitis media, and pneumonia) at all visits after Visit 1 (Day 1).

Height in centimeters and body weight in kilograms will be obtained in predose examinations on Day 1 and entered in the eCRF, along with BMI.

7.6.2 Vital Sign Measurements

Blood pressure (systolic and diastolic), respiratory rate (breaths per minute) and pulse rate will be measured by the investigator, subinvestigator or designee at Visit 1 (Day 1), Visit 2 (Day 2), Visit 3 (Day 3), optional Visit 1 (Day 4), Visit 4 (Day 5), optional Visit 2 (Day 6), Visit 5 (Day 9), Visit 6 (Day 15) and Visit 7 (Day 22) (or early termination).

Blood pressure, pulse rate and respiratory rate will be measured after the patient has rested in a sitting position for at least 3 minutes.

The investigator or subinvestigator will consider whether any abnormal changes from baseline (predose at Visit 1, Day 1) are clinically significant (see Section 7.6.5.6). Results of blood pressure, pulse rate and respiratory rate measurements will be entered in the eCRF.

7.6.3 Electrocardiography

A 12-lead ECG will be performed by the investigator, subinvestigator or designee at Visit 1 (Day 1), Visit 2 (Day 2) and Visit 7 (Day 22) (or early termination). The ECG will be performed after the patient has rested for at least 3 minutes.

The investigator or subinvestigator will assess whether the ECG is normal or abnormal (see Section 7.6.5.6). If the ECG is deemed abnormal and clinically significant, the investigator or subinvestigator will contact the CRO as per the medical monitoring plan, and it will be recorded as an AE in the eCRF. Result of ECG and its interpretation will also be entered in the eCRF.

7.6.4 Clinical Laboratory Tests

7.6.4.1 Laboratory Parameters

Patients will remain in a sitting or supine position during blood collection. Blood and urine samples for clinical laboratory tests will be collected, and the date of specimen collection will be entered in the eCRF. The blood sample volumes for clinical laboratory, serum antibody titer and immunological tests are shown in Table 7-4.

Table 7-4 Blood Sample Volumes

Parameter	Total blood sample volume (per time point)
Hematology tests	2 mL
Blood chemistry tests Hepatitis B virus surface antigen Hepatitis C virus antibody HIV antigen/antibody	3.5 - 5 mL
Serum influenza virus antibody titer	3.5 mL

7.6.4.2 Routine Laboratory Tests

Routine hematology, blood chemistry, and urinalysis parameters (Table 7-5) will be measured by the clinical laboratory (see Section 7.6.4.5). Blood and urine samples for routine laboratory tests will be collected at Visit 1 (Day 1), Visit 4 (Day 5), Visit 6 (Day 15) and Visit 7 (Day 22) (or early termination).

Table 7-5 Routine Laboratory Tests

Category	Evaluation items
Hematology tests	Hematocrit, Hemoglobin, Platelet count, Erythrocytes (red blood cells), Leukocytes (white blood cells) with differential (eosinophil count, basophil count, neutrophil count, monocyte count, lymphocyte count)
Blood chemistry tests	Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Total bilirubin, Direct bilirubin, Indirect bilirubin, Alkaline phosphatase (ALP), Gamma glutamyl transpeptidase (GGT), Lactate dehydrogenase (LDH), BUN, Creatinine, Uric acid, Calcium (Ca), Chloride (Cl), Potassium (K), Sodium (Na), Total protein, Albumin, and C-reactive protein (CRP)
Urinalysis (Qualitative)	Glucose, Occult blood, Protein, and Urobilinogen

The investigator or subinvestigator will assess whether any abnormal changes from baseline (predose at Visit 1, Day 1) are clinically significant (see Section 7.6.5.6).

7.6.4.3 Immunological Tests

Patients with liver disease, including known chronic hepatitis B and untreated hepatitis C are excluded from enrollment in this study. Patients with untreated HIV infection are also excluded.

The following antigen/antibody tests will be performed for baseline demographic information and to inform clinical management if previously undiagnosed conditions are reported: hepatitis B virus surface (HBs) antigen, hepatitis C virus (HCV) antibody, and HIV antigen/antibody will be measured predose at Visit 1 (Day 1) by the clinical laboratory (see Section 7.6.4.5).

7.6.4.4 Pregnancy Tests

Except for postmenopausal women (defined as cessation of regular menstrual periods for 2 years or more and confirmed by a follicle-stimulating hormone test) and those who are surgically sterile by hysterectomy, bilateral oophorectomy, or tubal ligation, all female patients will undergo a urine pregnancy test at Visit 1 (Day 1, predose), Visit 4 (Day 5) and Visit 7 (Day 22) or early termination.

7.6.4.5 Sample Collection, Storage, and Shipping

Blood and urine samples and nasopharyngeal/pharyngeal swabs (nasopharyngeal swabs are the preferred method of virology collection as they are the most accurate, but pharyngeal swabs will be acceptable if nasopharyngeal swabs cannot be performed) will be collected by the investigator, subinvestigator or designee and sent to the clinical laboratory for processing. Sample collection, handling, labeling, storage, shipping, etc. will be performed according to procedures specified in a separate document.

The sponsor may use any residual blood and/or swab samples collected from patients for the purposes of this study or for future scientific research. When the sponsor decides to perform the test/research, a detailed plan and procedures will be defined. Other than further virology testing, any future use of samples will follow appropriate consent from patients following review by an independent ethics committee. The results of the

test/research will be reported in documents separate from the clinical study report for this study.

7.6.5 Adverse Events Assessments

7.6.5.1 Performing Adverse Event Assessments

An AE is defined as any untoward medical occurrence in a patient administered a pharmaceutical product (including a study drug) during the course of a clinical investigation. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product.

An elective surgical procedure not associated with a worsening of a known underlying medical condition is not considered an AE, and therefore will not be considered an SAE despite requiring hospitalization. However, complications of the procedure will be considered an AE and may be considered an SAE if hospitalization is prolonged (or any other SAE criteria is met). A hospitalization or prolongation of a hospitalization for reasons other than an AE would not be considered an SAE.

AEs will be found by the patient's spontaneous complaint, patient comment cards, or as a result of non-leading questions, physical examination, vital signs, or laboratory tests. AEs include any occurrences that are new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities. Medical histories which are reported at the baseline and worsen following the exposure to the study drug will be considered as AEs. Lack of efficacy or fluctuation in influenza symptoms will not constitute an AE in this study.

The investigator or subinvestigator is responsible for assessing AEs. AEs should be fully investigated and recorded in detail including start date, end date (if outcome is other than recovering, not recovered, or unknown), severity, seriousness with its category, relationship with the study drug, action taken to manage the AE, and outcome of the AE in the eCRF.

7.6.5.2 Timing

AEs will be collected from the time of informed consent through Visit 7 (Day 22). If a patient withdraws early from the study, the investigator or subinvestigator will make an effort to collect AEs for 21 days after the last dose of the study drug. All AEs will be followed until resolution, stabilization, the condition becomes chronic, or 35 days after the last study drug administration. Serious treatment-related AEs or AEs related to abnormal liver function tests shown in Appendix 5 will be followed until resolution, stabilization, the condition becomes chronic, or the patient becomes lost to follow-up.

7.6.5.3 Severity

The severity of an event will be categorized by the investigator or subinvestigator according to the following definitions based on the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 [11]:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)*
Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
Grade 4: Life-threatening consequences; urgent intervention indicated
Grade 5: Death related to AE

* Instrumental ADLs refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
** Self-care ADLs refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The highest severity during the period in which the AE occurred will be recorded in the eCRF.

7.6.5.4 Relationship

The relationship of an event to the study drug will be determined by the investigator or subinvestigator according to the following criteria:

Related: An AE which can be reasonably explained as having been caused by the study drug. For example, a similar event has been reported previously, or increase/decrease of the dose affects the occurrence or seriousness of the AE, etc.
Not related: An AE which cannot be reasonably explained as having been caused by the study drug.

7.6.5.5 Expectedness

A treatment-related AE is considered expected if it is listed in the subsection "Expected Adverse Reactions" under the section "Undesirable Effects" of "SUMMARY OF DATA AND GUIDANCE FOR INVESTIGATORS" in the current investigator's brochure (IB) for S-033188. The current version of the Prescribing Information for Tamiflu® (oseltamivir phosphate) capsules/Tamiflu® for oral suspension should also be used for oseltamivir expectedness assessments. Expectedness will be assessed by the sponsor.

