

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 Patients with Influenza at High Risk of Influenza Complications
Shionogi Study Number:	1602T0832
ClinicalTrials.gov Registration No.	NCT02949011
Study Document	Protocol Version 3 (Amendment 2)

History of Protocol Amendments

Version 1 (Original)	05 August 2016
This version of the protocol was not used to conduct the study	
Version 2	16 September 2016
This version of the protocol was not used to conduct the study	
Version 3	31 October 2016

CLINICAL STUDY PROTOCOL: 1602T0832

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Study Number:	1602T0832
Study Phase:	3
Product Name:	S-033188
IND Number:	126653
EudraCT Number:	2016-002688-32
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Issue Date:

Version 1 (Original):	5 August 2016
Version 2 (Amendment 1):	16 September 2016
Version 3 (Amendment 2):	31 October 2016

*: 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.

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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 Patients with Influenza at High Risk of Influenza Complications

Study Number:

1602T0832

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 improvement of influenza symptoms in patients with influenza

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

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

Health Economic Outcomes Research Objectives:

- To compare the total quality-of-life detriment by measuring the ^{CPI} 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 2157 patients diagnosed with influenza randomly assigned in a 1:1:1 ratio to receive a single, oral dose of S-033188, oseltamivir 75 mg BID for 5 days, 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 table below presents the dosing schedule for the 3 treatment groups.

Treatment Group	Day 1	Day 2	Day 3	Day 4	Day 5*
S-033188					
Oseltamivir placebo	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				
S-033188 placebo (weight < 80 kg)	2 tablets				
S-033188 placebo (weight ≥ 80 kg)	4 tablets				
Placebo					
Oseltamivir placebo	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 5 PM, dosing will be completed on Day 6.

Study Population:

Male and female patients ≥ 12 years old with influenza A and/or B infection at high risk* of developing influenza complications within 48 hours of symptom onset

* Definition of high risk adapted from Centers for Disease Control and Prevention (CDC) criteria listed in the inclusion criteria below.

Criteria for Inclusion and Exclusion:

Inclusion Criteria:

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

1. Patients or their legal guardians who provide written informed consent to participate in the study on a voluntary basis. 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 ≥ 12 years at the time of signing the informed consent/assent form.
3. Patients with a duration of influenza symptoms confirmed by all of the following:

- a. Fever $\geq 38^{\circ}\text{C}$ (axillary) during the predose examinations or > 4 hours after dosing of antipyretics if they were taken
- b. At least 1 each of the following general and respiratory symptoms associated with influenza (excluding those that are chronic and existed in the 30 days prior to the influenza episode) is present with a severity of moderate or greater:
 - i. General symptoms (headache, feverishness or chills, muscle or joint pain, or fatigue)
 - ii. Respiratory symptoms (cough, sore throat, or 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 1°C from normal body temperature)
 - b. Time when the patient experiences at least 1 new general or respiratory symptom
5. If a women of childbearing potential, agrees 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).
6. Patients will be considered at high risk* of influenza complications due to the presence of at least 1 of the following inclusion criteria:
 - a. Asthma or chronic lung disease (such as chronic obstructive pulmonary disease or cystic fibrosis)
 - b. Endocrine disorders (including diabetes mellitus)
 - c. Residents of long-term care facilities (eg, nursing homes)
 - d. Compromised immune system (including patients receiving corticosteroids not exceeding 20 mg of prednisolone or equivalent, and patients being treated for human immunodeficiency virus (HIV) infection with a CD4 count > 350 cells/ mm^3 within the last 6 months)
 - e. Neurological and neurodevelopmental disorders (including disorders of the brain, spinal cord, peripheral nerve, and muscle, eg, cerebral palsy, epilepsy [seizure disorders], stroke, muscular dystrophy, or spinal cord injury)
 - f. Heart disease (such as congenital heart disease, congestive heart failure, or coronary artery disease), excluding hypertension without any other heart-related symptoms
 - g. Adults aged ≥ 65 years
 - h. American Indians and Alaskan Natives
 - i. Blood disorders (such as sickle cell disease)
 - j. Metabolic disorders (such as inherited metabolic disorders and mitochondrial disorders)
 - k. Morbid obesity (body mass index ≥ 40)
 - l. Women who are within 2 weeks postpartum and are not breastfeeding

* Definition of high risk adapted from CDC criteria.

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 with known allergy to oseltamivir (Tamiflu®).
3. Patients unable to swallow tablets or capsules.
4. Patients who have previously received S-033188.
5. Patients weighing < 40 kg.
6. Patients who have been exposed to an investigational drug within 30 days prior to the predose examinations.
7. Women who are pregnant, breastfeeding, or have a positive pregnancy test at the predose examinations. The following female patients who have documentation of either a or b below do not need to undergo a pregnancy test at 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
8. Patients with concurrent infections at the predose examinations requiring systemic antimicrobial therapy.
9. Patients with liver disease associated with hepatic impairment.
10. Patients with cancer within the last 5 years (unless nonmelanoma skin cancer).
11. Patients with untreated HIV infection or treated HIV infection with a CD4 count below 350 cells/mm³ in the last 6 months.
12. Patients with immunosuppression following organ or bone marrow transplants.
13. Patients exceeding 20 mg of prednisolone or equivalent dose of chronic systemic corticosteroids.
14. Patients who have received peramivir, laninamivir, oseltamivir, zanamivir, rimantadine, umifenovir or amantadine within 30 days prior to the predose examinations.
15. Patients who have received an investigational monoclonal antibody for a viral disease in the last year.
16. Patients with current creatinine clearance ≤ 60 mL/min (≤ 30 mL/min in Japan).
17. Patients who, in the opinion of the investigator, would be unlikely to comply with required study visits, self-assessments, and interventions.

Test Drug, Dose, and Mode of Administration:

Patients randomized to S-033188 will receive either 2 tablets of S-033188 20 mg if they weigh < 80 kg at Screening, or 4 tablets of S-033188 20 mg if they weigh ≥ 80 kg at Screening and 1 capsule of oseltamivir placebo BID for 5 days.

Control Drug, and Placebo, Dose, and Mode of Administration:

Patients randomized to oseltamivir will receive 1 capsule of oseltamivir 75 mg BID for 5 days and either 2 tablets of S-033188 placebo if they weigh < 80 kg at Screening or 4 tablets of S-033188 placebo if they weigh \geq 80 kg at Screening.

Patients randomized to placebo will receive either 2 tablets of S-033188 placebo if they weigh < 80 kg at Screening or 4 tablets of S-033188 placebo if they weigh \geq 80 kg at Screening and 1 capsule of oseltamivir placebo BID for 5 days.

Duration of Treatment:

5 days

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 (ET).

- Systemic antiviral drugs (excluding antiretrovirals for the treatment of HIV infection or herpes simplex virus (HSV) suppressive therapy)
- Antimicrobial* and antifungal drugs**
- Antipyretics/analgesics except provided acetaminophen/paracetamol***
- Antitussives and expectorants
- Combination cold remedies
- Antihistamines**
- 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, and ears or by inhalation will be prohibited.

*** Low dose aspirin for cardiovascular disease prophylaxis will be acceptable.

Efficacy Assessments:**Primary Endpoint:**

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

Secondary Endpoints:

- Proportion of patients positive for 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 (RT-PCR) at each time point
- AUC 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 symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue)
- Time to improvement in the 4 systemic symptoms (headache, feverishness/chills, muscle/joint pain, and fatigue)
- Time to improvement in the 3 respiratory symptoms (cough, nasal congestion, and sore throat)
- Time to resolution of fever
- Proportion of patients reporting normal temperature at each time point
- Body temperature at each time point
- Time to improvement of each influenza symptom
- Time to return to preinfluenza health status
- Requirement for systemic antibiotics for infections secondary to influenza infection
- Incidence of influenza-related complications (hospitalization, death, sinusitis, bronchitis, otitis media, and radiologically confirmed pneumonia)
- Intrahousehold infection rate (for Japan only)

Other Endpoints:

- Serum influenza antibody titer
- Polymorphic and treatment-emergent amino acid substitutions in the PA gene
- Drug susceptibility in patients with evaluable virus
- Health Economic Outcomes
 - CPI
 - WP questionnaire

Safety Assessments:

Frequencies of adverse events (AEs), serious AEs, vital sign measurements, physical examinations, electrocardiography (ECGs), and clinical laboratory tests

Pharmacokinetic Assessments:

For the measurement of plasma S-033447 concentrations, blood samples will be collected at Visits 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), at Visits 3 (Day 3) and 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 to support the primary analyses for efficacy. Statistical testing will be performed at the 2-sided significance level of 0.05 unless stated otherwise.

Primary Efficacy Analysis:

The primary efficacy analysis will be performed on the primary endpoint, the time to improvement of influenza symptoms, by comparing S-033188 and placebo using the stratified generalized Wilcoxon test with composite symptom scores at baseline, preexisting and worsened symptom at baseline, and region as stratification factors.

Furthermore, the Kaplan-Meier curves will be plotted for each treatment group, and the median time to improvement of symptoms and its 95% confidence interval will be calculated. The same analysis in the PPS will be performed as a sensitivity analysis.

