2. SYNOPSIS

Sponsor: Shionogi	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of Finished Product Not applicable	**Volume:**	:
Name of Active Ingredient: Baloxavir marboxil (S-033188)	**Page:**	

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

Investigators and Study Centers: This was a multicenter study conducted at 551 sites, including 242 sites in the United States, 142 sites in Japan, 48 sites in APAC (including Australia, New Zealand, Philippines, and South Korea), 98 sites in Europe (Belgium, Germany, Hungary, Latvia, Poland, Romania, and Spain), and 21 sites in South Africa.

Publication (reference): Not applicable

Studied Period:

11 Jan 2017 (first patient signed Informed Consent Form) to 20 Apr 2018 (last patient completed)

Phase of Development: 3

Objectives:

Primary efficacy objective:

- To evaluate the efficacy of a single, oral dose of baloxavir marboxil 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 baloxavir marboxil 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 baloxavir marboxil compared with placebo by measuring the secondary endpoints in patients with influenza
- To evaluate the efficacy of a single, oral dose of baloxavir marboxil 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) and drug susceptibility in patients with evaluable virus

Safety objectives:

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

Pharmacokinetic (PK) objective:

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

Health economic outcomes research objective:

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

Methodology:

This was a randomized, double-blind, multicenter, parallel-group, placebo- and active-controlled study designed to evaluate the efficacy and safety of a single oral dose of baloxavir marboxil (40 or 80 mg depending on body weight) in patients ≥ 12 years old with influenza A and/or B infection, within 48 hours of symptom onset, and at high risk of developing influenza complications. Eligible patients were randomized in a 1:1:1 ratio to receive a single, oral dose of baloxavir marboxil (for 1 day, baloxavir marboxil group), repeated doses of oseltamivir (75 mg BID for 5 days, oseltamivir group), or placebo (placebo group). Patients were also stratified by the following 4 factors: baseline symptom score (≤ 14 or ≥ 15), preexisting and worsened symptom (if a patient had at least 1 of 3 symptoms [namely cough, muscle or joint pain, or fatigue] that was preexisting and worsened, the patient was assigned to the "Yes" category, otherwise "No"), region (Asia, North America/Europe, or Southern Hemisphere), and patient's weight (< 80 kg or ≥ 80 kg). The patients received the assigned study drug without regard to meals.

The study drug (baloxavir marboxil or matching placebo) was administered orally at the study center on Day 1 (initial dose) within 48 hours of onset of symptoms. Following receipt of the first dose of oseltamivir or matching placebo at the study center, patients received oseltamivir or matching placebo BID for 5 days. During the period of the efficacy and safety assessments (22 days), patients returned to the study center at Visit 2 to Visit 7 (Day 2, Day 3, Day 5, Day 9, Day 15, and Day 22) and some patients visited the study center at Optional Visit 1 (Day 4) and/or Optional Visit 2 (Day 6). The end of the study was defined as the last patient's last visit.

For efficacy assessment, patients self-measured/assessed the following outcome measures from predose on Day 1 through Day 14.

- Body temperature

  Axillary temperature was measured by the patient at predose on Day 1, and then 4 times daily (morning, noon, evening, and bedtime) until Day 3 and

BID (morning and evening) from Days 4 to 14.

- Severity of 7 influenza symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue)

  Severity of the symptoms was assessed by the patient on a 4-point rating scale (0, None; 1, Mild; 2, Moderate; 3, Severe) at predose on Day 1, and then BID (morning and evening) until Day 9 and once daily (evening) from Days 10 to 14.

- Assessment of health

  Health status was self-assessed by the patient on a scale of 0 (worst possible health) to 10 (normal health [for his/her age and condition]) at predose on Day 1 and then once daily (evening) until Day 14.

To perform virus typing and subtyping, and to measure virus titer and the amount of virus RNA, nasopharyngeal/pharyngeal swabs were collected predose at Visit 1 (Day 1) and at Visit 2 to Visit 5 (Days 2, 3, 5, and 9). Specimens were also collected from some patients at Optional Visit 1 (Day 4) and Optional Visit 2 (Day 6). When the investigator or subinvestigator determined that influenza symptoms were ongoing, specimens were also collected at Visit 6 (Day 15) and Visit 7 (Day 22) or early termination.

In order to calculate the intrahousehold infection rate, the patients at study centers in Japan were interviewed about household cases of influenza predose at Visit 1 (Day 1) and at Visit 2 to Visit 6 (Day 1 to Day 15).

For safety assessment, the following examinations and measurements were performed.