7.6.5.6 Adverse Event Assessment of Clinical Laboratory and Other Safety Parameters

For any abnormal laboratory test results (hematology, blood chemistry, or urinalysis) or other safety assessments (eg, physical examination, vital signs, ECG) that vary following exposure to the study drug from baseline, the investigator or subinvestigator will determine whether these results are clinically significant. Abnormal laboratory test results are defined as value outside the reference range. For test results which are abnormal at baseline and worsen following the initiation of the study, the investigator or subinvestigator must also determine whether these results are clinically significant. Any test results which are considered to be clinically significant by the investigator or

subinvestigator will be recorded as AEs. If the abnormal laboratory finding is associated with a disease or organ toxicity, the investigator should report only the disease or organ toxicity as AEs.

The investigator or subinvestigator will consider test results to be clinically significant in the following circumstances:

- Test result leads to any of the outcomes included in the definition of an SAE (see Section 7.6.5.7).
- Test result leads to a concomitant drug treatment or other therapy.
- Test result requires additional diagnostic testing or other medical intervention.
- Test result meets the management and discontinuation criteria for abnormal liver function tests (Appendix 5).

Test results meeting the management and discontinuation criteria for abnormal liver function tests (Appendix 5) will require evaluation and additional testing, and the results will be recorded on the liver function abnormality follow-up form.

7.6.5.7 Serious Adverse Events

7.6.5.7.1 Definition

An SAE is defined by regulation as any AE occurring at any dose that results in any of the following outcomes:

Death
Life-threatening condition
Hospitalization or prolongation of existing hospitalization
Persistent or significant disability/incapacity
Congenital anomaly/birth defect
Other medically important condition

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. Test results that meet the following criterion are considered as SAE. The investigator or subinvestigator will determine the seriousness of AEs.

AST or ALT > 3 × Upper limit of normal (ULN) and total bilirubin > 2 × ULN.

7.6.5.7.2 Reporting Serious Adverse Events

All information regarding SAEs, including the SAE itself, associated medications, and SAE narratives, must be entered into electronic data capture (EDC) within 24 hours from the point in time when the investigator first becomes aware of the SAE. If EDC becomes unavailable, all SAEs must be reported to the CRO or sponsor in detail utilizing the SAE

form. Upon availability of EDC, this information must then be entered into EDC. All SAEs must be reported regardless of causal relationship to the study drug. A sample of the SAE form can be found in the Site Regulatory Binder. Follow-up information on the SAE may be requested by the sponsor.

When reporting SAEs, the investigator should record the diagnosis whenever possible. If no diagnosis is available at the time of reporting, individual signs and symptoms can be reported.

In the event of any SAE reported or observed during the study, whether or not attributable to the study drug, site personnel must report within 24 hours. SAEs can be reported by fax, phone, e-mail, or via EDC system (if available).

If follow-up is required or requested, the investigator should enter the new information into EDC. Discharge summaries, consultant reports, autopsy reports, or other relevant documents must be evaluated by the investigator and all relevant information must be included on the follow-up SAE form. Copies of these reports may also be requested by the sponsor.

Appropriate remedial measures should be taken by the investigator using his/her best medical judgment to treat the SAE. These measures and the patient's response to these measures should be recorded. Clinical, laboratory, and diagnostic measures should be employed by the investigator as needed to adequately determine the etiology of the event.

Any SAEs occurring after the AE assessment period specified in Section 7.6.5.2, that are considered to be related to study drug by the investigator must be reported to the CRO or the sponsor.

The investigator will be responsible for reporting all SAEs to the IRB or EC through the head of the study center in accordance with applicable regulatory requirements. The sponsor will be responsible for reporting SAEs to the regulatory authorities as required by the applicable regulatory requirements.

7.6.5.8 Liver Function Abnormalities

When liver function abnormalities meet any of the following criteria the investigator must report these abnormalities to the sponsor within 24 hours:

- AST or ALT > 3 × upper limit of normal (ULN) and total bilirubin (TBL) > 2 × ULN
- AST or ALT > 3 × ULN and prothrombin time international normalized ratio (PT-INR) > 1. 5

In addition, liver function abnormalities meeting any of the following criteria need to be managed according to Appendix 5:

- AST or ALT > 5 × ULN
- AST or ALT > 3 × ULN with signs and symptoms compatible with hepatitis or hypersensitivity

7.6.5.9 Special Situations - Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error of the study drug (as defined below) must be reported to the CRO or sponsor via fax or email by the investigator using a Special Situations Report Form as soon as possible. If there are associated SAE, investigator will report an SAE as well.

- Abuse - persistent or sporadic, intentional excessive use of an investigational product(s), which is accompanied by harmful physical or psychological effects.
- Misuse - Intentional and inappropriate use of an investigational product(s) other than as directed or indicated at any dose.
- Overdose - Intentional or unintentional intake of a dose of investigational product(s) higher than the assigned dose in the protocol.
- Medication Error - any unintended error in the prescribing, dispensing or administration of an investigational product(s). Cases of patients missing doses of investigational product(s) are not considered reportable as medication errors.

7.6.5.10 Pregnancy

Female patients should be instructed to immediately contact the investigator or subinvestigator if they become pregnant during the study. In addition, the investigator or subinvestigator must attempt to collect pregnancy information on any female partners of male study patients who become pregnant while he is enrolled in the study. Pregnancy information must be reported to the CRO or sponsor as described below.

All pregnancies that occur during the study must be reported within 24 hours of becoming aware of the pregnancy, and the Pregnancy Form will be faxed or emailed to the CRO or sponsor by the investigator. Pregnancy complications and elective terminations due to medical reasons must also be reported as an AE or SAE as appropriate. Spontaneous abortions must be reported as an SAE. The outcome of the pregnancy should be followed and must also be reported using the Pregnancy Form to the

CRO or sponsor via fax or email. All pregnancies that are confirmed after the end of the study but within 3 months of last study drug dose should be reported to the CRO or sponsor and followed to completion by the study center. The outcome of the pregnancy (ie, birth, miscarriage, abortion) should be reported to the CRO or sponsor as described above.

7.7 Other Assessment

7.7.1 Serum Antibody Titer Test

Blood samples will be collected predose at Visit 1 (Day 1) and Visit 7 (Day 22). Specimens will be handled according to Section 7.6.4.5.

The clinical laboratory will measure serum antibody titers for the influenza A and B viruses.

7.7.2 Polymorphic and Treatment-emergent Amino Acid Substitutions

As a part of the virology test, PA gene sequencing of virus will be performed to evaluate the incidence and characteristics of polymorphic and treatment-emergent amino acid substitutions in patients with evaluable virus. This sequencing will be performed using specimens obtained from all patients in the S-033188 treatment group and 100 patients in the placebo group. The virology testing facility (see Section 10.1) will perform the gene sequencing according to procedures or a protocol specified in a separate document. Access to the gene sequencing data will be limited. Specific details of who will have access to each endpoint will be specified in a separate document.

7.7.3 Drug Susceptibility Testing for Test Substances

As a part of the virology test, the ViroSpot™ assay and the NA-star® assay will be performed to evaluate the drug susceptibility for S-033188 and oseltamivir acid using evaluable virus at baseline sample in patients. The virology testing facility (see Section 10.1) will perform the drug susceptibility testing according to procedures or a protocol specified in a separate document.

7.7.4 Health Economic Outcomes

7.7.4.1 EuroQol-5 Dimensions-5 Levels (EQ-5D-5L)

The EQ-5D-5L will be recorded electronically predose on Day 1, and then twice daily (morning and evening) until Day 9, and once daily (evening) from Days 10 to 14. Finally, EQ-5D-5L will be measured at Visit 7 (Day 22) to estimate a baseline quality-of-life (QOL) measure. The questionnaire will be completed at Visit 7 (Day 22) or at the earliest clinic visit following alleviation of symptoms. [redacted]

EQ-5D-5L is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L questionnaire consists of 2 pages: the EQ-5D-5L descriptive system and the EQ visual analogue scale (VAS). The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each of

which is divided into 5 levels. The EQ VAS records the patient's self-rated health on a 20-cm vertical visual analogue with "the best health you can imagine" as 100 and "the worst health you can imagine" as 0.

The date of assessment, EQ-5D-5L descriptive system score, and EQ VAS score will be recorded in the eDiary.

7.7.5 Work Productivity (WP) Questionnaire

The WP questionnaire will be completed at Visit 7 (Day 22), or at the earliest clinic visit following alleviation of symptoms. The WP questionnaire consists of 4 questions regarding employment, number hours worked, productivity while at work, and requirement for personal assistance. WP questionnaire is included in Appendix 3.