Secondary Efficacy Analysis for Primary Endpoint:

In addition, a secondary efficacy analysis will be performed on the comparison of the primary endpoint by comparing between S-033188 and oseltamivir using the same statistical methods as used for the primary efficacy analysis. 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 number 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 and preferred term 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, ECGs, 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: CPI

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

$\Delta\Delta\text{QTcF}$	placebo-subtracted changes from baseline in the QTcF interval
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AR	adverse reactions
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
$\text{AUC}_{0-\text{inf}}$	area under the plasma concentration-time curve extrapolated from time 0 to infinity
$\text{AUC}_{0-\text{last}}$	area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration after dosing
BA	bioavailability
BCRP	breast cancer resistance protein
BID	twice daily
BMI	body mass index
BLQ	below the limit of quantification
BUN	blood urea nitrogen
C_{24}	plasma concentration 24 hours postdose
CDC	Centers for Disease Control and Prevention
CEN	cap-dependent endonuclease
CI	confidence interval
C_{max}	maximum plasma concentration
COPD	chronic obstructive pulmonary disease
CrCl	creatinine clearance
CRO	contract research organization
CRP	C-reactive protein
CV	coefficient of variation
CYP	cytochrome P450
DSMB	Data Safety Monitoring Board
ECG	electrocardiography
eCRF	electronic case report form
eDiary	electronic diary
ePRO	electronic patient-reported outcome
CPI	CPI
EU	European Union

FDA	Food and Drug Administration
FE	food effect
Feu ₀₋₇₂	fraction of dose excreted in urine from time 0 to 72 hours postdose
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GMP	Good Manufacturing Practice
h-CE	hepatic carboxylesterase
Hct	hematocrit
hERG	human ether a-go-go related gene
Hgb	hemoglobin
HIPAA	Health Information Portability and Accountability Act
IC ₅₀	half maximal inhibitory concentration
ICH	International Conference on Harmonisation
ICH-GCPs	International Conference on Harmonisation-Good Clinical Practices
IEC	Independent Ethics Committee
IND	investigational new drug
INR	international normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	intent-to-treat
ITTI	intention-to-treat infected
IUD	intrauterine device
IUS	intrauterine system
IWRS	interactive web response system
LDH	lactate dehydrogenase
LFT	liver function test
MATE	multidrug and toxin extrusion protein
MDCK	Madin-Darby canine kidney
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger RNA
N	number of non-missing observations
NA	neuraminidase
NASH	non-alcoholic steatohepatitis
NOAEL	no observed adverse effect level
NPAE	neuropsychiatric adverse events
OATP	organic anion transporting polypeptide
PA	polymerase acidic protein

PD	pharmacodynamic
P-gp	P-glycoprotein
PK	pharmacokinetic
PPS	per-protocol set
PT	prothrombin time
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
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2,z}$	terminal elimination half-life
TBL	total bilirubin
TCID	tissue culture infective dose
TEAE	treatment-emergent adverse event
UGT	UDP glucuronosyltransferase
ULN	upper limit of normal
US	United States
VAS	Visual Analog Scale
WBC	white blood cell (count)
WHODD	World Health Organization Drug Dictionary
WOCBP	women of childbearing potential
WP	work productivity

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 38°C to 40°C 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. 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 Centers for Disease Control and Prevention (CDC) has recommended against the use of amantadine for the treatment and prophylaxis of influenza virus infection [3], 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.

While for most people influenza is a mild and self-limiting illness, for some individuals, comorbidities and demographic factors may result in a higher risk of influenza related complications. These complications include influenza pneumonia, secondary bacterial pneumonia, bronchitis, sinus and ear infections, hospitalization, and death. Influenza is also considered to make some chronic health conditions worse, such as asthma and congestive heart failure. The CDC classifies people at high risk of developing flu related complications [4].

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 clinical studies are summarized below.

1.1 Nonclinical Studies

1.1.1 Pharmacology

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1.1.2 Safety

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1.1.3 Pharmacokinetics

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1.2 Clinical Studies

CPI [Redacted]

1.2.1 Single-ascending Dose Study (CPI [Redacted])

CPI [Redacted]

[Redacted]

CPI [Redacted]

1.2.2 Relative Bioavailability and Food Effect Study CPI [Redacted])

CPI [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

1.2.3 Drug-Drug Interaction Study with Midazolam CPI [Redacted])

CPI [Redacted]

CPI [Redacted]

[Redacted]

[Redacted]

1.2.4 Drug-drug Interaction Study with Itraconazole (CPI [Redacted])

CPI [Redacted]

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[Redacted]

1.2.5 Thorough QT/QTc Study (CPI [Redacted])

CPI [Redacted]

[Redacted]

CPI [Redacted]

[Redacted]

1.2.6 Phase 2 Proof-of-Concept and Dose-finding Study

(CPI [Redacted])

CPI [Redacted]

[Redacted]

[Redacted]

[Redacted]

CPI [Redacted]

[Redacted]

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1.3 Comparator Data

1.3.1 Oseltamivir Clinical Efficacy and Safety

1.3.1.1 Oseltamivir Efficacy

Oseltamivir (Tamiflu[®]) is a neuraminidase 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 (NPAE) 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 adverse reactions 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 adverse reactions include hypersensitivity reactions, altered level of consciousness, cardiac arrhythmia, elevated liver enzymes, eczema, dermatitis, rash, and urticaria. Rare adverse reactions 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 High Risk Populations

The median duration of influenza illness in older patients (≥ 65 years) and in patients with chronic cardiac and/or respiratory disease receiving oseltamivir 75 mg twice daily (BID) for 5 days was not reduced significantly. The total duration of fever was reduced by 1 day in the oseltamivir-treated groups. In influenza-positive older people, the incidence of specified lower respiratory tract complications (mainly bronchitis) treated with antibiotics was statistically significantly lower in the oseltamivir-treated group (12% [29/250]) compared with the placebo-treated group (19% [52/268]; $p = 0.0156$). In influenza-positive patients with chronic cardiac and/or respiratory disease, the combined incidence of lower respiratory tract complications (mainly bronchitis) treated with antibiotics was 17 % (22/133) in the placebo-treated group and 14 % (16/118) in the oseltamivir-treated group ($p = 0.5976$) [9].

1.3.1.4 Oseltamivir Dosing

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

1.3.1.5 Oseltamivir Dosing and Renal Impairment

Oseltamivir 75 mg BID is recommended for individuals with a creatinine clearance (CrCl) of > 60 mL/min (≥ 30 mL/min in Japan), and dose adjustment is required for lower CrCl. If patients are enrolled in the study and found to have a CrCl ≤ 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. CrCl 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>.

2. STUDY OBJECTIVES

2.1 Primary Efficacy Objective

The primary 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 improvement of influenza symptoms in patients with influenza

2.2 Secondary Efficacy Objectives

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

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

- 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 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 influenza virus infection

2.6 Health Economic Outcomes Research Objectives

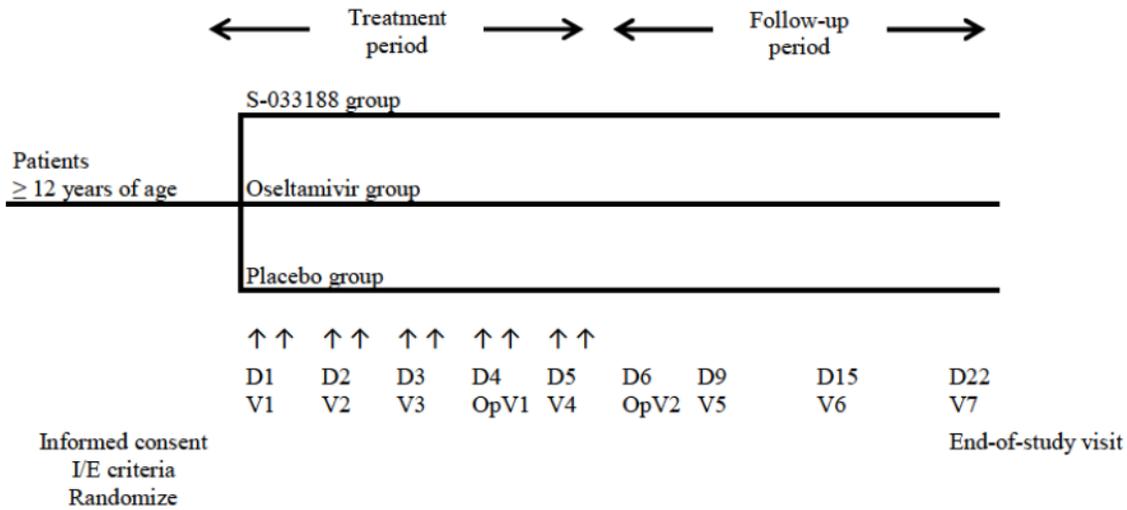
- To compare the total quality-of-life detriment by measuring the CPI and a work productivity (WP) questionnaire, in patients treated with of S-033188 compared with oseltamivir 75 mg BID for 5 days and placebo

3. INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a randomized, double-blind, multicenter, parallel-group, placebo- and active-controlled study. Approximately 2157 patients diagnosed with influenza virus infection will be randomly assigned in a ratio of 1:1:1 to receive a single, oral dose of S-033188, oseltamivir 75 mg BID for 5 days, 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. A maximum of 9 visits will occur during a period of 22 days to assess efficacy and 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, Dose Selection, and Control Group

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 adult and adolescent patients with influenza virus infection at high risk of influenza complications.