- Physical examination

  Full physical examination or symptom-focused physical examination was performed at every visit including optional visits and at early termination. Influenza-related complications (defined as meeting specific diagnostic criteria for sinusitis, bronchitis, otitis media, and radiologically proven pneumonia) were also investigated at all visits after Visit 1 (Day 1).

- Vital sign measurement

  Vital signs were measured at every visit including optional visits and at early termination.

- Electrocardiography (ECG)

  ECG was performed at Visit 1 (Day 1), Visit 2 (Day 2), Visit 7 (Day 22), and at early termination.

- Clinical laboratory tests

  Clinical laboratory tests were performed at Visit 1 (Day 1), Visit 4 (Day 5), Visit 6 (Day 15), Visit 7 (Day 22), and at early termination.

- Adverse events

  Adverse events were collected from the time of informed consent through Visit 7 (Day 22). If a patient withdrew early from the study, the investigator or subinvestigator made an effort to collect AEs for 21 days after the last dose of the study drug.

For PK assessments, blood samples were collected for the measurement of plasma S-033447 concentrations.

In addition, serum influenza antibody titer, substitutions of amino acid residues in the PA region, drug susceptibility, and health economic outcomes using EQ-5D-5L questionnaire/EQ Visual Analog Scale (VAS) and WP questionnaire were evaluated in this study.

Number of Patients (Planned and Analyzed):

Planned: 2157 patients (719 patients in each treatment group)

Consented: 2592 patients

Randomized: 2184 patients (730 patients in the baloxavir marboxil group, 725 patients in the oseltamivir group, 729 patients in the placebo group)

Analyzed for efficacy:

- Intention-to-treat Infected (ITTI) population: 1163 patients (388 patients in the baloxavir marboxil group, 389 patients in the oseltamivir group, 386 patients in the placebo group)
- Per-protocol Set (PPS) population: 1000 patients (335 patients in the baloxavir marboxil group, 332 patients in the oseltamivir group, 333 patients in the placebo group)

Analyzed for safety: 2178 patients (730 patients in the baloxavir marboxil group, 721 patients in the oseltamivir group, 727 patients in the placebo group); 6 patients received no study drug and were excluded from the Safety population

Analyzed for PK concentration: 664 patients in baloxavir marboxil group

Analyzed for PK parameters: 664 patients in baloxavir marboxil group

Analyzed for PK/PD relationships: 618 patients (232 patients in the baloxavir marboxil group, 386 patients in the placebo group)

Diagnosis and Main Criteria for Inclusion:

Patients ≥ 12 years of age with influenza, who provided written informed consent/assent prior to initiation of the study and met all of the following inclusion criteria were enrolled:

- Fever with an axillary temperature of ≥ 38°C and at least 1 of the general symptoms (headache, feverishness or chills, muscle or joint pain, and fatigue) with moderate-to-severe intensity and at least 1 of the respiratory symptoms (cough, sore throat, and nasal congestion) with moderate-to-severe intensity due to influenza, within 48 hours of onset of influenza symptoms at the predose examinations (Screening)
  - The onset of influenza symptoms was defined as either the time of the first increase of 1°C or more than the patient's normal body temperature or the occurrence of at least one new general or respiratory symptom.
- Considered at high risk for influenza complications (as defined by the Centers for Disease Control [CDC]; see full description in Section 9.3.1).
- Women of childbearing potential were to agree with the use of a highly effective method of contraception for 3 months after the first dosing of study

drug.

Patients who met any of the following exclusion criteria were not enrolled:

- Had severe influenza requiring inpatient treatment
- Had known allergy to oseltamivir (Tamiflu®)
- Unable to swallow tablets or capsules
- Previously received baloxavir marboxil
- Exposed to an investigational drug within 30 days prior to the predose examinations
- Weighed < 40 kg
- Women who were breastfeeding or had a positive pregnancy test in the predose examinations
- Had a concurrent infection requiring systemic antimicrobial therapy
- Had liver disease associated with hepatic impairment
- Had cancer within the last 5 years (unless nonmelanoma skin cancer)
- Had untreated HIV infection or treated HIV infection with a CD4 count < 350 cells/mm^3 in the last 6 months
- Receiving immunosuppression following organ or bone marrow transplants
- Use of 20 mg of prednisolone or equivalent dose of chronic systemic corticosteroids
- Use of anti-influenza virus drug within 30 days prior to the predose examinations
- Received investigational monoclonal antibody for a viral disease within 1 year prior to the predose examinations
- Current creatinine clearance ≤ 60 mL/min (≤ 30 mL/min in Japan)*
- Patients who, in the opinion of the investigator, would have been unlikely to comply with required study visits, self-assessments, and interventions

*Because dose adjustment of oseltamivir phosphate was not allowed in this study, patients with known renal impairment (judged by the current creatinine clearance value) were excluded or discontinued after randomization if identified after randomization.