The WP questionnaire will be completed on paper.

7.8 Withdrawal of Patients from the Study or Study Drug

The investigator will make every reasonable attempt to complete the study for each enrolled patient. A patient may withdraw for any reason. The investigator will advise the sponsor about the withdrawal of any patient by the IRT.

The investigator will withdraw a patient from the study or the study drug treatment for any of the following reasons:

- A serious or intolerable AE occurs and the investigator considers that the patient should be withdrawn because of the AE.
- The patient requests to be withdrawn from the study.
- The patient becomes lost to follow-up.
- The investigator determines that the patient should be withdrawn based on the management and discontinuation criteria for abnormal liver function tests (Appendix 5).
- The investigator determines that the patient should be withdrawn because of other reasons.

In the event of a patient's withdrawal, the investigator will promptly notify the sponsor and will make every effort to complete the early termination assessments. All patients withdrawn due to AEs will be followed until resolution of the AEs, until the unresolved AEs are judged by the investigator to have stabilized, or the patient becomes lost to follow-up. The date of completion (for patients who completed the study), date of discontinuation (for patients who discontinued from the study prematurely), period of discontinuation, and reason for discontinuation will be entered in the eCRF. Completion of the study for each patient is defined as the case that the patient completed the follow-up period.

7.8.1 Clinical Progression or Lack of Response

In cases where on clinical review, patients appear to be deteriorating clinically or have not responded to the study drug, the investigator should consider the possibility of

secondary infections, decompensation of underlying conditions, or progression of influenza. Patients should be assessed, and investigations should be performed as clinically indicated.

In the event an investigator considers that the influenza has not responded and wishes to treat with open-label oseltamivir (not provided by the sponsor), the patient should stop all blinded study drugs. Since unblinding of the study drugs would not alter the management of the patients, unblinding in this situation is discouraged, and the patients should remain in the study for follow-up as described in Section 7.8. Such cases should be discussed urgently with the sponsor or sponsor's designated Medical Monitors.

7.9 Appropriateness of Measurements

7.9.1 Primary Efficacy Endpoint

Time to alleviation of symptoms is defined as the time to alleviation of 7 influenza symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue). Time to alleviation of symptoms has been commonly used as a measure of the efficacy of anti-influenza virus drugs, thereby enabling a comparison with the results from clinical studies of currently available medications. This justifies the selection of time to alleviation of symptoms as the primary endpoint of this study.

7.9.2 Secondary Efficacy Endpoints

Available nonclinical data suggest that a single oral dose of S-033188 can provide rapid relief of influenza symptoms. In addition, influenza symptoms were relieved significantly earlier in patients who received a 40 mg single oral dose of S-033188 compared to placebo in the Phase 2 proof-of-concept and dose-finding study (Study 1518T0821). Thus, the benefits of S-033188 can be evaluated based on the change in the total score of influenza symptoms at 24 hours post-dose, which is a measure of the speed of symptomatic improvement.

The time to cessation of viral shedding by virus titer and by reverse transcription polymerase chain reaction (RT-PCR) will provide data to indicate when both culturable viable virus and viral elements have become undetectable by viral titer and PCR, respectively. This permits an evaluation of 'viral shedding' that is analogous to infectivity, where an index case (the patient) is producing virus in nasal secretions and can infect close contacts.

In addition, the efficacy of S-033188 can be examined in detail by assessing the changes over time in the scores of symptoms and time to resolution of fever, and the benefits of S-033188 in improving QOL can be examined by assessing time to resumption of normal activity.

An assessment of the intrahousehold infection rate will provide useful information on the transmissibility of influenza infection after treatment with S-033188. This assessment will conducted only in Japan.

7.9.3 Safety Endpoints

Monitoring patients for AEs and treatment-related AEs will provide important information to examine the safety of S-033188.

7.9.4 Plasma Drug Concentrations

Assessing the PK of S-033447 in patients will provide important information for the future clinical use of S-033188.

7.9.5 Other Endpoints

The benefits of S-033188 in improving QOL can be examined by assessing the time to return to preinfluenza health status and the change in the score of the QOL questionnaire EQ-5D-5L.

An understanding of potential amino-acid substitutions in S-033188-exposed patients will be gained by exploring polymorphic and treatment-emergent amino acid substitutions in the PA gene in S-033188-exposed patients at baseline and at the last evaluable time point, with sequencing of approximately 100 placebo-exposed patients performed as a control.

7.10 Allowable Time Window

Measurements will be performed according to the schedule as shown in Appendix 1. The time window shown in Table 7-6 may be accepted for parameters other than blood sample collection for the measurement of plasma drug concentrations. Blood samples for the measurement of plasma drug concentrations will be collected within the time window shown in Table 7-7. Data obtained outside of this time window will be handled as missing data for the Visit, except for plasma drug concentration data.

Table 7-6 Allowable Time Window

Visit (Day)	Allowable time window [a]
Predose at Visit 1 (Day 1)	Predose on Day 1
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)	Day 3 - Day 4
Optional-Visit 1 (Day 4)	Day 4
Visit 4 (Day 5)	Day 5 - Day 6
Optional-Visit 2 (Day 6)	Day 6
Visit 5 (Day 9)	Day 7 - Day 11
Visit 6 (Day 15)	Day 12 - Day 18
Visit 7 (Day 22)	Day 19 - Day 25
Early termination	Date of early termination + 3 days

a Except for blood sample collection for the measurement of plasma drug concentrations.

Table 7-7 Allowable Time Window for Blood Sample Collection for the Measurement of Plasma Drug Concentrations

Measurement	Visit (Day)	Allowable time window
Blood sample collection for the measurement of plasma drug concentrations	Visit 1[a] (Day 1)	0.5 to 4 hours post-dose (Day 1)
	Visit 2 (Day 2)	Day 2
	Visit 3[a] (Day 3)	Day 3 - Day 4
	Visit 4 (Day 5)	Day 5 - Day 6
	Visit 6[a] (Day 15)	Day 12 - Day 18

a To be performed if circumstances permit.

8. STUDY ACTIVITIES

The overall schedule of events for the study is presented in Appendix 1.

8.1 Poststudy Access to the Study Drug

There will be no availability of study drug once the patient has completed the study.

9. PLANNED STATISTICAL METHODS

9.1 General Considerations

The statistical analysis and PK analysis will be performed by the sponsor or designee. The detailed statistical analysis methods will be specified in a statistical analysis plan (SAP) and PK analysis plan according to this section of the study protocol. If analyses deviated from those outlined in the protocol, the reason for deviation from the protocol must be described in the SAP and PK analysis plan. The SAP and PK analysis plan will be finalized before scheduled unblinding.

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

All statistical tests will be performed at the 0.05 significance level using two-sided tests, except where otherwise noted. The primary endpoint will first be compared between the S-033188 and placebo groups for patients (primary analysis). Together with the primary efficacy analysis, comparison between the S-033188 group and the oseltamivir group (secondary analysis) will be conducted in a hierarchical manner so as to maintain control of overall Type I error. For Japan, control of overall Type I error is not required for the secondary efficacy analysis of primary endpoint.

All patient study data will be presented in listings. In general, all tables will be presented by treatment group. Individual patient data will be presented by treatment group and by patient. All analyses and tabulations will be performed by using both the SAS Version 9.2 or higher and WinNonlin Version 6.2.1 or higher.

9.2 Determination of 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 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 patents 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.

Rationale for the target sample size:

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).

The median times to alleviation of symptoms in the three placebo-controlled clinical trials of oseltamivir were 116.5, 103.3 and 93.3 hours in the placebo group, respectively [5, 9, 10]. Taking this into account, it was assumed that the median time to alleviation of symptoms in the placebo group will be 100 hours.

In the Phase 2 study for the otherwise healthy patients with influenza virus infection, the median 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. The difference in the median time between 40-mg and placebo was 28.2 hours.

Based on the difference in the Phase 2 study, the difference between the S-033188 group and the placebo group is assumed to be 28 hours (72 hours in the S-033188 group, 100 hours in the placebo group). If the ratio of the median time to alleviation between the S-033188 group and the placebo group remains the same (ie, 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).

The required sample size has been calculated based on the conservative assumption of a 28 hour difference in the median time to alleviation of symptoms between the S-033188 group and the placebo group to ensure at least a 90% power in the efficacy evaluation and to accumulate a larger safety database [12].