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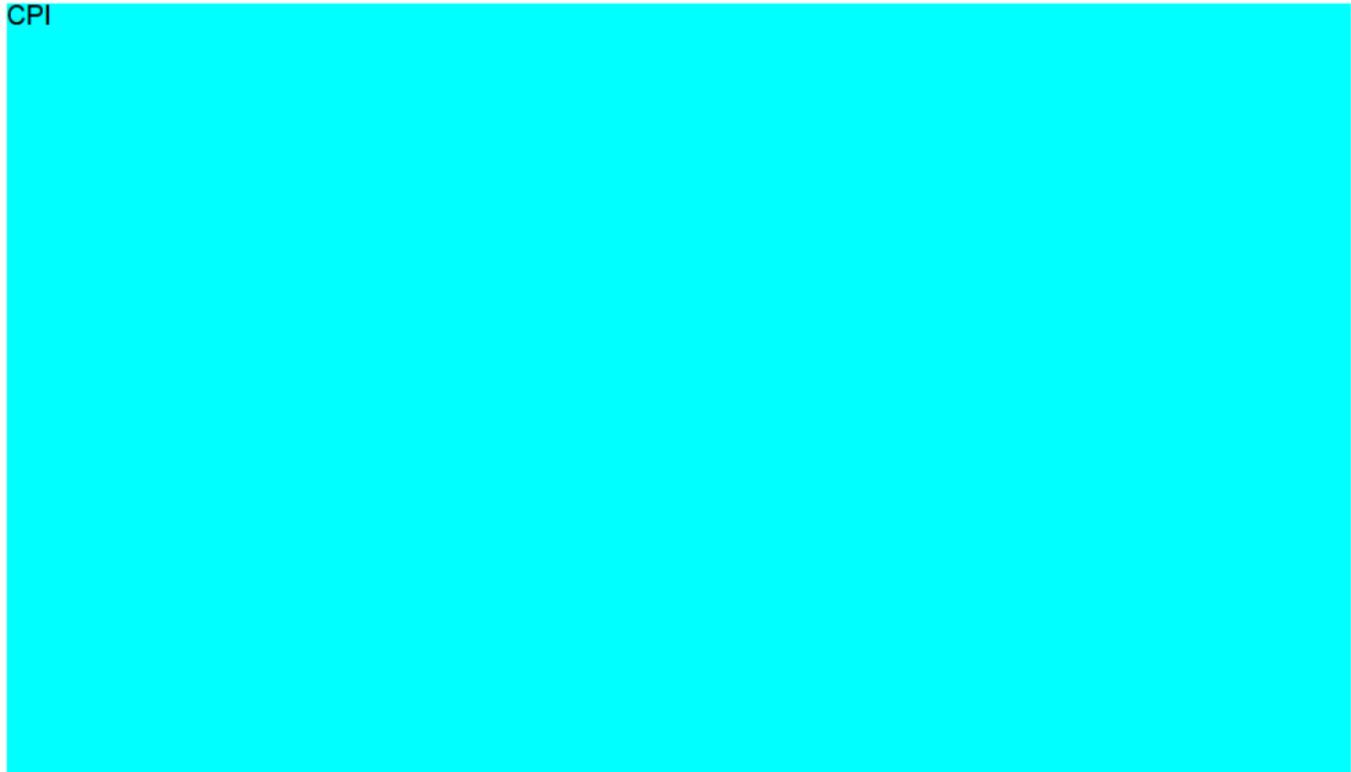


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3.2.1 Risk Benefit Assessment

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Oseltamivir is an established anti-influenza antiviral with a well-defined safety profile as discussed in [Section 1.3.1](#). Clinical trials of oseltamivir have consistently shown improvement in the time to alleviation of symptoms in otherwise healthy individuals with

acute uncomplicated influenza, although efficacy at preventing severe disease has not been demonstrated in randomized controlled trials. However, a significant body of observational data supports its utility in these patients, and most national treatment guidelines encourage its use.

S-033188 resulted in more rapid symptom alleviation compared to placebo in the Phase 2 study in otherwise healthy patients with acute uncomplicated influenza. S-033188 also resulted in rapid and profound reductions in viral titer and viral load, suggesting a rapid resolution of viral shedding. The potent antiviral efficacy and rapid reduction in viral shedding should lead to resolution of symptoms in an otherwise healthy population and may have similar efficacy in a population at high risk of complications

3.2.2 Placebo Rationale in High Risk Population

Many authorities, including the CDC, recommend antiviral therapy as soon as possible after the onset of symptoms for individuals with influenza at high risk for complications [10, 11].

However, meta-analyses of randomized controlled trials of neuraminidase treatment of both otherwise healthy and high risk individuals resulted in a conclusion that there was a lack of good evidence demonstrating an effect on complications. Of note, based on data from all subjects enrolled in treatment trials of oseltamivir, oseltamivir did not affect the number of hospitalizations, confirmed pneumonias, or deaths. In children with asthma, there was no evidence of a benefit for reducing the risks of complications [4, 8]. Other meta-analyses suggested a reduction in the risk of lower respiratory tract complications and hospital admissions, but an increase in the occurrences of nausea and vomiting [12].

Metanalyses of observational studies of the treatment of influenza concluded that early treatment with oseltamivir may reduce mortality (odds ratio, 0.23 [95% CI, 0.13 to 0.43]) and hospitalization (odds ratio 0.75 [95% CI, 0.66 to 0.89]), but this evidence was considered potentially biased due to confounding and of low quality [13]. Other meta-analyses concluded that early neuraminidase inhibitor in patients hospitalized with influenza compared to no treatment did not reduce the incidence of radiologically-confirmed pneumonia, but did reduce mortality [14]. Additionally, a systematic review and meta-analysis of studies following the 2009-2010 influenza A (H1N1) pandemic suggested that early neuraminidase treatment reduced the likelihood of severe outcomes compared with no treatment [15].

The lack of good quality randomized control trial evidence to guide prescribing of antiviral treatment is reflected in clinical practice. In the US, only 15% of individuals considered “high risk” and presenting early to clinical care with an acute respiratory illness were prescribed an antiviral. Of those high risk individuals with PCR-confirmed influenza who presented within 48 hours of symptom onset, 58% were prescribed an antiviral [16].

This study protocol ensures that 66% of patients presenting with rapid influenza diagnostic test (RIDT)-confirmed influenza or symptoms consistent with influenza will

be treated with an antiviral, thus reflecting the current standard of care. Regular clinical assessments of patients will ensure that any clinical deterioration is identified, and interventions can be instituted for patient management. Investigators will have the option of stopping study drug therapy and initiating commercially-available influenza treatment in cases where this is considered clinically indicated. Unblinding of study drug in this scenario would not be necessary since it would not influence future clinical management.

3.3 Study Duration

3.3.1 Study Duration in Individual Patients

Each patient will be enrolled in the study for a total of 22 days.

3.3.2 Planned Study Duration for the Study

The planned study duration is from CPI



3.3.3 End of Study

The end of the study will be 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) with influenza A and/or B virus infection considered to be at high risk of developing influenza complications, with typical systemic and respiratory symptoms of influenza, whose new symptoms were first noticed ≤ 48 hours prior to the predose examinations.

Approximately 2157 patients will be enrolled. Patients with fever and symptoms consistent with 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 or their legal guardians who provide written informed consent to participate in the study on a voluntary basis. 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 ≥ 12 years at the time of signing the informed consent/assent form.
3. Patients with a duration of influenza symptoms confirmed by all of the following:
 - a. Fever $\geq 38^{\circ}\text{C}$ (axillary) during the predose examinations or within the 4 hours prior if antipyretics were taken
 - b. At least 1 each of the following general and respiratory symptoms associated with influenza (excluding those that are chronic and existed in the 30 days prior to the influenza episode) is present with a severity of moderate or greater:
 - i. General symptoms (headache, feverishness or chills, muscle or joint pain, or fatigue)
 - ii. Respiratory symptoms (cough, sore throat, or 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 1°C from normal body temperature)
 - b. Time when the patient experiences at least 1 new general or respiratory symptom
5. If a women of childbearing potential (WOCBP), agrees 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).
6. Patients will be considered at high risk* of influenza complications due to the presence of at least 1 of the following inclusion criteria:

- a. Asthma or chronic lung disease (such as chronic obstructive pulmonary disease [COPD] or cystic fibrosis)
- b. Endocrine disorders (including diabetes mellitus)
- c. Residents of long-term care facilities (eg, nursing homes)
- d. Compromised immune system (including patients receiving corticosteroids not exceeding 20 mg of prednisolone or equivalent, and patients being treated for human immunodeficiency virus (HIV) infection with a CD4 count > 350 cells/mm³ within the last 6 months)
- e. Neurological and neurodevelopmental disorders (including disorders of the brain, spinal cord, peripheral nerve, and muscle, eg, cerebral palsy, epilepsy [seizure disorders], stroke, muscular dystrophy, or spinal cord injury)
- f. Heart disease (such as congenital heart disease, congestive heart failure, or coronary artery disease), excluding hypertension without any other heart-related symptoms
- g. Adults aged ≥ 65 years
- h. American Indians and Alaskan Natives
- i. Blood disorders (such as sickle cell disease)
- j. Metabolic disorders (such as inherited metabolic disorders and mitochondrial disorders)
- k. Morbid obesity (body mass index [BMI] ≥ 40)
- l. Women who are within 2 weeks postpartum and are not breastfeeding

* Definition of high risk adapted from Centers for Disease Control and Prevention (CDC) criteria.