Test Product, Dose and Mode of Administration, Lot Number:

Test drug: Baloxavir marboxil 20-mg tablets

Dose and Mode of Administration:

Patients randomized to baloxavir marboxil received a single oral dose of either 2 or 4 tablets of baloxavir marboxil 20 mg (based on body weight of < 80 kg or ≥ 80 kg at Screening, respectively) and oseltamivir placebo (1 capsule) BID on Day 1 followed by oseltamivir placebo (1 capsule) BID on Days 2 to 5. If only 1 dose of oseltamivir placebo was taken on Day 1 due to the patient being randomized after 17:00, dosing was completed on Day 6.

Lot Number: [redacted]

Duration of Study Treatment: Up to 5 days as follows:

Baloxavir marboxil group: single dose of baloxavir marboxil on Day 1 + oseltamivir placebo BID on Days 1 to 5

Placebo group: single dose of baloxavir marboxil placebo on Day 1 + oseltamivir placebo BID on Day 1 to 5

Oseltamivir group: single dose of baloxavir marboxil placebo on Day 1 + oseltamivir BID on Days 1 to 5

Reference Therapy, Dose and Mode of Administration, Lot Number:

Placebo:

- Baloxavir marboxil placebo tablets
- Oseltamivir placebo capsules

Active Comparator: Oseltamivir 75-mg capsules

Dose and Mode of Administration:

Patients randomized to oseltamivir received 1 capsule of oseltamivir 75 mg BID for 5 days (Days 1 to 5) and a single oral dose of either 2 or 4 tablets of baloxavir marboxil placebo (based on body weight of < 80 kg or ≥ 80 kg at Screening, respectively) on Day 1.

Patients randomized to placebo received a single oral dose of either 2 or 4 tablets of baloxavir marboxil placebo (based on body weight of < 80 kg or ≥ 80 kg at Screening, respectively) on Day 1 and 1 capsule of oseltamivir placebo BID on Days 1 to 5.

Lot Number:

- Baloxavir marboxil placebo tablets: [redacted]
- Oseltamivir placebo capsules: [redacted]
- Oseltamivir 75-mg capsules: [redacted]

Criteria for Evaluation:

Efficacy Assessment:

Primary Endpoint:

The time to improvement of influenza symptoms (with modification for preexisting symptoms), defined as the time from the start of study treatment to the improvement of influenza symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue), was the primary endpoint of this study. The improvement of influenza symptoms was defined as the time when all of a patient's influenza symptoms had been alleviated, maintained, or improved for a duration of at least 21.5 hours (24 hours − 10%).

Secondary Endpoints:

- 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 was below the limit of detection, and the time between the initiation of the study treatment and the first time when virus RNA by RT-PCR was below the limit of detection, respectively.
- Proportion of patients with positive influenza virus titer and the proportion of patients with positive influenza virus RNA determined by reverse transcription

polymerase chain reaction (RT-PCR) at each time point

Defined as the percentage of patients whose virus titer was not less than the lower limit of quantification among those assessed for virus titer, and the percentage of patients with detectable virus RNA among those assessed by RT-PCR, respectively.

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

  Defined as the change from baseline in virus titer and the change from baseline in amount of virus RNA, respectively. Baseline was defined as the last value obtained before Visit 1 (predose).

- The area under the concentration-time curve (AUC) adjusted by baseline in virus titer and in the amount of virus RNA (RT-PCR)

  Defined as AUC adjusted by baseline in virus titer and AUC adjusted by baseline in amount of virus RNA, respectively. The AUC was calculated using the trapezoidal method.

- Proportion of patients whose symptoms had been improved at each time point

  Defined as the percentage of patients whose symptoms had been improved at each time point.

- 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 symptoms was defined as the time when all of 7 influenza symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue) had 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%).

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

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

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

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

- 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 was defined as the time when the patient's self-measured axillary temperature became less than 37ºC and was maintained at less than 37ºC for at least 12 hours.

- Proportion of patients reporting normal temperature at each time point

  Defined as the percentage of patients whose axillary temperature dropped to

less than 37ºC after the initiation of the study treatment at each time point evaluated.

- Body temperature at each time point

  Defined as the measured axillary temperature.

- Time to improvement of each influenza symptom

  Defined as the time between the initiation of the study treatment and the improvement of individual symptom.

- Time to return to preinfluenza health status

  Defined as the time from the initiation of the study treatment to the first time when the health status score was equal to or higher than the preinfluenza health status score.