Patients will be randomized on a 2:1 basis to either S-033188 or placebo and a follow-up period will be 336 hours (14 days). Assuming that time to alleviation follows an exponential distribution, the study requires 618 patients as the ITTI population, for the S-033188 group and the placebo group in total, 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 62 patients for the S-033188 group and 31 patients for the placebo group in 12 to 19 years age stratum, 350 patients for the S-033188 group and 175 patients for the placebo group in 20 to 64 years age stratum.

Comparison vs oseltamivir: 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 9-1 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 9-1 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
(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%

9.3 Analysis Populations

The following analysis populations will be analyzed for this study based on enrolled patients with GCP compliance:

The ITTI 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. The population will be analyzed according to the treatment to which the patients were randomized.

The safety population includes all randomized patients who receive at least one dose of the study drug. The population will be analyzed according to the treatment that the patients actually received, rather than the treatment to which the patients were randomized.

The per-protocol set (PPS) includes all randomized patients who are included in the ITTI population and do not meet any of the following conditions:

- Patients with any protocol inclusion or exclusion violations
- Patients with study procedure violations
- Patients with inadequate follow-up

The PK concentration population includes all patients who receive at least one dose of S-033188 and have at least one evaluable PK assay result of S-033447. This population will be used for the concentration listing.

The PK parameter population includes all patients with at least one PK parameter of S-033447 estimated. This population will be used for PK parameter listing and summary, and for the plotting and summary of the concentration-time data.

9.4 Handling of Missing Data

Missing data will not be replaced for the primary analyses. A sensitivity analysis will follow a predefined rule for missing data.

9.5 Patient Disposition

Among the patients randomized to each treatment group, the number and percentage of patients who complete the study and the number and percentage of patients who prematurely discontinue the study will be summarized by treatment group. In addition, reasons leading to study discontinuation will be summarized for each treatment group.

The number and percentage of patients for the randomized patients included in the ITTI, safety and PPS populations will also be presented

9.6 Demographic and Baseline Characteristics

Demographic and baseline characteristics for the ITTI population will be summarized with descriptive statistics by treatment group.

9.7 Extent of Exposure and Treatment Compliance

For ITTI and safety populations, whether each patient receives the study drug or not will be presented in a listing. The number of days when the study drug is taken and the percent compliance will be summarized with descriptive statistics by the treatment group for the safety population.

9.8 Prior Therapies

Prior therapies for drugs will be coded using the World Health Organization (WHO) Drug Dictionary. In the ITTI population and the safety population, the number of patients using each prior drug will be counted by treatment group. The number of patients using each prior therapy will also be counted. Patients who have received prior therapy(ies) will be listed for the safety population.

9.9 Concomitant Therapies

Concomitant therapies for drugs will be coded using the WHO Drug Dictionary. In the ITTI population and the safety population, the number of patients using each concomitant drug will be counted by treatment group. The number of patients using each concomitant therapy will also be counted. Patients who have received concomitant therapy(ies) will be listed for the safety population.

9.10 Efficacy Analyses

9.10.1 Primary Efficacy Endpoint

The primary efficacy endpoint is time to alleviation of symptoms.

Time to alleviation of symptoms is defined as the time between the initiation of the study treatment and the alleviation of influenza symptoms. The alleviation of influenza 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%).

9.10.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include the following variables.

1. Proportion of patients positive for influenza virus titer and proportion of patients positive by RT-PCR at each time point
   Defined as the percentage of patients whose virus titer is not less than the lower limit of quantification among those assessed for virus titer, and the percentage of patients with detectable virus RNA among those assessed by RT-PCR, respectively.

2. Change from baseline in virus titer and in the amount of virus RNA (RT-PCR) at each time point
   Defined as the change from baseline in virus titer and the change from baseline in

the amount of virus RNA, respectively. Baseline is defined as the last value obtained before Visit 1 (predose).

3. Area under the curve adjusted by baseline in virus titer and in the amount of virus RNA (RT-PCR)
   Defined as AUC of change from baseline in virus titer and AUC of change from baseline in the amount of virus RNA, respectively. AUC is calculated using the trapezoidal method.

4. Time to cessation of viral shedding by virus titer and by RT-PCR
   Defined as the time between the initiation of the study treatment and first time when the virus titer is BLQ, and the time between the initiation of the study treatment and first time when virus RNA by RT-PCR is BLQ, respectively.

5. Proportion of patients whose symptoms has been alleviated at each time point
   Defined as the percentage of patients whose symptoms are alleviated at each time point.

6. Time to alleviation of the 4 systemic symptoms
   Defined as the time between the initiation of the study treatment and the alleviation of the 4 systemic symptoms (headache, feverishness or chills, muscle or joint pain, and fatigue).

7. Time to alleviation of the 3 respiratory symptoms
   Defined as the time between the initiation of the study treatment and the alleviation of the 3 respiratory symptoms (cough, sore throat and nasal congestion).

8. Change from baseline in composite symptom score at each time point
   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. “None”, “Mild”, “Moderate” and “Severe” will be scored as 0, 1, 2 and 3, respectively. Baseline is defined as the last value obtained before Visit 1 (predose).

9. Time to resolution of fever
   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 37ºC and is maintained at less than 37ºC for a duration of at least 12 hours.

10. Proportion of patients reporting normal temperature at each time point
    Defined as the percentage of patients whose axillary temperature drops to less than 37ºC after the initiation of the study treatment in the analysis population.

11. Body temperature at each time point
    Defined as measured axillary temperature.

12. Time to alleviation of individual symptoms
    Defined as the time between the initiation of the study treatment and the alleviation of individual symptom. The alleviation of a symptom is defined as the time when the symptom is assessed as 0 (None) or 1 (Mild), for duration of at least 21.5 hours (24 hours − 10%).

13. Time to return to preinfluenza health status
    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]). Then the same information will be taken as part of the eDiary. Return to preinfluenza health status is defined as time from the initiation of the study treatment to time to the same number on scale for preinfluenza health status.

14. Incidence of influenza-related complications
    Defined as the percentage of patients in the analysis population 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.

9.10.3 Analyses of Efficacy Endpoints

The ITTI will be the primary population for all efficacy analyses. The PPS will be used for sensitivity analysis of the primary efficacy endpoint. The analysis of each efficacy endpoint will consist of comparison between S-033188 and placebo using data of the two age strata combined (ie, 12 to 64 years age), and comparison between S-033188 and oseltamivir using data of 20 to 64 years age stratum.

9.10.3.1 Analyses of Primary Endpoint

9.10.3.1.1 Primary Analysis

Comparison of time to alleviation of symptoms (S-033188 group vs placebo group):

Time to alleviation of symptoms will be compared between the S-033188 group and the placebo group using the stratified generalized Wilcoxon test with composite symptoms score at baseline (≤ 11 or ≥ 12) and region (Japan/Asia or Rest of the world) as stratification factors.

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

9.10.3.1.2 Secondary Analysis

Comparison of time to alleviation of symptoms (20 to 64 years age stratum of S-033188 group vs oseltamivir group):

Among patients aged 20 to 64 years, time to alleviation of symptoms will be compared between the S-033188 group and the oseltamivir group using the stratified generalized Wilcoxon test with composite symptoms score at baseline and region as stratification

factors.

Together with the primary efficacy analysis, this comparison will be conducted in a hierarchical manner so as to maintain control of overall Type I error. For Japan, control of overall Type I error is not required for the secondary efficacy analysis of primary endpoint.

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

9.10.3.1.3 Other Analyses

The Kaplan-Meier curves will be plotted for each treatment group, and the median time to alleviation of symptoms and its 95% CI will be calculated. In addition, the group difference in median of the time to alleviation of symptoms and its 95% CI will be also calculated.

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

9.10.3.2 Analyses of Secondary Endpoints

The following secondary efficacy endpoints will be compared between the S-033188 group and the placebo group, and between the S-033188 group and the oseltamivir group (in adults):

1. Proportion of patients positive for influenza virus titer and proportion of patients positive by RT-PCR at each time point

   Only patients whose virus titer/RT-PCR predose at Visit 1 are greater than or equal to the lower limit of quantification will be included in the analyses. Mantel-Haenszel test will be used by each visit to compare the proportion of patients positive for virus titer/RT-PCR between two groups, where composite symptoms score at baseline and region are stratification factors.

2. Change from baseline in virus titer and in the amount of virus RNA (RT-PCR) at each time point

   Only patients whose virus titer predose at Visit 1 are greater than or equal to the lower limit of quantification will be included in the analyses. Van Elteren test will be used by each visit to compare the change from baseline in influenza virus titer between two groups, where composite symptoms score at baseline and region will be used as stratification factors. For only patients whose virus RNA predose at Visit 1 are detected, similar analysis will be conducted for the change from baseline in the amount of virus RNA.