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 with known allergy to oseltamivir.
3. Patients unable to swallow tablets or capsules.
4. Patients who have previously received S-033188.
5. Patients weighing < 40 kg.
6. Patients who have been exposed to an investigational drug within 30 days prior to the predose examinations.
7. Women who are pregnant, breastfeeding, or have a positive pregnancy test at the predose examinations. The following female patients who have documentation of either a or b below do not need to undergo a pregnancy test at 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

8. Patients with concurrent infections at the predose examinations requiring systemic antimicrobial therapy.
9. Patients with liver disease associated with hepatic impairment.
10. Patients with cancer within the last 5 years (unless nonmelanoma skin cancer)
11. Patients with untreated HIV infection or treated HIV infection with a CD4 count below 350 cells/mm³ in the last 6 months.
12. Patients with immunosuppression following organ or bone marrow transplants.
13. Patients exceeding 20 mg of prednisolone or equivalent dose of chronic systemic corticosteroids.
14. Patients who have received peramivir, laninamivir, oseltamivir, zanamivir, rimantadine, umifenovir or amantadine within 30 days prior to the predose examinations.
15. Patients who have received an investigational monoclonal antibody for a viral disease in the last year.
16. Patients with current CrCl \leq 60 mL/min (\leq 30 mL/min in Japan).
17. 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 be recorded, including the 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 will be entered in the electronic case report form (eCRF). Rescreening will be permitted, but patients who do not meet the temperature 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 that contain 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

Patients who are qualified for entry will be randomly assigned in a ratio of 1:1:1 according to the assignment procedures specified in [Section 5.4](#) to receive S-033188, oseltamivir, or matching placebo as stated in [Table 5-1](#). Oseltamivir/placebo should be dosed 12 hours apart and can be taken without regard to food/meals (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

Treatment Group	Day 1	Day 2	Day 3	Day 4	Day 5*
S-033188					
Oseltamivir placebo	2 capsules				
S-033188 40mg (weight < 80 kg)	2 tablets				
S-033188 80 mg (weight ≥ 80 kg)	4 tablets				
Oseltamivir					
Oseltamivir 75 mg	2 capsules				
S-033188 placebo (weight < 80 kg)	2 tablets				
S-033188 placebo (weight ≥ 80 kg)	4 tablets				
Placebo					
Oseltamivir placebo	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 5 PM, dosing will be completed on Day 6.

5.3 Selection and Timing of Dose for Each Patient

Patients will be randomly assigned to 1 of 3 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 < 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

Each patient who is qualified for entry in the study will be randomized to S-033188, oseltamivir, or placebo in a ratio of 1:1:1. An interactive web response system (IWRS) will be used to assign patients to numbers for which treatment has already been randomly assigned. The randomization will use the stratified randomization method for balancing the following 4 factors: baseline symptom score (≤ 14 , ≥ 15), preexisting and worsened symptom (Yes, No: if a patient has at least 1 of 3 symptoms [namely cough, muscle or joint pain, or fatigue] that is preexisting and worsened, the patient will be assigned to the 'Yes' category, otherwise 'No'), region (Asia, North America/Europe, southern hemisphere), and weight (< 80 kg, ≥ 80 kg). The registration center manager will prepare and complete the randomization procedures/processes.

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 IWRS will be used for central patient randomization and study drug assignment. IWRS 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, the investigator, all 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, IWRS clinical coordinators, IWRS vendor staff, the unblinded statistician on the Data Safety Monitoring Board (DSMB), and 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 IWRS.

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. Following emergency unblinding, patients should remain in the study until the end of the follow-up period where practical.

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

5.6 Packaging and Labeling

The study drugs will be supplied in wallet cards 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 labeled 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 IWRS or on the label according to local regulations. Study drug should not be used after the expiry or use by date. All packaged and labeled 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 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 following 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 the 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 Study Site

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 the sponsor'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 (coadministration of S-033188, oseltamivir, and placebo) will be recorded in the source documents and the eCRFs. Patients must bring their tablet 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 tablet card is empty. The investigator or subinvestigator will review the tablet cards to verify that the correct number of doses has 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. Based on 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 the study drugs as directed.

6. RESTRICTIONS

6.1 Prior Therapy

Prior therapies are defined as therapies that 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 ET) 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 ET.

- Systemic antiviral drugs (excluding antiretrovirals for the treatment of HIV infection or herpes simplex virus (HSV) suppressive therapy)
- Antimicrobial* and antifungal drugs**
- Antipyretics/analgesics except provided acetaminophen/paracetamol***
- Antitussives and expectorants
- Combination cold remedies
- Antihistamines**
- 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, and ears or by inhalation will be prohibited.

*** Low dose aspirin for cardiovascular disease prophylaxis will be acceptable.

6.2.2 Rescue Therapy (Noninvestigational 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 or paracetamol 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/paracetamol 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/paracetamol 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/paracetamol or more than 4 hours after acetaminophen/paracetamol administration.

6.3 Other Restrictions

6.3.1 Contraception

Women of childbearing potential (WOCBP) should use 1 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 device (IUD)
- Intrauterine 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 is included in [Appendix 1](#).

7.1 Informed Consent

The investigator or subinvestigator will fully explain the nature of the study to a patient and parent(s)/legally acceptable representative using the Institutional Review Board (IRB)/Independent 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.

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.

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. Informed consent will be obtained from parent(s)/legally acceptable representative of all patients. A patient cannot be entered the study until his/her parent(s)/legally acceptable representative has signed and dated the consent form.

7.2 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: preexisting date of written informed consent by the patient/guardian, date of birth, sex, ethnicity, race, current smoking status, prior therapy, and medical history. Medical history will include any previous medical condition requiring hospitalization, all concurrent medical conditions, surgical history (within 12 months), presence or absence of influenza vaccination within the last 6 months, and duration of influenza symptoms.

7.2.1 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.

7.2.2 Meals

To collect information on meals before and after the initial study treatment (coadministration of S-033188, oseltamivir, and 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 Interactive Response Technology (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. With Table 7-1 as a guide, the patient will measure body temperature when it is possible to do so. 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
Days 1 to 3	Morning	- 9:59
	Noon	10:00 to 14:59
	Evening	15:00 to 19:59
	Bedtime	20:00 -
Days 4 to 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
Days 1 to 9	Morning	- 11:59
	Evening	18:00 -
Days 10 to 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 it 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 Windows of Assessment as a Guide: Assessment of Health

Assessment Period	Time Period of a Day	Time Window as a Guide
Days 1 to 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 CPI

The CPI 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), Optional Visit 1 (Day 4), Visit 4 (Day 5), Optional Visit 2 (Day 6), and Visit 5 (Day 9), as well as at Visit 6 (Day 15) and Visit 7 (Day 22) if the investigator determines that flu symptoms are persisting. 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, patients 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 Pharmacokinetic 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), and at 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 -20°C or below. Detailed procedures for the sample collection, handling, and shipping to the bioanalytical laboratory 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

A full physical examination will be performed at Visit 1 (Day 1) and 7 (Day 22) according to the normal practice of the clinical study site by the investigator or subinvestigator in order to check for any AEs (see Section 7.6.5.1). In addition, symptom-focused physical examinations 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 and entered in the eCRF, along with BMI, at the predose examinations only.

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 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). 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

12-lead ECG will be performed by the investigator or designee at Visits 1 (Day 1), 2 (Day 2), and 7 (Day 22). 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. Results of the ECG and its interpretation also will be entered in the eCRF.

7.6.4 Clinical Laboratory Tests

7.6.4.1 Laboratory Parameters

Blood and urine samples for clinical laboratory tests will be collected Visits 1 (Day 1), 4 (Day 5), 6 (Day 15), and 7 (Day 22), and the date of specimen collection will be entered in the eCRF. Patients will remain in a sitting or supine position during blood collection. The blood sample volumes for clinical laboratory, serum influenza antibody titer, and immunological tests are shown in Table 7-4 below.

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	3.5 - 5 mL
Hepatitis C virus antibody	
HIV antigen/antibody	
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).

Table 7-5 **Routine Laboratory Tests**

Category	Evaluation Items
Hematology tests	Hematocrit (Hct), hemoglobin (Hgb), platelet count, erythrocyte count, and leukocyte (white blood cell [WBC]) count with differential (eosinophil count, basophil count, neutrophil count, monocyte count, lymphocyte count)
Blood chemistry tests	Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBL), direct bilirubin, indirect bilirubin, alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH), blood urea nitrogen (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 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 predose at Visit 1 (Day 1), Visit 4 (Day 5), and Visit 7 (Day 22) or ET.

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 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 Event 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 investigational 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 an investigational product, whether or not considered related to the investigational 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 nonleading 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 that are reported at baseline and worsen 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 the start date, end date (if outcome is other than recovering, not recovered, or unknown), severity, seriousness with a reason of seriousness, 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:

- **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.

Severity assessment will be based upon The Common Terminology Criteria for Adverse Events (CTCAE, Version 4), and can be found at:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

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 that 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 that cannot be reasonably explained as having been caused by the study drug.

7.6.5.5 Expectedness

An AE is expected if it is listed in Expected Adverse Reactions:

- S-033188: In Section “Undesirable Effects” of “SUMMARY OF DATA AND GUIDANCE FOR INVESTIGATORS” in the current Investigator's Brochure (IB) for S-033188.
- Oseltamivir phosphate (Tamiflu®): The current version of the Prescribing Information in the US for oseltamivir phosphate capsules in accordance with its approved license/marketing authorization.

7.6.5.6 Adverse Event Assessment of Clinical Laboratory and Other Safety Parameters

For laboratory test results (hematology, blood chemistry, or urinalysis) that worsen from baseline or other abnormal safety assessments (eg, physical examinations, vital sign measurements, ECGs), the investigator or subinvestigator will consider whether these results are clinically significant. Abnormal laboratory test results are defined as values outside the reference range. For test results that are abnormal at baseline and significantly worsen following the initiation of the study, the investigator or subinvestigator must also consider whether these results are clinically significant. Any test results that are considered to be clinically significant by the investigator or subinvestigator are to be recorded as AEs. If an abnormal laboratory finding is associated with disease or organ toxicity, the investigator should report only the disease or organ toxicity as an AE.

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 7.6.5.7.1)
- Test result leads to a change in study drug dosing or discontinuation from the study
- 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 identified in [Section 7.6.5.8](#)

In addition, when any test result meets the management and discontinuation criteria for liver function abnormalities ([Section 7.6.5.8](#)), the results of further assessments and required follow-up should be recorded in the Liver Event Form.