- Requirement for systemic antibiotics for infections secondary to influenza infection

  Defined as the percentage of patients who took antibiotics for any of the predefined complications (sinusitis, otitis media, bronchitis, and pneumonia).

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

  Defined as the percentage of patients in the analysis population who experienced each influenza-related complication (any influenza-related complication, death, hospitalization, sinusitis, otitis media, bronchitis, or radiologically confirmed pneumonia) as an AE that developed after the initiation of the study treatment.

Other Endpoints:

- Serum influenza antibody titer

  Defined as the ratio of the antibody titer on Day 22 to that on Day 1.

- Polymorphic and treatment-emergent amino acid substitutions in the PA region

  The polymorphic amino acid substitution(s) in the PA region was defined as the percentage of patients who had polymorphic amino acid substitution(s) on Day 1 compared with the reference sequence. The treatment-emergent amino acid substitution(s) in the PA region was defined as the percentage of patients who had treatment-emergent amino acid substitution(s) at the last RT-PCR-positive time point compared with the baseline sequence on Day 1.

- Drug susceptibility in patients with evaluable virus

  The drug susceptibility in patients with evaluable virus was defined as the 50% effective concentration (EC_{50}) for S-033447 at baseline, 50% inhibitory concentration (IC_{50}) for oseltamivir at baseline, ratio of EC_{50} for S-033447 relative to EC_{50} for the reference strain, and the ratio of IC_{50} for oseltamivir relative to IC_{50} for the reference strain.

- Health economic outcomes
  - EQ-5D-5L

    The change from baseline in the index value calculated from the EQ-

5D-5L questionnaire and that in EQ VAS score at each time point. The EQ-5D-5L score was converted to the EQ-5D-5L index value using the conversion table proposed by Ikeda et al (see Section 9.5.1.3.4.1).

– Work productivity questionnaire

The WP questionnaire consists of 4 questions regarding employment, hours worked, productivity while at work, and requirement for personal assistance. The percentage of absenteeism due to influenza illness, the percentage of work productivity loss due to influenza illness, and the time required for personal assistance due to influenza illness were calculated based on the answers to the questions.

- Intrahousehold infection rate (analyzed only for participants in Japan)

Defined as the percentage of intrahousehold members (except for patient him/herself) who were diagnosed as having influenza during the period from Days 1 to 15.

Safety Assessment:

Safety assessment was made with respect to the frequencies of AEs, serious AEs, vital sign measurements, physical examinations, ECG results, and clinical laboratory test results.

Pharmacokinetics Assessment:

For the measurement of plasma S-033447 concentrations, blood samples were collected at Visit 2 (Day 2) and Visit 4 (Day 5). Samples were also collected from some patients 0.5 to 4 hours postdose at Visit 1 (Day 1), at Visit 3 (Day 3), and at Visit 6 (Day 15).

Statistical Methods:

All statistical testing was performed at the 2-sided significance level of 0.05 unless stated otherwise.

Efficacy:

(1) Analysis Populations

The ITTI population consisted of all patients with a confirmed diagnosis of influenza virus infection, who received the study drug, and were enrolled at sites with good clinical practice (GCP) compliance. Confirmation of influenza virus infection was based on the results of RT-PCR on Day 1. The PPS consisted of all patients who were included in the ITTI population and did not meet any of the following conditions:

- Ineligible patients
- Patients with noncompliance of treatment (ie, treatment compliance rate < 60%)
- Patients with inadequate follow-up (ie, had no symptom data after initial treatment)
- Patients who had taken any prohibited medications
- Patients with incorrect treatment allocation
- Patients with important protocol deviations

The ITTI population was the primary population for all efficacy analyses. The PPS was

the secondary analysis population, and was used for sensitivity analysis of the primary efficacy endpoint.

(2) Primary Endpoint (Time to Improvement of Influenza Symptoms)

As a primary analysis of the primary endpoint in the ITTI population, the time to improvement of influenza symptoms was compared between the baloxavir marboxil group (40 mg and 80 mg combined) and the placebo group or the oseltamivir group using the stratified Peto-Prentice's generalized Wilcoxon test with the composite symptom score at baseline (≤ 14 or ≥ 15), preexisting and worsened symptom (yes or no; if a patient had at least 1 of 3 symptoms [namely cough, muscle or joint pain, or fatigue] that was preexisting and worsened, the patients was assigned to the "Yes" category, otherwise "No"), and the region (Asia, North America/Europe, Southern Hemisphere) as the stratification factors.

The Kaplan-Meier curves were plotted for each treatment group, and the median time to improvement of influenza symptoms and its 95% confidence interval (CI) were calculated. In addition, the treatment group difference in the median time to improvement of symptoms and its 95% CI were calculated.