3. Area under the curve adjusted by baseline in virus titer and in the amount of virus RNA

   Only patients whose virus titer predose at Visit 1 are greater than or equal to the lower limit of quantification will be included in the analyses. Van Elteren test will be used to compare AUC of virus titer adjusted by baseline between two groups, where composite symptoms score at baseline and region will be used as

stratification factors. For only patients whose virus RNA predose at Visit 1 are detected, similar analysis will be conducted for AUC of the amount of RNA adjusted by baseline.

4. Time to cessation of viral shedding by virus titer and by RT-PCR
   Only patients whose virus titer/RT-PCR predose at Visit 1 are greater than or equal to the lower limit of quantification will be included in the analyses.The stratified generalized Wilcoxon test will be used, where composite symptoms score at baseline and region are stratification factors.

5. Proportion of patients whose symptoms has been alleviated at each time point
   Mantel-Haenszel test will be used by time point to compare success proportion of resolution of patients whose symptoms alleviated between two groups, where composite symptoms score at baseline and region are stratification factors.

6. Time to alleviation of the 4 systemic symptoms
   The stratified generalized Wilcoxon test will be used, where composite symptoms score at baseline and region are stratification factors.

7. Time to alleviation of the 3 respiratory symptoms
   The stratified generalized Wilcoxon test will be used, where composite symptoms score at baseline and region are stratification factors.

8. Change from baseline in composite symptoms score at each time point
   Analysis of covariance (ANCOVA) will be used by time point to compare the change from baseline in the composite symptoms score between two groups, where composite symptoms score at baseline and region will be used as covariates.

9. Time to resolution of fever
   The stratified generalized Wilcoxon test will be used, where composite symptoms score at baseline and region are stratification factors.

10. Proportion of patients reporting normal temperature at each time point
    Mantel-Haenszel test will be used by time point to compare success proportion of resolution of fever between two groups, where composite symptoms score at baseline and region are stratification factors.

11. Body temperature at each time point
    ANCOVA will be used by time point to compare body temperature between two groups, where composite symptoms score at baseline and region will be used as covariates.

12. Time to alleviation of individual symptoms
    The stratified generalized Wilcoxon test will be used, where composite symptoms score at baseline and region are stratification factors. Patients whose symptoms at baseline are assessed as 0 (None) or 1 (Mild) will be excluded from the analysis.

13. Time to return to preinfluenza health status

The stratified generalized Wilcoxon test will be used, where composite symptoms score at baseline and region are stratification factors.

14. Incidence of influenza-related complications (hospitalization, death, sinusitis, bronchitis, otitis media, and radiologically confirmed pneumonia)
    Fisher's exact test will be used to compare incidence of hospitalization, death, sinusitis, otitis media, bronchitis, and radiologically confirmed pneumonia between two groups.

9.11 Safety Analyses

The safety population will be used for safety analyses.

9.11.1 Adverse Events

AEs will be classified by system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA). Of reported AEs on the eCRF, AEs reported after the initial dose of randomized study drug will be used for safety analyses.

The number of patients who experience at least 1 AE, deaths, other SAEs, and AEs leading to withdrawal will be counted for each treatment group. The incidences and their 95% CI will be calculated by using the Clopper-Pearson method. The number of those AEs, which are counted by cases reported, will also be presented. Treatment-related AEs will be summarized in the same manner as AEs described above.

The number and percentage of patients who experience AEs by MedDRA system organ class and preferred term will be presented for each treatment group. The summary for action taken with the study drug, timing of onset, severity, and outcome will be presented by system organ class and preferred term.

All AEs, including those occurring prior to the initiation of the study treatment, will be listed.

9.11.2 Vital Signs

For each of the vital signs, summary statistics of observation and the change from baseline will be presented by treatment group for each scheduled time point. Baseline is defined as the last value obtained before the initiation of the study treatment.

9.11.3 Clinical Laboratory Analysis

For each of laboratory tests, summary statistics of observation and the change from baseline will be presented by treatment group for each scheduled time point. Baseline is defined as the last value obtained before the initiation of the study treatment.

Qualitative laboratory test data at baseline and at scheduled time point will be classified according to test category, and the frequency of each pair will be presented in a two-dimensional contingency table by treatment group.

9.11.4 Electrocardiography

ECG will be performed to assess the presence of acute conditions that may exclude patients or conditions in the opinion of the investigator or that may be considered AEs during the study. The frequency of ECG findings will be summarized by treatment group.

9.12 Pharmacokinetic Analysis

Plasma S-033447 concentration data will be plotted against the actual sampling time to determine the PK of S-033447. Plasma S-033447 concentration 24 hours (acceptable time window: 20 to 28 hours) post-dose (C_{24}) will be listed and summarized with the number of non-missing observations (N), arithmetic mean (Mean), standard deviation (SD) and coefficient of variation (CV%, calculated by SD/Mean × 100), geometric mean (Geometric Mean) and coefficient of variation for geometric mean (CV% Geometric Mean, calculated by $[\exp(sd^2)-1]^{1/2} \times 100$, where sd is the standard deviation for natural log [ln]-transformed data), median, minimum and maximum values. C_{24} will be plotted against body weight.

Specification of PK parameters for analysis, statistical level of significance to be used, procedures for accounting for missing, unused or spurious data, procedures for reporting deviations from the original statistical plan, and selection of patients to be included in the analyses population(s) will be presented in the PK analysis plan or PK analysis report as appropriate.

PK parameters reported will be detailed in the PK analysis plan. Other parameters may be added if deemed appropriate.

If needed, the relationships between C_{24} and efficacy endpoints may be assessed across dose groups. The PK/Pharmacodynamic (PD) analysis for each efficacy endpoint will include all patients who have the value of C_{24} and each evaluable PD assay result.

9.13 Other Analysis

9.13.1 Serum Influenza Antibody Titer

Serum antibody titers measured at Visit 1 (Day 1) and Visit 7 (Day 22) will be categorized, and the frequency of each category will be tabulated by treatment group. The ratio of value at Visit 7 to that at Visit 1 will be categorized, and the frequency of each category will be tabulated by treatment group. For the ratio (Visit 7/Visit 1), the geometric mean value will also be calculated, and S-033188 group will be compared with the placebo group regarding the geometric mean ratio, using the Wilcoxon rank sum test.

9.13.2 Polymorphic and Treatment-emergent Amino Acid Substitutions in the PA Gene

This analysis will be conducted for the patients in S-033188 and placebo groups and the methodological details will be specified in the SAP.

9.13.3 Drug Susceptibility Testing for Test Substances

This analysis will be conducted for all patients and further details will be specified in the

SAP.

9.13.4 Health Economic Outcomes

9.13.4.1 EuroQol-5 Dimensions-5 Levels and EuroQol Visual Analog Scale

The combination of 5 scores for EQ-5D-5L and the VAS will be presented as:

Changes in the index value from baseline to each time point
Change in the VAS score from baseline to each time point

9.13.4.2 Work Productivity (WP) Questionnaire

Analysis variables and analysis methods will be specified in SAP.

9.13.5 Intrahousehold infection rate

The definition of the endpoint and the analysis method for the endpoint will be specified in the SAP.

9.14 Interim Analysis

No interim analysis is planned for this study.

10. ADMINISTRATIVE CONSIDERATIONS

10.1 Study Administrative Structure

Sponsor for Japan and Other Asian Countries:	Shionogi & Co., Ltd. 1-8, Doshomachi 3-chome, Chuo-ku, Osaka 541-0045, Japan
Sponsor for the United States:	Shionogi Inc. 300 Campus Drive, Florham Park, NJ 07932 USA
Sponsor's Contact:	[redacted]
Sponsor's Chief Medical Officer:	[redacted]
Medical Monitor in PRA – Japan and Taiwan:	[redacted]
Medical Monitor in PRA – the United States:	[redacted]
Medical Monitor in PRA – Asian countries except Japan and Taiwan:	[redacted]
Investigator and Medical	Multicenter

Institution:	
Study Monitoring:	[redacted]
Registration Center, IRT:	[redacted]
Clinical Laboratory for Japan and other Asian countries:	[redacted]
Clinical Laboratory for the United States:	[redacted]
Bioanalytical Laboratory:	[redacted]
Virology Testing Facility:	[redacted]

	[redacted]
eDiary:	[redacted]

10.2 Institutional Review Board (IRB) Approval

The IRB/IEC will safeguard the rights, safety, and well-being of the patients by reviewing the following study documents: the protocol, informed consent/assent form, written information on patient recruitment procedures (if applicable), other written information given to the patients, IB, safety updates, annual progress reports (if applicable), and any significant revisions to these documents. The investigator or the sponsor will provide these study documents to the IRB/IEC. The IRB/IEC will be appropriately constituted in accordance with ICH GCP, and local requirements, as applicable. The study will be undertaken only after the IRB/IEC has given full approval and the investigator has received a document being approved.