7.6.5.7 Serious Adverse Events

7.6.5.7.1 Definition

An SAE is defined by international regulations as an 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 an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical intervention to prevent 1 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. The investigator or subinvestigator will determine the seriousness of all AEs. Test results that meet the following criterion are considered an SAE:

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

Hospitalization for preplanned procedures or for elective procedures to treat a preexisting condition that did not worsen after study start will not be considered AEs or SAEs. The exception is when the patient experiences another event or has an outcome that is fatal, is life-threatening, leads to prolonged hospitalization, or is considered to be medically significant during/following the procedure. Where applicable, the diagnosis should be reported as the AE instead of the individual symptoms and signs.

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 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 the SAE via EDC or if EDC is unavailable, prepare an SAE Form and fax or e-mail the completed form within 24 hours to:

CRO SAE hotline – North America:
Telephone: PPO [REDACTED]

Fax: PPO
PPO

OR

CRO SAE hotline – Europe and Asia-Pacific:

Telephone: PPO

Fax: PPO
PPO

If follow-up is required or requested, the investigator should enter the new information into EDC. Discharge summaries, medical reports from other departments or other hospitals, autopsy reports, or other relevant documents must be evaluated by the investigator and all relevant information must be included in the follow-up SAE report. 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 is considered to be related to study drug by the investigator must be reported to the sponsor.

The investigator will be responsible for reporting all SAEs to the IRB or IEC through the head of the medical institution in accordance with the local regulatory requirement. The sponsor or its designee 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 $> 3 \times$ upper limit of normal (ULN) and total bilirubin (TBL) $> 2 \times$ ULN
- AST or ALT $> 3 \times$ 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 $> 5 \times$ ULN
- AST or ALT $> 3 \times$ 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 (the sponsor's medical monitor) via fax by the investigator using a Special Situations Report Form as soon as possible. If the special situation that occurred is an SAE, the investigator will complete the SAE Form 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

If a female patient becomes pregnant during the study, the investigator (or subinvestigator) must instruct her to discontinue all study drugs and inform the sponsor immediately. In addition, the investigator (or subinvestigator) must attempt to collect pregnancy information on any female partners of male study patients who become pregnant while the patient is enrolled in the study. Pregnancy information must be reported to the CRO or sponsor as described below.

All pregnancies that occur after the first dose of the study drug through the follow-up period must be reported to the sponsor or CRO within 24 hours of the investigator (or subinvestigator) becoming aware of the pregnancy and the Pregnancy Form will be faxed to the sponsor or CRO by the investigator. Pregnancy complications and elective terminations for 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, which must be faxed to the sponsor. All pregnancies that are confirmed after the follow-up visit but within 3 months of last study drug dose should be reported to the sponsor and followed to completion by the study site. At the end of the pregnancy (ie, birth, miscarriage, abortion), the outcome should be reported to the CRO or sponsor.

7.7 Other Assessments

7.7.1 Serum Influenza 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 testing, 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 CPI

CPI

7.7.5 Work Productivity Questionnaire

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

The work productivity questionnaire will be completed on paper.

7.8 Withdrawal of Patients from the Study or Study Treatment

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 IWRS.

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 is lost to follow-up
- The investigator determines that the patient should be withdrawn because of other reasons
- The investigator determines that the patient should be withdrawn based on the management and discontinuation criteria for abnormal liver function tests

In the event of a patient's withdrawal, the investigator will promptly notify the sponsor and will make every effort to complete the end-of-study (or ET) assessments. All patients withdrawn due to AEs will be followed until resolution of any AEs, until the unresolved AEs are judged by the investigator to have stabilized, or the patient is lost to follow-up. The date of completion (if completed the follow-up period), date of discontinuation (if discontinued before Day 22), period of discontinuation, and reason for discontinuation will be entered in the eCRF.

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, commercially-available influenza antivirals (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

The time to improvement of symptoms is defined as the time to improvement of 7 influenza symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue). The 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. Since some “high risk” individuals may have underlying chronic diseases that share some symptoms with those of influenza (ie, cough in a patient with chronic lung disease), a modification of time to alleviation has been included in this protocol to permit improvement of a symptom that may have been present before the onset of influenza but worsened by influenza, or maintenance of a preexisting symptom that has not been worsened by the onset of acute influenza. This is a novel and untested endpoint but is considered by the sponsor to be a reasonable approach to avoid confounding of results due to persistent preexisting symptoms that cannot be completely alleviated.

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).

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 the time to resolution of fever.

Examining the change from baseline in influenza virus titer will enable the assessment of the relationship between antiviral activity and clinical symptoms.

An assessment of the intra-household infection rate will provide useful information on the transmissibility of influenza infection after treatment with S-033188.

7.9.3 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 CPI .

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.

7.9.4 Safety Endpoints

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

7.9.5 Plasma Drug Concentrations

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

7.10 Allowable Time Windows

Measurements will be performed according to the schedule as shown in [Appendix 1](#). The time windows 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 Acceptable Time Windows for the Measurement of Plasma Drug Concentrations

Visit (Day)	Acceptable Time Window ^a
Predose at Visit 1 (Day 1)	Predose on Day 1
Postdose at Visit 1 (Day 1)	QOL assessment with CPI : by 0.5 hour postdose on Day 1 Other measurements: 0.5 to 4 hours postdose on Day 1
Visit 2 (Day 2)	Day 2
Visit 3 (Day 3)	Day 3 to Day 4
Optional Visit 1 (Day 4)	Day 4
Visit 4 (Day 5)	Day 5 to Day 6
Optional Visit 2 (Day 6)	Day 6
Visit 5 (Day 9)	Day 7 to Day 11
Visit 6 (Day 15)	Day 12 to Day 18
Visit 7 (Day 22)	Day 19 to 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 Acceptable Time Windows for Blood Sample Collection
for the Measurement of Plasma Drug Concentrations**

Measurement	Visit (Day)	Acceptable Time Window
Blood sample collection for the measurement of plasma drug concentrations	Visit 1 ^a (Day 1)	0.5 to 4 hours postdose (Day 1)
	Visit 2 (Day 2)	Day 2
	Visit 3 ^a (Day 3)	Day 3 to Day 4
	Visit 4 (Day 5)	Day 5 to Day 6
	Visit 6 ^a (Day 15)	Day 12 to 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 a 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 will 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 nonmissing 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 2-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, a 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 the 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 and by patient. All analyses and tabulations will be performed by using both 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 is 1185 patients (395 patients for each treatment group). It is assumed that the RT-PCR-positive rate will be 55% of the randomized population. Therefore, 2157 patients (719 patients for each treatment group) 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 of the time to improvement of influenza symptoms is to compare between the S-033188 group and placebo group.

The median of the time to alleviation of symptoms in the placebo-controlled clinical trial of oseltamivir for high risk patients was estimated to be 161.0 hours (95% CI: 117.3, 215.5) in the placebo group [6]. Based on this result and the fact that the proposed study

will use a modified primary endpoint, it was assumed that the median time to improvement of influenza symptoms in the placebo group will be 150 hours.

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

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

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

Using a 1:1 randomization ratio between the S-033188 group and the oseltamivir group, the ITTI population of oseltamivir will be 395 patients. Table 9-1 shows the statistical power to compare between the S-033188 group and the oseltamivir group under several sets of assumed time to improvement of influenza symptoms.

Table 9-1 Statistical Power to Compare Between S-033188 and Oseltamivir

Median Time to Alleviation of Symptoms (S-033188, Oseltamivir)	Statistical Power for Comparison Between S-033188 and Oseltamivir by Generalized Wilcoxon Test
(114 hours, 126 hours)	22.3%
(108 hours, 126 hours)	45.3%
(102 hours, 126 hours)	71.5%
(96 hours, 126 hours)	90.2%

9.3 Analysis Populations

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

- **Intention-to-treat infected population** includes all patients who receive the study drug with a confirmed duration of influenza symptoms. 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.
- **Safety population** includes all randomized patients who receive at least 1 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.
- **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 deviations
 - Patients with study procedure deviations
 - Patients with inadequate follow-up
- **PK concentration population** includes all patients who receive at least 1 dose of S-033188 and have at least 1 evaluable PK assay result of S-033447. This population will be used for the concentration listing.
- **PK parameter population** includes all patients with at least 1 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 percent of patients who complete the study and the number and percent of patients who prematurely discontinue from 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 percent 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 the 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 received prior therapy 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 summarized by treatment group. The number of patients using each concomitant therapy will also be counted. Patients who received concomitant therapies will be listed for the safety population.

9.10 Efficacy Analyses

The ITTI will be the primary population for efficacy analyses. The PPS will be used for sensitivity analyses.

9.10.1 Primary Efficacy Endpoint Analyses

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

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

- Maintenance of baseline severity is as follows:
 - Severe → Severe
 - Moderate → Moderate
- For new symptoms at baseline (ie, the predose examinations), alleviation of symptoms assessment will not be modified
 - Alleviation of symptoms is as follows:
 - Severe → mild or absent
 - Moderate → mild or absent

Once all of a patient's influenza symptoms are alleviated, maintained, or improved as defined above, the endpoint for that patient will be reached, 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 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 < the lower limit of quantification among those assessed for virus titer, and the percentage of patients with detectable virus RNA among assessed by RT-PCR, respectively.

- 2) Change from baseline in virus titer and in the amount of virus (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 the initial dose.

- 3) AUC adjusted by baseline in virus titer and in the amount of virus RNA (RT-PCR)

Defined as AUC, where AUC is the area under the curve, 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 < the lower limit of quantification and the time between the initiation of the study treatment and first time when virus RNA by RT-PCR is < the lower limit of quantification, respectively.

- 5) Proportion of patients whose symptoms has been alleviated at each time point

Defined as the percentage of patients whose primary endpoints are improved after the initiation of the study treatment in the analysis population by each time point.