For the submission to countries other than Japan, these comparisons were conducted in a hierarchical manner so as to maintain control of overall type I error.

The same analysis was performed using the PPS population as a sensitivity analysis.

Additional sensitivity analyses of the primary endpoint included comparisons between the baloxavir marboxil group and the placebo group or the oseltamivir group using the stratified log-rank test with composite symptom score at baseline (≤ 14 or ≥ 15), preexisting and worsened symptom (yes or no), and the region (Asia, North America/Europe, Southern Hemisphere) as the stratification factors. Patients who did not experience improvement of influenza symptoms were censored at the last observation time point. Similar analyses were performed using alternative definitions for censoring patients who did not experience improvement of influenza symptoms before discontinuing from the study. Also, the time to improvement of symptoms, excluding the cough symptom, was compared between the baloxavir marboxil group and the placebo group or the oseltamivir group using the same analysis method.

(3) Secondary Endpoints

The following secondary efficacy endpoints were compared between the baloxavir marboxil group and the placebo group, and between the baloxavir marboxil group and the oseltamivir group in the ITTI population:

- Time to cessation of viral shedding by influenza virus titer and by virus RNA

  Patients with positive influenza virus titer on Day 1 and available sample on Day 9 were included in this analysis. The stratified Peto-Prentice's generalized Wilcoxon test was used, where the composite symptom score at baseline, preexisting and worsened symptom, and region were used as the stratification factors. For patients with positive influenza virus RNA determined by RT-PCR on Day 1, similar analysis was conducted for the time to cessation of viral shedding by RT-PCR.

- Proportions of patients with positive influenza virus titer and positive influenza

virus RNA determined by RT-PCR at each time point

Patients with positive influenza virus titer/influenza virus RNA determined by RT-PCR on Day 1 were included in this analysis. The proportion of patients positive for influenza virus titer/virus RNA (RT-PCR) at each scheduled time point was calculated. The corresponding 95% CIs were calculated by the Clopper-Pearson method. The Mantel-Haenszel test with baseline composite symptom score (≤14 or ≥ 15), preexisting and worsened symptom (yes or no), and region (Asia, North America/Europe, Southern Hemisphere) as stratification factors was used to compare these endpoints between treatment groups at each scheduled time point.

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

  Patients with positive influenza virus titer on Day 1 were included in this analysis. The van Elteren test was used to compare the change from baseline in influenza virus titer between 2 groups at each scheduled time point, where the composite symptom score at baseline, preexisting and worsened symptom, and region were used as the stratification factors. For patients with positive influenza virus RNA determined by RT-PCR on Day 1, a similar analysis was conducted for the change from baseline in amount of virus RNA.

- AUC adjusted by baseline in influenza virus titer and in amount of virus RNA

  Patients with positive influenza virus titer on Day 1 and available sample on Day 9 were included in this analysis. The van Elteren test was used to compare AUC of virus titer adjusted by baseline between the 2 groups, where the composite symptom score at baseline, preexisting and worsened symptom, and region were used as the stratification factors. For patients with positive influenza virus RNA determined by RT-PCR on Day 1, similar analysis was conducted for the AUC of the amount of RNA adjusted by baseline.

- Proportion of patients whose symptoms had been improved at each time point

  The Mantel-Haenszel test was used to compare the proportion of patients whose symptoms improved at each time point between the 2 groups, where the composite symptom score at baseline, preexisting and worsened symptom, and region were used as the stratification factors.

- Time to alleviation of symptoms

  The stratified Peto-Prentice's generalized Wilcoxon test was used, where the composite symptom score at baseline, preexisting and worsened symptom, and region were used as the stratification factors. The Kaplan-Meier survival curve was plotted for each treatment group, and the median time and its 95% CI were calculated. In addition, the treatment group difference in median time was estimated.

- Time to improvement of the 4 systemic symptoms/3 respiratory symptoms

  The same analysis methods as used for the time to alleviation of symptoms were applied.

- Time to resolution of fever

The stratified Peto-Prentice's generalized Wilcoxon test was used, where the composite symptom score at baseline, preexisting and worsened symptom, and region were used as the stratification factors.

- Proportion of patients reporting normal temperature at each time point

  The Mantel-Haenszel test was used to compare the proportion of patients reporting normal temperature between the 2 groups at each scheduled time point, where the composite symptom score at baseline, preexisting and worsened symptom, and region were used as the stratification factors. Patients who had a body temperature at baseline was < 37ºC or not collected were excluded from the analysis.