Amendments to the protocol will be subject to the same requirements as the initial review. The investigator will submit all periodic reports and updates as required by the IRB/IEC. The investigator will inform the IRB/IEC of any reportable AEs.

10.3 Ethical Conduct of the Study

The study will be conducted in accordance with all appropriate regulatory requirements and under protocol approved by the IRB/IEC. The study will be conducted in accordance with current ICH GCP, all appropriate patient privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki.

10.4 Patient Information and Consent/Assent

The investigator will generate an informed consent/assent form for the study. The sponsor will provide the investigators with a proposed informed consent/assent form that complies with the ICH GCP guidelines and regulatory requirements. The consent/assent form will include all the elements required by the ICH GCP and any additional elements required by local regulations and will be reviewed and approved by the appropriate IRB/IEC before use. The sponsor must agree to any changes to the proposed consent/assent form suggested by the investigator prior to submission to the IRB/IEC, and the IRB/IEC approved version must be provided to the site monitor after IRB/IEC approval.

The investigator or subinvestigator will explain the nature, purpose and methods,

reasonable anticipated benefits and potential hazards of the study to the patient in simple terms by using the consent/assent form approved by the IRB/IEC before the patient is entered the study. The method of obtaining and documenting informed consent/assent will comply with ICH GCP and all applicable regulatory requirement(s).

10.5 Trial Participation Card

Patients will be provided with a Trial Participation Card that provides the address and telephone number of the main contact for information on the study drugs and emergency contacts. The investigator and IRB will be instructed to keep this in their possession at all times.

10.6 Patient Confidentiality

Procedures for protecting patient privacy must adhere to applicable data privacy laws and regulations. In order to maintain patient privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the patient by the patient number. The investigator will grant site monitor(s) and auditor(s) of the sponsor or a designee and regulatory authorities access to all source documents for verification of data collected on the eCRFs and for verification of the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations. The investigator and the sponsor are responsible for ensuring that sensitive information is handled in accordance with local requirements (eg, Health Information Portability and Accountability Act [HIPAA]). Appropriate consent and authorizations for use and disclosure and/or transfer (if applicable) of protected information must be obtained.

Data on patients collected on eCRFs during the study will be documented in an anonymous fashion and the patient will only be identified by the patient ID. In the emergent or rare event that for safety or regulatory reasons it is necessary to identify a patient, the sponsor, and the investigator are bound to keep this information confidential.

10.7 Study Monitoring

The sponsor or designee will monitor the study to ensure that the study is conducted in accordance with ICH GCP requirements and protocol. The study monitoring will be performed by a representative of the sponsor (site monitor) through on-site monitoring visits as frequently as necessary and frequent communications (e-mail, letter, telephone, and fax). The site monitor will review data recorded on the eCRFs, verify the eCRFs entries with direct access to source documents, collect any safety/efficacy information on patients, verify that amounts of unused study drug are accurate, and check retention of source documents and essential documents.

10.8 Case Report Forms and Source Documents

10.8.1 Case Report Forms

The sponsor or designee will supply eCRFs for each enrolled patient will be provided and historical information and study data, which are specified by the protocol, will be recorded on eCRFs by the investigator. All patient data from study visits must be

collected on source documents and promptly entered in the eCRFs in accordance with the specific instructions given. eCRF entries will be performed by an investigator, subinvestigator, and study coordinator(s) with written authorization. Data should be entered within 3 days after each patient's visit.

When queries are generated to the study center for resolution by the sponsor or designee, eCRF data will be corrected or a response will be recorded in accordance with the specific instructions given. The investigator must ensure that data reported in the eCRF is accurate, complete, legible, and timely and sign the eCRFs to verify the integrity of the data recorded.

A list of the reference ranges for all laboratory tests to be undertaken will be collected prior to the initiation of the study. The list of reference ranges for all laboratory tests should be updated if they are changed during the study. If a central laboratory has been selected to perform any or all tests, it is essential that the reference ranges for all laboratory tests to be performed at the laboratory should also be collected.

10.8.2 Source Data and Source Documents

Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, and patient status. However, the following data will be allowed as data which can be directly recorded in the eCRF:

- Reason for use of prior therapy and/or concomitant therapy
- Severity, seriousness, and causal relationship to the study drug of AE
- Any comments entered in the eCRF

Listed below are the data managed only in the eCRF (ie, items automatically-calculated by the EDC system):

- Age
- BMI
- Respiratory rate (breaths/min)

The investigator must maintain the source documents such as laboratory reports, complete medical history, and physical examination reports. All the source documents must be made accessible for verification by the site monitor(s), auditor(s), the IRB/IEC, regulatory authority inspector(s). Direct access to these documents must be guaranteed by the investigator, subinvestigator, or study coordinator, who must provide support at all times for these activities. For all sources of original data required to complete the eCRFs, the sponsor and the site staff must thoroughly understand the nature and location of the source documents. If electronic records are maintained at the study center, the method of verification must be specified in document within the study center.

10.8.3 External Data

The following data will be reported in separate documents from the eCRFs.

- Plasma concentrations of S-033447 (determined according to procedures specified in a separate document)
- Results of virology tests (determined according to procedures specified in a separate document)
- Safety laboratory test

10.9 Committees

10.9.1 Independent Data Monitoring Committee

No independent data monitoring committee will be established for this study.

10.10 Termination or Suspension of the Study

10.10.1 Termination or Suspension of the Entire Study

The sponsor may prematurely terminate or suspend the study at any time for the following reasons:

- Ensuring safety of the study is difficult due to safety concerns (eg, occurrence of many serious treatment-related AEs)

- Achieving the purpose of the study is considered impossible (eg, inadequate recruitment of patients)

If the study is prematurely terminated or suspended, the sponsor should promptly inform the investigators. The investigator or subinvestigator should promptly inform the participating patients and change the study treatment to other appropriate therapy.

For withdrawal criteria for individual patients, see Section 7.8.

10.10.2 Termination or Suspension of the Study by Study Center

The investigator may prematurely terminate or suspend the study in the study center with agreement of the sponsor at any time when the investigator considers that ensuring safety of the study is difficult due to safety concerns (eg, occurrence of many SAEs).

The sponsor may request the investigator to prematurely terminate or suspend the study in the study center at any time when major violations/deviations of protocol, other procedures, and ICH GCP guidelines were not improved.

If the study is prematurely terminated or suspended, the investigator or subinvestigator should promptly inform the corresponding IRB/IEC and participating patients and change the study treatment to other appropriate therapy(ies).

10.11 Protocol Modifications and Deviations

The investigator will conduct the study in compliance with the protocol provided by the sponsor and approved by the IRB/IEC and the regulatory authority(ies). Modifications to the protocol should not be performed without agreement of both the investigator and the

sponsor. Changes to the protocol will require written IRB/IEC approval prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to the patients.

The investigator or subinvestigator should document any deviation from the protocol and the reason. If the investigator deviates from the protocol or makes a change to the protocol to eliminate an immediate hazard(s) to the patients, the record should be immediately submitted to the sponsor, the study center, and the IRB/IEC by the investigator and the IRB/IEC will provide expedited review and approval. After obtaining approval from the IRB/IEC, the investigator must obtain a written agreement of the sponsor through the study center.

When deviation from the protocol is required to eliminate immediate hazard(s) to the patients, the investigator will contact the sponsor, if circumstances permit, to discuss the planned course of action. Any deviations from the protocol must be fully documented in the source document.

10.12 Data Management

The sponsor will be responsible for data management and analysis. These procedures are specified in a separate document.

10.13 Retention of Data

The study documents must be maintained in accordance with the ICH GCP guidelines and applicable regulatory requirements. The investigator and study center should take measures to prevent accidental or premature destruction of these documents.

If the sponsor is granted manufacturing and marketing approval for the drug, the sponsor will promptly notify the head of the study center in writing.