- 6) Time to alleviation of symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue)

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 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%).

- 7) Time to improvement in the 4 systemic symptoms (headache, feverishness or chills, muscle/joint pain, and fatigue)

Defined as the time between the initiation of the study treatment and the improvement in the 4 systemic symptoms. The assessment follows the criteria for the primary endpoint.

- 8) Time to improvement in the 3 respiratory symptoms (cough, nasal congestion, and sore throat)

Defined as the time between the initiation of the study treatment and the improvement in the 3 respiratory symptoms. The assessment follows the criteria for the primary endpoint.

- 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 temperature becomes $< 37^{\circ}\text{C}$ and is maintained at $< 37^{\circ}\text{C}$ 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 temperature resolves to $< 37^{\circ}\text{C}$ 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 improvement of each influenza symptom

Defined as the time between the initiation of the study treatment and the alleviation of each influenza symptom. The alleviation of a symptom is defined as the time when the symptom is assessed as 0 (None) or 1 (Mild), for a 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]). 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) Requirement for systemic antibiotics for infections secondary to influenza infection

Defined as the percentage of patients treated with systemic antibiotics.

15) Incidence of influenza-related complications (hospitalization, death, sinusitis, bronchitis, otitis media, and radiologically confirmed pneumonia)

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 adverse event 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

9.10.3.1 Analyses of Primary Endpoint

9.10.3.1.1 Primary Analysis

The stratified generalized Wilcoxon test will be applied to the primary endpoint with some stratification factors, namely baseline symptom score (≤ 14 , ≥ 15), preexisting and worsened symptom (Yes, No), and region (Asia, North America/Europe, Southern Hemisphere) to evaluate the efficacy of S-033188 compared with placebo.

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

9.10.3.1.2 Secondary Analysis

The same analysis method and endpoint as the primary analysis will be used to evaluate the efficacy of S-033188 compared with oseltamivir.

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 the PPS will be performed as a sensitivity analysis.

9.10.3.1.3 Other Analyses

In addition, a Kaplan-Meier survival curve will be plotted for each group, and the median times, the differences of the median times, and their 95% CIs will be calculated.

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

9.10.3.2 Analyses of Secondary Endpoints

- 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 \geq the lower limit of quantification will be included in the analyses. The summary table by each time

point will be made. The Mantel-Haenszel test at each time point will be used to compare the proportion of patients with positive virus titer/RT-PCR between S-033188 and oseltamivir/placebo with baseline symptom score (≤ 14 , ≥ 15), preexisting and worsened symptom (Yes, No), and region (Asia, North America/Europe, Southern Hemisphere) as stratification factors.

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

Only patients whose virus titer/RT-PCR predose at Visit 1 are \geq the lower limit of quantification will be included in the analyses. The van Elteren test will be used by each time point to compare the S-033188 with oseltamivir/placebo, where baseline symptom score (≤ 14 , ≥ 15), preexisting and worsened symptom (Yes, No), region (Asia, North America/Europe, Southern Hemisphere) will be included as stratification factors. Summary statistics will be calculated by time point and by treatment group.

- 3) AUC adjusted by baseline in virus titer and in the amount of virus RNA (RT-PCR)

Only patients whose virus titer/RT-PCR predose at Visit 1 are \geq the lower limit of quantification will be included in the analyses. The same statistical methods as 2) change from baseline in virus titer and the amount of virus RNA (RT-PCR) at each time point will be used. Summary statistics will be calculated by treatment group.

- 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 \geq the lower limit of quantification will be included in the analyses. The same analyses as the primary endpoint will be performed.

- 5) Proportion of patients whose symptoms has been alleviated at each time point

The same analyses as 1) proportion of patients positive for influenza virus titer and proportion of patients positive by RT-PCR will be used.

- 6) Time to alleviation of symptoms

The same analyses as the primary endpoint will be performed.

- 7) Time to improvement in the 4 systemic symptoms (headache, feverishness or chills, muscle/joint pain, and fatigue)

The same analyses as the primary endpoint will be performed.

- 8) Time to improvement in the 3 respiratory symptoms (cough, nasal congestion, and sore throat)

The same analyses as the primary endpoint will be performed.

- 9) Time to resolution of fever

The same analyses as the primary endpoint will be performed.

10) Proportion of patients reporting normal temperature at each time point

The summary table by each time point will be made. The Mantel-Haenszel test at each time point will be used to compare the proportion of resolution of fever between S-033188 and oseltamivir/placebo with baseline symptom score (≤ 14 , ≥ 15), preexisting and worsened symptom (Yes, No), and region (Asia, North America/Europe, Southern Hemisphere) as stratification factors.

11) Body temperature at each time point

The summary table by each time point will be made. The analysis of covariance (ANCOVA) will be used by each time point to compare body temperature between S-033188 and oseltamivir/placebo, where composite symptoms score at baseline, and preexisting and worsened symptom (Yes, No), and region (Asia, North America/Europe, Southern Hemisphere) will be used as covariates.

12) Time to improvement of each influenza symptom

The same analyses as the primary endpoint will be done. Patients whose symptoms at baseline are assessed as 0 (None), 1 (Mild), 2 (Moderate) but preexisting and not worsened, or 3 (severe) but preexisting and not worsened will be excluded from the analysis.

13) Time to return to preinfluenza health status

The same analyses as the primary endpoint will be performed.

14) Requirement for systemic antibiotics for infections secondary to influenza infection

A summary table will be created. The Fisher's exact test will be used to compare the percentage of patients who used systemic antibiotics for infections secondary to influenza infection between S-033188 and oseltamivir/placebo.

15) Incidence of influenza-related complications (hospitalization, death, sinusitis, bronchitis, otitis media, and radiologically-confirmed pneumonia)

A summary table will be created. Fisher's exact test will be used to compare the incidence between S-033188 and oseltamivir/placebo.

9.11 Safety Analyses

The safety population will be used for safety analyses.

9.11.1 Adverse Events

Adverse events 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 experienced 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, also will be presented. Treatment-related AEs will be summarized in the same manner as AEs described above.

The number and percentage of patients who experienced AEs by MedDRA system organ class (SOC) and preferred term (PT) will be presented for each treatment group. The summary for timing of onset, severity, action taken with the study drug, and outcome will be presented by SOC and PT. 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 2-dimensional contingency table by treatment group.

9.11.4 Electrocardiography

Electrocardiography will be performed to assess the presence of acute conditions that may exclude patients or conditions in the opinion of the investigator 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) postdose (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 $SD/Mean \times 100$), 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 analysis populations 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 the C_{24} and the 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 Analyses

9.13.1 Serum Influenza Antibody Titer

Serum influenza 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 the 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 the 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 CPI [redacted] and CPI [redacted]

The combination of the CPI [redacted] and the CPI [redacted] will be presented as:

- change in the index value from baseline to each time point
- change in the CPI [redacted] from baseline to each time point

9.13.4.2 Work Productivity Questionnaire

Analysis variables and analysis methods will be specified in the SAP.

9.13.5 Intra-household 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. If the study extends beyond 1 Northern Hemisphere influenza season, an interim analysis may be considered.

10. ADMINISTRATIVE CONSIDERATIONS

10.1 Study Administrative Structure

Sponsor for Japan, Taiwan, South Korea, and Hong Kong: Shionogi & Co., Ltd.
(Head Office) 1-8, Doshomachi 3-chome, Chuo-ku, Osaka 541-0045, Japan

Sponsor for North America: Shionogi Inc.
300 Campus Drive, Florham Park, NJ 07932 USA

Sponsor for Australia, Europe, New Zealand, and South Africa: Shionogi Ltd.
5th floor, 33 Kingsway, London WC2B 6UF, United Kingdom

Sponsor's Contact: PPO [redacted]

PPO [redacted]

PPO [redacted]

Sponsor's PPO [redacted]: PPO [redacted]
PPO [redacted] PPO [redacted]

Medical Monitor in CPI [redacted] CPI [redacted]
Medical Monitor in CPI [redacted] CPI [redacted]

Medical Monitor in CPI
[Redacted]

PPO
[Redacted]

Investigator and Study Center:
Study Monitoring:

Multicenter
CPI
[Redacted]

CPI
[Redacted]

Clinical Laboratory for North
America:

CPI
[Redacted]

Clinical Laboratory for Europe:

CPI
[Redacted]

Clinical Laboratory for
Asia-Pacific:

CPI
[Redacted]

Bioanalytical Laboratory:

CPI
[Redacted]

Registration Center, **CPI** :

CPI
[Redacted]

[Redacted]

[Redacted]

Virology Testing Laboratory:

CPI
[Redacted]

CPI
[Redacted]

eDiary:

CPI
[Redacted]

10.2 Institutional Review Board or Independent Ethics Committee 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 Form, written information on patient recruitment procedures (if applicable), other written information given to the patients, Investigator's Brochure, 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

The investigator will generate an informed consent form for the study. The sponsor will provide the investigators with a proposed informed consent form that complies with the ICH GCP and regulatory requirements. The consent 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 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, methods, reasonable anticipated benefits, and potential hazards of the study to the patient in simple terms by using the consent form approved by the IRB/IEC before the patient is entered into the study. The method of obtaining and documenting informed consent will comply with ICH GCP and all applicable regulatory requirements.

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 monitors and auditors 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 number. 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 a designee will monitor the study to ensure that the study is conducted in accordance with ICH GCP requirements and the 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 will supply eCRFs. The eCRF 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 are promptly entered in the eCRFs in accordance with the specific instructions given. Electronic case report form entries will be performed by an investigator, subinvestigator, and study coordinator who are authorized in documentation. Data should be entered within 3 days after each patient's visit.