- Body temperature at each time point

  Analysis of covariance (ANCOVA) with baseline composite symptom score, preexisting and worsened symptom (yes or no), region (Asia, North America/Europe, Southern Hemisphere), and body temperature at baseline as covariates was used to compare the endpoint between 2 groups and calculate the least squares mean and corresponding standard errors and 95% CI.

- Time to improvement of individual symptoms

  The same analysis methods used for the time to alleviation of symptoms were applied.

- Time to return to preinfluenza health status

  The same analysis methods used for the time to alleviation of symptoms were applied. Patients whose health status score at baseline was equal to or higher than the preinfluenza health status score were excluded from the analysis.

- Requirement for systemic antibiotics for infections secondary to influenza infection

  The proportion and the corresponding 95% CI were calculated by treatment group. The 95% CIs were calculated by the Clopper-Pearson method. Fisher's exact test was used to compare the proportion between 2 groups.

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

  The same analysis method used for the requirement for systemic antibiotics for infections secondary to influenza infection was applied.

Safety:

The Safety population consisted of all randomized patients who received at least 1 dose of the study drug. Adverse events were coded to System Organ Classes and Preferred Terms using the Medical Dictionary for Regulatory Activities (MedDRA), Version 19.1. Adverse events reported after the initial dose of study drug (treatment-emergent) were evaluated in the safety analyses. The number and proportion of patients who experienced at least 1 AE, treatment-related AEs, deaths, serious adverse events (SAEs), and AEs leading to withdrawal were summarized by treatment group. The corresponding 95% CIs were calculated using the Clopper-Pearson method. In addition, the proportion in the baloxavir marboxil group was compared with the value in the placebo group or the oseltamivir group using the Fisher's exact test. The number of those AEs, which were counted by case reported, was also presented. In addition, the number and proportion of patients who experienced AEs in each category for severity, outcome, and time-of-onset were summarized descriptively by SOC and PT for each treatment group. All AEs, including those occurring prior to the initiation of the study treatment, were listed.

Summary statistics for vital signs and quantitative laboratory test data were presented by treatment group for each scheduled time point and for the change from baseline to each time point. In addition, observed values were classified into 3 categories (within the normal range, higher than normal, or lower than normal) and summarized. The frequency of each category was summarized by treatment group at each scheduled time point. Qualitative laboratory test data at baseline and at scheduled time points were classified according to test category, and the frequency of each category was presented by treatment group at each scheduled time point. The frequency of each ECG finding (categorized as normal, abnormal-not clinically significant, or abnormal-clinically significant) was summarized by treatment group at each scheduled time point.

Other Endpoints:

Statistical methods for the other endpoints were as follows:

- Serum influenza antibody titer

  Serum antibody titers measured on Day 1 and Day 22 and the ratio of the value at Day 22 to the value at Day 1 were categorized, and the frequency of each category and the corresponding percentage were summarized by influenza virus subtype based on RT-PCR and treatment group. For the ratio (Day 22/Day 1), the geometric mean value was also calculated, the Wilcoxon rank sum test was used to compare the ratio between the baloxavir marboxil group and the placebo group or the oseltamivir group.

- Polymorphic and treatment-emergent amino acid substitutions in the PA region

  The patients who had determination of the amino acid sequence of PA were evaluated in the analysis. For the baloxavir marboxil group and the placebo group, amino acid residues on Day 1 and those at the last RT-PCR-positive time point were cross-tabulated by amino acid position in PA, influenza virus type and subtype of sequence sample and treatment group, in consideration of reference sequence.

- Drug susceptibility of evaluable virus

EC_{50} and IC_{50} at baseline, and the ratios of EC_{50} at baseline relative to EC_{50} for a reference stain and of IC_{50} at baseline relative to IC_{50} for a reference stain, were summarized descriptively by influenza virus type and subtype based on RT-PCR and treatment group (including overall group).

- Changed in EQ-5D-5L and EQ-VAS

  The summary statistics for the change in the EQ-5D-5L index value and that in EQ VAS score were presented by scheduled time point for each treatment group.

- Work productivity questionnaire

  The summary statistics for the percentage of absenteeism due to influenza illness and the percentage of work productivity loss due to influenza illness were presented by treatment group. As for the time required for personal assistance due to influenza illness, the summary statistics for the number of days required for personal assistance were presented by treatment group.

- Intrahousehold infection rate

  The Poisson regression model was used to estimate the intrahousehold infection rate and its 95% CI of each treatment group, and the intrahousehold infection rate was compared between the treatment groups. The patients who had no household members or for whom all household members had already been infected by Day 1 were excluded from the analysis.

P**harmacokinetics:**

(1) Plasma Concentrations

The PK Concentration population consisted of all patients who received at least 1 dose of S-033188 and had at least 1 evaluable PK assay result of S-033447. The PK Parameter population consisted of all patients with at least 1 PK parameter of S-033447 estimated.