Records will be retained for either of the following periods, whichever is later:

- Until the approval day of manufacturing/marketing of the study drug or 3 years after the decision to terminate the development is made
- 3 years after the date of discontinuation or completion of the study

However, the duration of retention may be prolonged with agreement with the sponsor. If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to an appropriate person willing to accept the responsibility.

10.14 Quality Control and Assurance

The sponsor or designee will implement and maintain quality control and quality assurance procedures with written standard operating procedures to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

This study will be conducted in accordance with the provisions of the Declaration of

Helsinki and all revisions thereof; in accordance with the ICH GCP, and as required by the applicable regulatory requirements.

The sponsor will provide training necessary for the study to the investigators and the study center personnel prior to the initiation of the study.

10.15 Publication and Disclosure Policy

All information regarding S-033188 provided by the sponsor to the investigator is privileged and confidential and must not be disclosed to any third party. The investigator agrees to use this information to accomplish the study and will not use it for any other purposes without consent from the sponsor. It is understood that there is an obligation to provide the sponsor with complete data obtained during the study. The information obtained from the study will be used for the development of S-033188 and may be disclosed to regulatory authorities, other investigators, corporate partners, or consultants as required.

The sponsor will retain the ownership of all data. All proposed publications based on the study will be subject to the sponsor's approval requirements.

The key design elements of this protocol will be posted in a publicly accessible database.

10.16 Financial Disclosure

The information on financial disclosure for investigators will be addressed in a separate agreement between the sponsor and the investigator.

11. REFERENCE LIST

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4. Centers for Disease Control and Prevention. CDC HEALTH ALERT: CDC Recommends against the Use of Amantadine and Rimandatine for the Treatment or Prophylaxis of Influenza in the United States during the 2005-06 Influenza Season. 2006.
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6. Jefferson T, Jones MA, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. Cochrane Database Syst Rev. 2012 Jan 18; 1: CD008965. doi; 2014;4: CD008965.
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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	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 [a]		X															
Rapid Influenza Diagnostic Test		X [b]															
Randomization		X															
Study Drug Dispensation		X															
Study Drug Administration		X	X	X	X	X											
Patient eDiary [c]	Body Temperature Measurement	X [d]	4 Times Daily		Twice Daily												
	Assessment of Severity of Influenza Symptoms	X [d]	Twice Daily								Once Daily						
	Assessment of Health	X [d]	Once Daily														
	Assessment of Health Prior to Influenza Symptoms	X [d]															
	EQ-5D-5L	X [d]	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 [e, f]															X [e]
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) [g]		X				X											X
Immunological Tests		X [h]															
Routine Laboratory Tests		X				X										X	X
Influenza Antibody Titer Test		X [h]															X

Nasopharyngeal (preferred)/pharyngeal (if nasopharyngeal cannot be collected) Swabs (Virology Test)	X [h]	X	X	X	X	X			X						X [i]	X [i, j]
Vital Sign Measurements	X	X	X	X	X	X			X						X	X
Electrocardiography	X	X														X
Pharmacokinetic Blood Samples	X [k]	X	X [k]		X										X [k]	
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	

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.

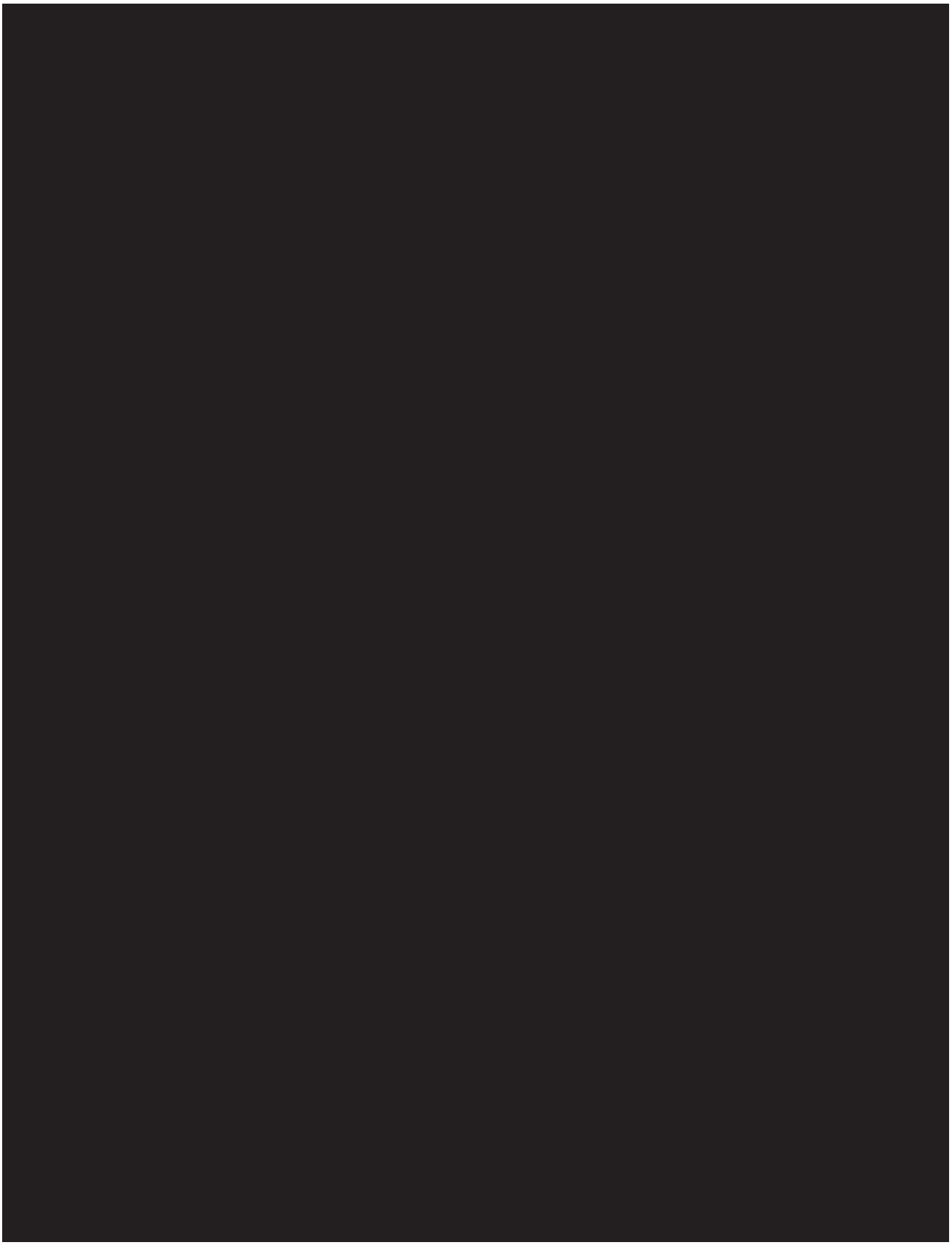
h Predose.