When queries are generated to the participating medical institutions for resolution by the sponsor or designee, eCRF data will be changed or a response will be recorded in accordance with the specific instructions given. The investigator must ensure that data reported on 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 a part of the documentation to be collected prior to the initiation of 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 all the reference ranges for the laboratory tests to be analyzed 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 can be directly recorded on an eCRF as source data:

- Reason for use of prior therapy or concomitant therapy
- Severity, seriousness, causal relationship to the study drug of AE
- Any comments inserted into eCRF

Listed below are data captured only in the eCRF (ie, items automatically-calculated by the electronic data capture system):

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

The investigator must maintain source documents, such as laboratory reports, and complete medical history and physical examination reports. All the source documents must be accessible for verification by the site monitor(s), auditor(s), the IRB/IEC, and inspections of regulatory authority. 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 eCRF, the nature and location of the source documents will be identified by the sponsor and the site staff. If electronic records are maintained at the medical institution, the method of verification must be specified in document within the medical institution.

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 test (determined according to procedures specified in a separate document)
- Safety laboratory tests

10.9 Committees

10.9.1 Independent Data Safety Monitoring Board

An independent DSMB will be established for this study. Details of the DSMB composition, roles and responsibilities, and processes will be documented in a separate DSMB charter.

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 serious, treatment-related AEs)
- Achieving the purpose of the study is considered impossible (eg, interim data suggesting lack of safety, inadequate recruitment of patients)

If the study is prematurely terminated or suspended, the sponsor will 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 Medical Institution

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 SAEs).

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

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

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 and the regulatory authorities. 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 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 by the investigator and the IRB will provide expedited review and approval. After obtaining approval from the IRB, 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 or a designee 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 as specified in the ICH GCP and as required by the 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 the longer of either 1 of the following periods:

- Until the approval day of manufacturing/marketing on the study drug or 3 years after the decision day on the discontinuation of development
- 3 years after the decision day on the 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 a person willing to accept the responsibility.

10.14 Quality Control and Assurance

The sponsor or a 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 supplied by the sponsor to the investigator is privileged and confidential. The investigator agrees to use this information to accomplish the study and will not use it for 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 clinical trial will be used toward the development of S-033188 and may be disclosed to regulatory authorities, other investigators, corporate partners, or consultants as required.

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

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

1. Reaper R, Landry, M. Rapid Diagnosis of Influenza. In Mandell, Douglas, and Bennett's Principle and Practice of Infectious Diseases: Latest Developments in Influenza With Accompanying Clinics Review Articles. First Edition. Elsevier Inc. 2014 p. 2011-2013.
2. Monto AS, Gravenstein S, Elliott M, Colopy M, Schweinle J. Clinical signs and symptoms predicting influenza infection. *Arch Intern Med.* 2000;160:3243-3247.
3. Centers for Disease Control and Prevention. CDC HEALTH ALERT: CDC recommends against the use of amantadine and rimantadine for the treatment or prophylaxis of influenza in the United States during the 2005-06 influenza season. 2006.
4. Centers for Disease Control and Prevention. People at high risk of developing flu-related complications. http://www.cdc.gov/flu/about/disease/high_risk.htm.
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6. Jefferson T, Jones MA, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in adults and children. *Cochrane Database of Systematic Reviews* 2014, Issue 4.
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9. European Medicines Agency. Tamiflu®: European Public Assessment Report – Product Information. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000402/human_med_001075.jsp&mid=WC0b01ac058001d124.
10. Influenza Antiviral Medications: Summary for Clinicians. Centers for Disease Control and Prevention. <http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm>. (Accessed 13 July 2016).
11. Fiore AE, Fry A, Shay D, et al. Antiviral agents for the treatment and chemoprophylaxis of influenza - Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2011;60:1–24.
12. Dobson J, Whitley RJ, Pocock S, Monto AS. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. *Lancet.* 2015 May 2;385(9979):1729-37. Erratum in: *Lancet.* 2015 May 2;385(9979):1728.

13. Muthuri SG, Venkatesan S, Myles PR et al PRIDE Consortium Investigators, Nguyen-Van-Tam JS. Impact of neuraminidase inhibitors on influenza A(H1N1)pdm09-related pneumonia: an individual participant data meta-analysis. *Influenza Other Respir Viruses*. 2016 May;10(3):192-204.
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15. Hsu J, Santesso N, Mustafa R, Brozek J, Hopkins JP, Cheung A, et al. Antivirals for treatment of influenza: a systematic review and meta-analysis of observational studies. *Ann Intern Med*. 2012;156(7):512-524.
16. Havers F, Flannery B, Clippard JR, Gaglani MJ, Zimmerman RK, et al. Use of influenza antiviral medications among outpatients at high risk for influenza-associated complications during the 2013-2014 influenza season. *Clin Infect Dis*. 2015;60(11):1677-1680.

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/ 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									
	CPI	X ^d	Twice Daily					Once Daily									
	Assessment of Health	X ^d	Once Daily														
Assessment of Health Prior to Influenza Symptoms		X ^d															
WP 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 (hematology and blood chemistry)		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 ^{h,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 Assessments	X	X	X	X	X	X			X						X	X
Record if Meal Eaten and Time	X															
Intrahousehold Infection Interview (for Japan only)	X	X	X		X				X						X	

D = day; eDiary = electronic diary; CPI [redacted]; ET = early termination; OpV= optional visit; V = visit; WOCBP = women of childbearing potential; WP = work productivity

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

Appendix 2

Quality-of-Life Questionnaire

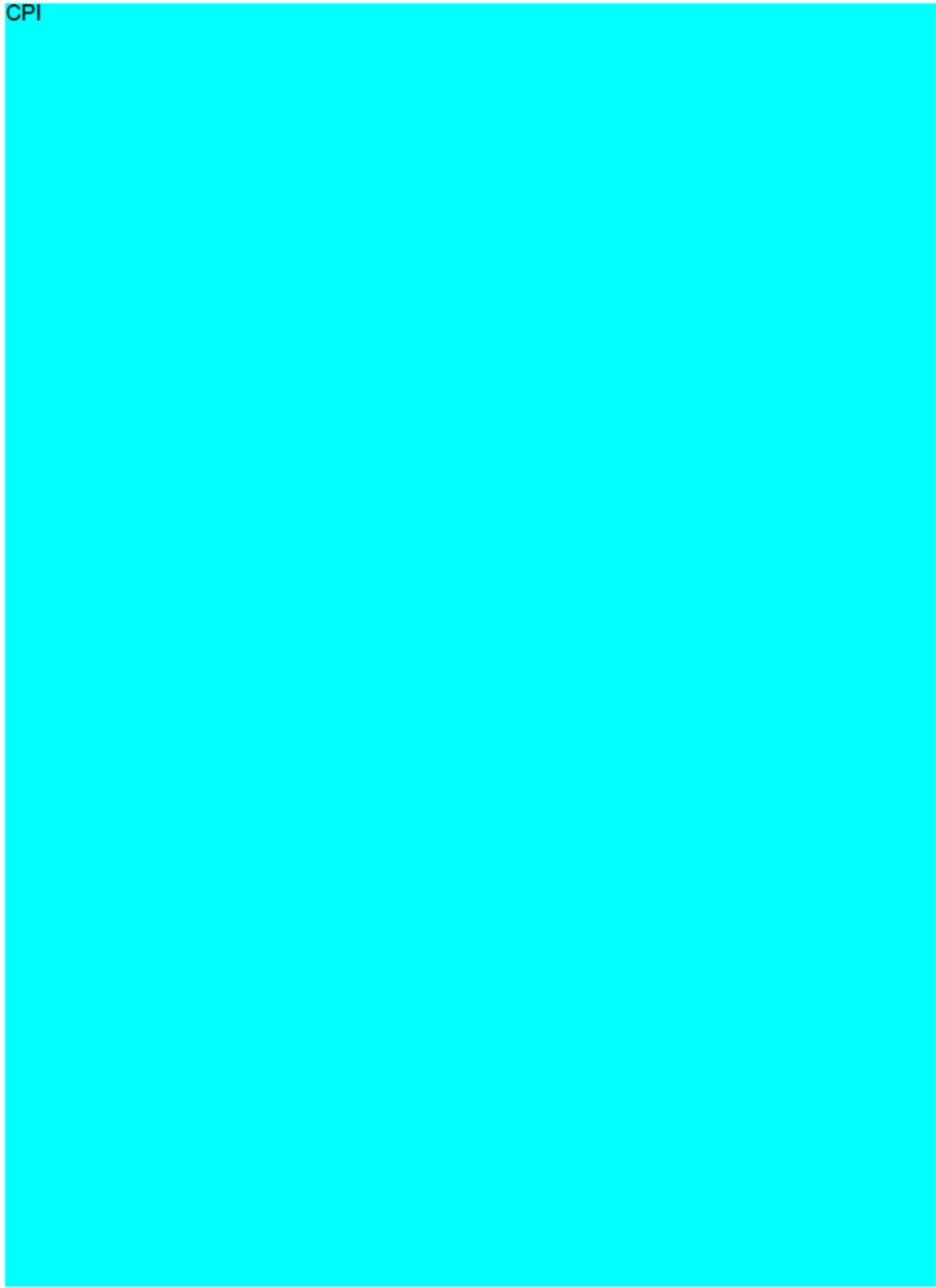
CPI [Redacted]

CPI [Redacted]