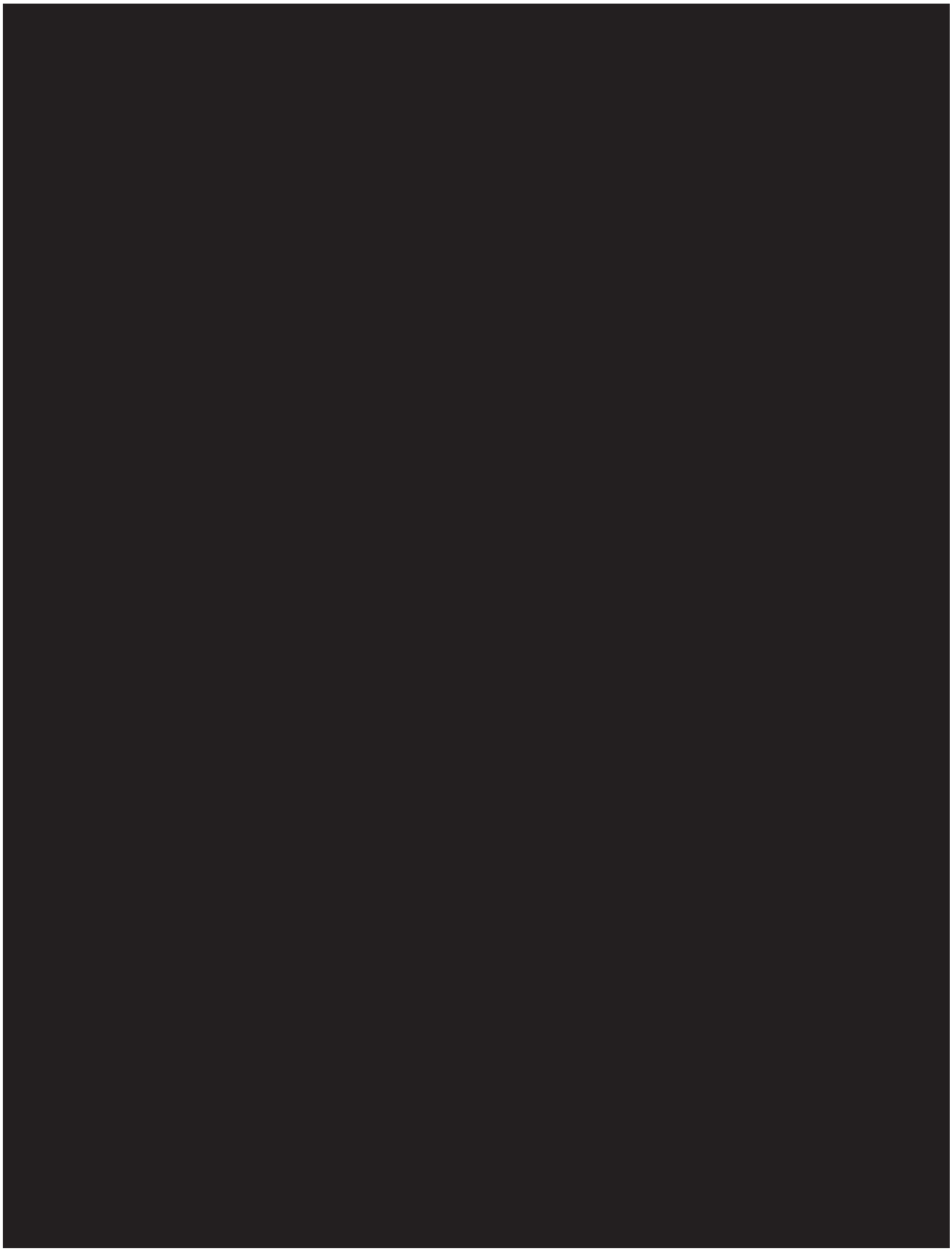
i Virology swabs will be collected if investigator determines that flu symptoms are persisting.

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).

Appendix 2 QOL Questionnaire (EuroQol-5 Dimensions–5 Levels)





Appendix 3 Work Productivity (WP) Questionnaire

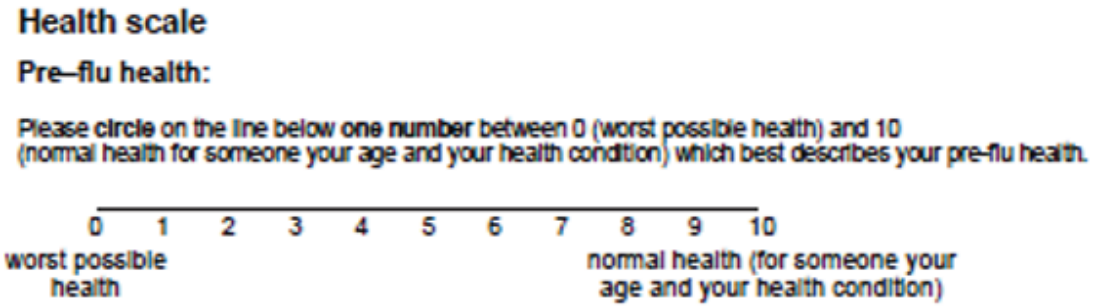
Work Productivity Questionnaire cover note:

To the investigator:

This questionnaire is designed to capture the impact of influenza symptoms on patients' ability to work and perform normal activities. We would like the patient to complete the questionnaire once, during the clinic visit following resolution of their symptoms

1. How many hours or days per week do you work (e.g., full or part time paid work, voluntary work, or studying)?
2. Due to your recent influenza illness, for how many hours or days were you unable to work? ___hours, or ____ days
3. Due to your recent influenza illness, for how many hours or days did you feel that your symptoms caused you to perform below your normal standard even though you attended work? ___hours, or _____days
4. Due to your recent influenza illness, for how many hours or days did you require someone to help you with your normal activities? ___ hours, or ___ days

Appendix 4 Assessment of Health Scale



Appendix 5 Management and Discontinuation Criteria for Abnormal Liver Function Tests

Management and Discontinuation Criteria for Abnormal Liver Function tests have been designed to ensure patient safety and evaluate liver event etiology. (See Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, FDA: 2009)

1. Abnormal Liver Chemistry Criteria:

The investigator or subinvestigator must review study patient laboratories to identify if any levels meet the following criteria:

a. AST or ALT > 5 × ULN

b. AST or ALT > 3 × ULN and total bilirubin > 2 × ULN or PT-INR > 1.5, if PT-INR is measured.

c. AST or ALT > 3 × ULN with signs or symptoms compatible with hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, rash, eosinophilia [>5%])

2. Action to be taken by Investigator:

If any abnormal liver chemistry criterion is met, the investigator or subinvestigator must do the following:

- Patients must be instructed to discontinue study medication immediately.
- Following the initial observed elevation, every effort should be made to have the patient return to the clinic within 72 hours to repeat liver function chemistries and for further hepatic evaluation.
- Every effort should be made to have the patients monitored 2 to 3 times per week until liver function chemistries (ALT, AST, ALP, total bilirubin) resolve, stabilize or return to within the normal range or to baseline levels.
- This event must be reported to the sponsor as soon as possible but no later than 72 hours of learning after its occurrence on the Liver Event Form.
- Consultation with a specialist such as a hepatologist is considered.
- Liver imaging (ie, ultrasound, magnetic resonance imaging (MRI), computerized tomography) is considered.
- For criteria b, the case must be reported as an SAE.

3. Follow-up Examination:

If any of the abnormal liver chemistry criteria are met, the following assessments should be performed at the follow-up visit(s) and documented in the Liver Event Form:

- Clinical symptoms course
- Alcohol use
- Risk factors for nonalcoholic steatohepatitis (NASH) such as diabetes, obesity and hypertriglyceridemia
- Autoimmune hepatitis/cholangitis
- Wilson's disease
- Laboratory Assessments
  - Viral hepatitis serology
    - Hepatitis A IgM antibody
    - Hepatitis B surface antigen (HBs antigen) and Hepatitis B core antibody (HBc antibody)
    - Hepatitis C RNA
    - Hepatitis E IgA antibody
    - Cytomegalovirus IgM antibody
    - Epstein-Barr viral capsid antigen IgM antibody
  - For patients with total bilirubin of > 1.5 × ULN, conjugated bilirubin should be measured
  - Complete blood count with differential to assess for eosinophilia

4. Restarting Study Medication Criteria

Patients that meet the abnormal liver chemistry criteria may re-start the administration of the study drug, but only if they do not meet the "Drug Discontinuation Criteria Due to Abnormal Liver Chemistry Tests".

Patients with ALT > 5 × ULN to ≤ 8 × ULN elevations for less than 2 weeks may restart the study drug may at the discretion of the investigator and sponsor if both of the following conditions are met:

- Subsequent liver function chemistries are lower or unchanged
- No signs or symptoms are consistent with hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, rash or eosinophilia [>5%])

All patients that have met abnormal liver chemistry criteria must still be monitored 2 to 3 times per week until liver function chemistries (ALT, AST, alkaline phosphatase, and total bilirubin) resolve, stabilize or return to within the normal range or to baseline levels.

5. Drug Discontinuation Criteria Due to Abnormal Liver Chemistry Tests

Patients must be discontinued from the study as described below:

AST or ALT > 8 × ULN, confirmed by follow-up testing (ie, initial abnormality is confirmed on subsequent testing), regardless of medical history or physical examination findings
AST or ALT > 5 × ULN, with elevations for more than 2 weeks or development of

concomitant signs or symptoms consistent with hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, rash or eosinophilia [>5%])
AST or ALT > 3 × ULN and total bilirubin > 2 × ULN or PT-INR > 1.5, if PT-INR measured, confirmed by follow-up testing (ie, initial abnormality is confirmed on subsequent testing), regardless of medical history or physical examination findings.
AST or ALT > 3 × ULN with signs or symptoms compatible with hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, rash or eosinophilia [>5%]), confirmed by follow-up testing (ie, initial laboratory abnormality is confirmed upon subsequent testing).
AST or ALT > 5 × ULN and the patient cannot be followed up weekly

Management and Discontinuation Criteria for Abnormal Liver Function Tests (LFT): Algorithm