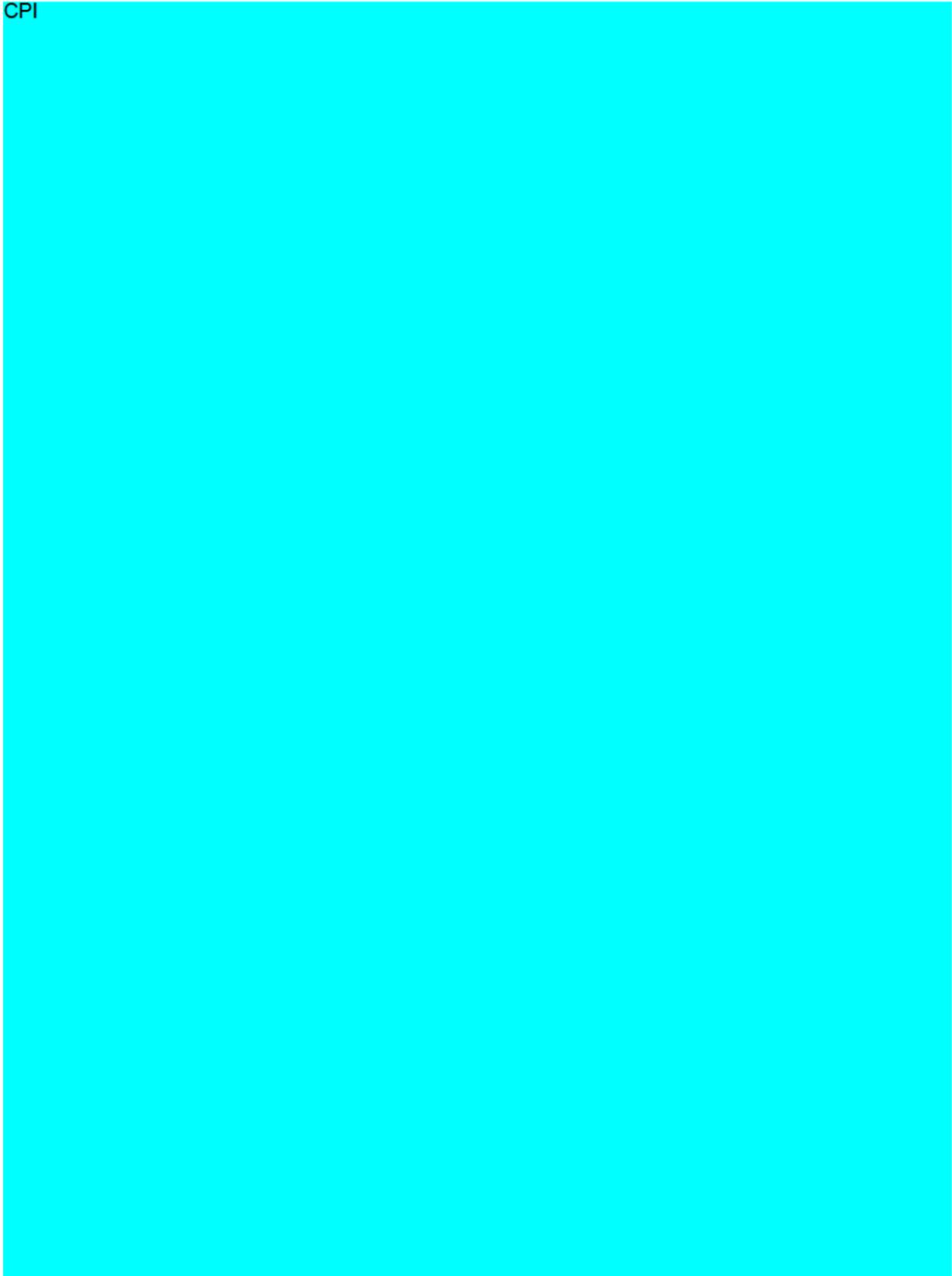
Study center name	
Patient identification code	
Visit	
Date	

Under each heading, please tick the ONE box that best describes your health TODAY.

CPI



CPI



Appendix 3 Work Productivity 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 earliest clinic visit following resolution of symptoms.

1. How many hours or days per week do you work (eg, full or part time paid work, voluntary work, or study)?
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 5 Management Criteria for Abnormal Liver Function Tests

Management 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 $> 5 \times$ ULN
- b. AST or ALT $> 3 \times$ ULN and total bilirubin (TBL) $> 2 \times$ ULN or PT-INR > 1.5 , if PT-INR is measured.
- c. AST or ALT $> 3 \times$ 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, TBL) 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
- Concomitant medications: OTC/herbal/dietary supplements (start and stop dates)
- 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 TBL of $> 1.5 \times \text{ULN}$, 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 restart 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 $\text{ALT} > 5 \times \text{ULN}$ to $\leq 8 \times \text{ULN}$ elevations for < 2 weeks may restart the administration of the study drug 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.

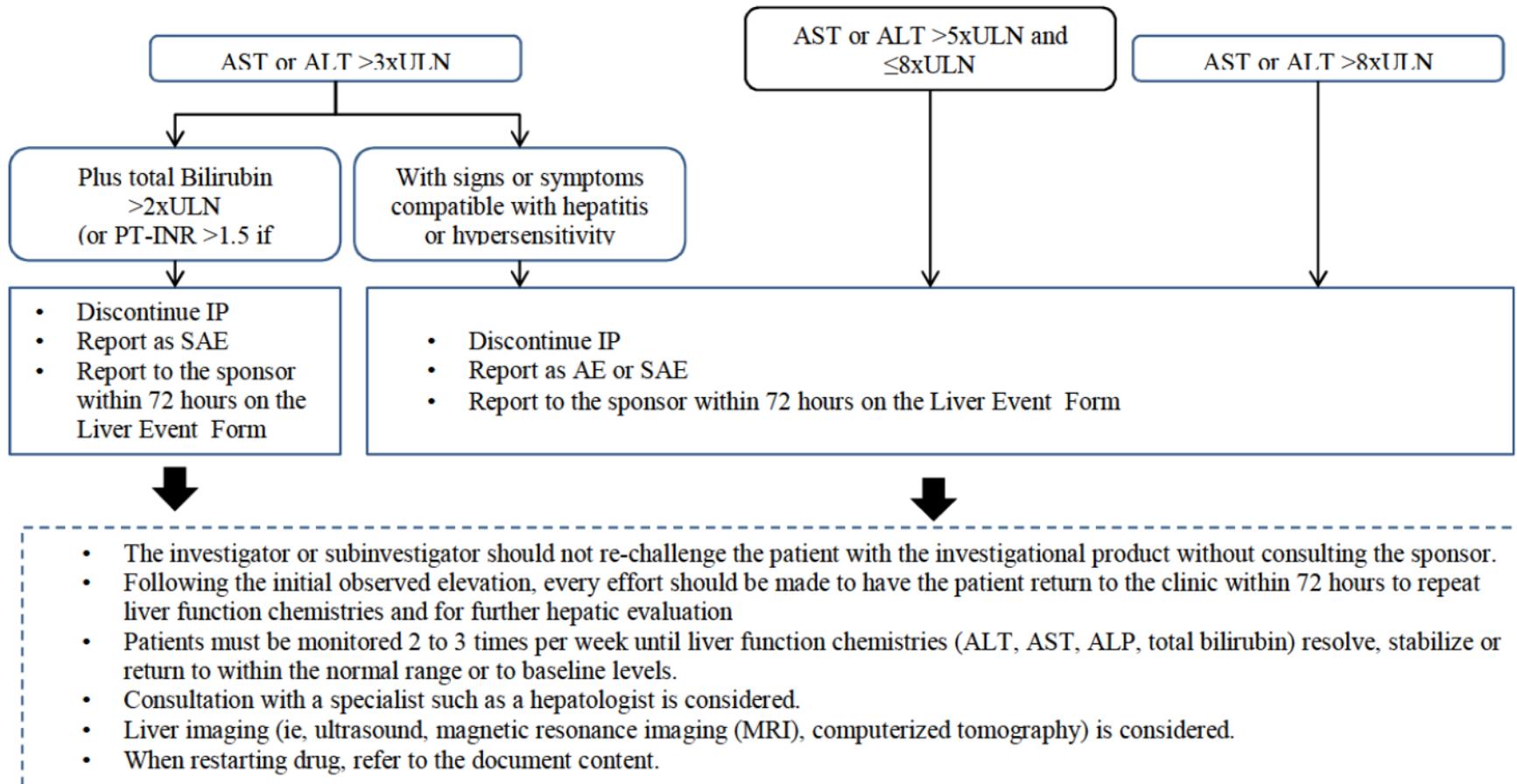
5. Drug Discontinuation Criteria Due to Abnormal Liver Chemistry Tests

Patients must be discontinued from the study as described below:

- a. AST or $\text{ALT} > 8 \times \text{ULN}$, confirmed by follow-up testing (ie, initial abnormality is confirmed on subsequent testing), regardless of medical history or physical examination findings

- b. AST or ALT $> 5 \times$ 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 [$>5\%$])
- c. AST or ALT $> 3 \times$ ULN and total bilirubin $> 2 \times$ 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
- d. AST or ALT $> 3 \times$ 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)
- e. AST or ALT $> 5 \times$ ULN and the patient cannot be followed up weekly

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



Approval of the Protocol

Product Name: S-033188

Study Protocol 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 Patients with Influenza at High Risk of Influenza Complications

Study Protocol Number: 1601T0832

Edition Number: 03

Issue Date: 31 October 2016

Sponsor signatory:

This clinical study protocol was subject to critical review and has been approved by the sponsor:

Refer to electronic signature page

PPO

PPO

ID PPO

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Date: day-month-year

Signature Page

Document Information

Short Title :	Clinical Study Protocol: T0832, Phase 3 HR study-Amendment 02
Name :	E_PC_T0832_Ph3 DBT-HR_Ed03_Approved
Object ID :	CPI

Signature

Date : Oct 31, 2016 05:34:00
(GMT)

Signed by : PPO
(Name and ID)

Justification : Approved as PPO

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