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

(2) Pharmacokinetic Parameters

The population PK model developed previously (Study S-033188-CB-272-N) was employed to calculate Bayesian estimations of PK parameters in individual patients. The individual maximum plasma concentration (C_{max}), the area under the plasma concentration curve from time 0 to infinity ($AUC_{0\text{-}inf}$), C_{24}, plasma concentrations of S-033447 at 72 hours postdose (C_{72}), and C_{96} after a single dose of baloxavir marboxil were calculated based on the Bayesian-estimated PK parameters.

(3) Pharmacokinetic/Pharmacodynamic (PK/PD) Analysis

The relationships between C_{24} of S-033447 and the efficacy endpoints were assessed. The PK/PD analysis was performed for each efficacy endpoint including all patients who had the value of C_{24} and each evaluable PD assay result.

Summary of Results

Study Population:

Of the 2184 patients randomized, 2075 completed the study: 697 (95.5%) in the baloxavir marboxil group, 683 (94.2%) in the oseltamivir group, and 695 (95.3%) in the placebo group. Of those patients, 1163 (388 patients in the baloxavir marboxil group, 389 patients in the oseltamivir group, and 386 patients in the placebo group) were included in the ITTI population as the primary efficacy analysis population. The ITTI population was comprised of all patients who received the study drug with a confirmed diagnosis of influenza virus infection (based on RT-PCR results) and were enrolled at sites with GCP compliance. The PPS population for the sensitivity analysis of the primary efficacy endpoint consisted of 1000 patients, including 335 in the baloxavir marboxil group, 332 in the oseltamivir group, and 333 in the placebo group.

The distributions of demographics, including sex, age, and BMI, were generally similar among the treatment groups in the ITTI population. The proportion of adolescent patients (12 to 19 years of age) was 4.9%, 5.7%, and 4.4% in the baloxavir marboxil, oseltamivir, and placebo groups, respectively. Baseline characteristics such as composite symptom scores and body temperature at baseline were also similar among the treatment groups. In each of the treatment groups, the time period between the onset of influenza and the study treatment was most commonly > 12 to ≤ 24 hours or > 24 to ≤ 36 hours. In the ITTI population, the proportion of patients who weighed ≥ 80 kg in each treatment group was 38.4% to 40.1% across the treatment groups. Most patients were white (ranging from 45.9% to 50.3% across the treatment groups) or Asian (ranging from 40.7% to 43.0% across the treatment groups) in the ITTI population. The predominant influenza virus strains tested in this study were the A/H3 subtype (46.9% to 48.8%) and the B subtype (38.3% to 43.5%) in each treatment group. As the number of patients infected with type A/H1N1pdm virus was very small in this study, results for this subgroup of patients will be presented within the tabular summaries of the subgroup analyses by virus type, but will not be discussed further within the text of this report.

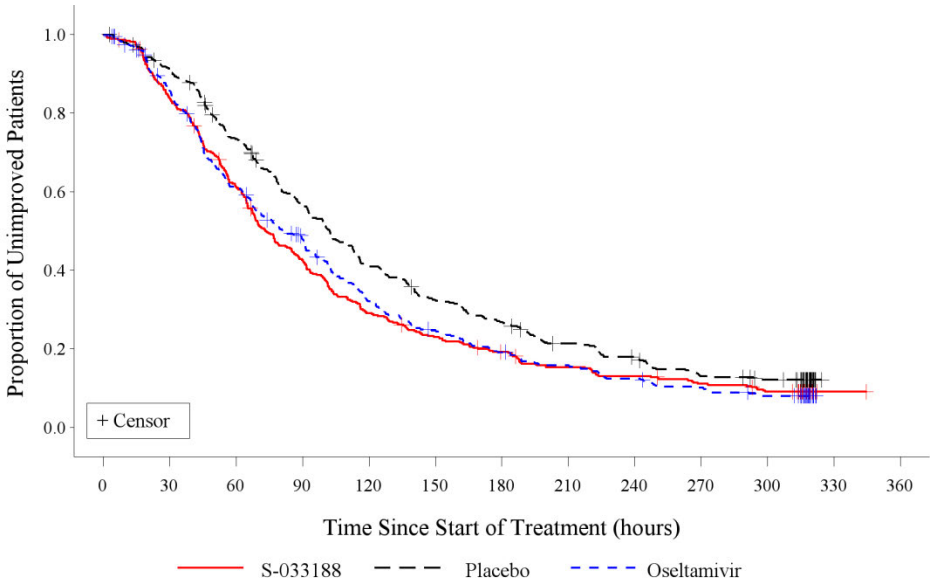
Efficacy:

(1) Primary Efficacy Endpoint

The median time to improvement of influenza symptoms in the ITTI population was 73.2 hours (95% CI: 67.2, 85.1) in the baloxavir marboxil group compared with 102.3 hours (95% CI: 92.7, 113.1) in the placebo group. In the primary analysis, a significant reduction in the time to improvement of symptoms was observed in the baloxavir marboxil group compared with the placebo group (median difference of -29.1 hours; generalized Wilcoxon test, p-value < 0.0001). The median time to improvement of symptoms was 81.0 hours (95% CI: 69.4, 91.5) in the oseltamivir group. The difference between the baloxavir marboxil group and the oseltamivir group (-7.7 hours) was not statistically significant. Similar results were observed in the sensitivity analysis using the stratified log-rank test. Kaplan-Meier curves for the time

to improvement of symptoms are shown below.

Time to Improvement of Symptoms (ITTI Population)



Patients who did not experience improvement of symptoms were treated as censored at the last observation time point.

A sensitivity analysis applying time to alleviation of symptoms (a traditional endpoint that does not adjust for preexisting symptoms associated with underlying conditions that may not be alleviated following treatment) also demonstrated a significant reduction in time to alleviation of symptoms compared with the placebo group, with a median difference of -25.8 hours; generalized Wilcoxon test p-value < 0.0001).

Subgroup analysis by influenza vaccine status (yes, no) was performed for the primary endpoint. For patients in the ITTI population who had received an influenza vaccine, the median time to improvement of influenza symptoms was numerically shorter (65.4 hours [95% CI: 52.6, 85.1]) in the baloxavir marboxil group compared with the placebo group (92.7 hours [95% CI: 76.1, 110.6]) and the oseltamivir group (90.0 hours [95% CI: 70.4, 103.7]); however, the difference between the baloxavir marboxil group and the placebo group or the oseltamivir group was not statistically significant (generalized Wilcoxon test, p = 0.1042 or p = 0.4069, respectively).

For patients in the ITTI population who had not received an influenza vaccine, the median time to improvement of symptoms was statistically significantly shorter in the baloxavir marboxil group (76.9 hours [95% CI: 68.4, 90.2]) compared with the placebo group (103.1 hours [95% CI: 93.2, 117.3]) (generalized Wilcoxon test, p-value = 0.0003; log-rank test p-value = 0.0018). However, the difference between the baloxavir marboxil group and the oseltamivir group (with a median time to improvement of influenza symptoms of 77.0 hours [95% CI: 66.8, 94.8]) was not statistically significant (generalized Wilcoxon test, p-value = 0.8998).

Subgroup analysis by viral subtype (A/H1N1pdm, A/H3, B) was also performed for the primary endpoint. The predominant influenza virus strain in the ITTI population was the A/H3 subtype, followed by B type. For patients infected with type A/H3 virus, the

median time to improvement of influenza symptoms was statistically significantly shorter in the baloxavir marboxil group (75.4 hours [95% CI: 62.4, 91.6]) compared with the placebo group (100.4 hours [95% CI: 88.4, 113.4]) (median difference of -25.0 hours; generalized Wilcoxon test p-value = 0.0141), but not compared with the oseltamivir group (68.2 hours [95% CI: 53.9, 81.0]) (median difference of 7.2 hours; generalized Wilcoxon test p-value = 0.1433).

For patients infected with type B virus, the median time to improvement of influenza symptoms was statistically significantly shorter in the baloxavir marboxil group (74.6 hours [95% CI: 67.4, 90.2]) compared with the placebo group (100.6 hours [95% CI: 82.8, 115.8]) (median difference of -26.0 hours; generalized Wilcoxon test p-value = 0.0138) and compared with the oseltamivir group (101.6 hours [95% CI: 90.5, 114.9]) (median difference of -27.1 hours; generalized Wilcoxon test p-value = 0.0251). In the oseltamivir group, the median time to improvement of influenza symptoms was longer for those infected with type B virus compared with those infected with type A/H3 virus.

(2) Secondary Efficacy Endpoints

Time to Cessation of Viral Shedding by Virus Titer

The median time to cessation of viral shedding determined by virus titer was 48.0 hours in the baloxavir marboxil group compared with 96.0 hours in the placebo group and the oseltamivir group. The time to cessation of viral shedding by virus titer was significantly reduced in the baloxavir marboxil group compared with the placebo group and compared with the oseltamivir group (median difference of -48.0 hours; stratified generalized Wilcoxon test, $p < 0.0001$ for both comparisons).

In the patients infected with type A/H3 virus, the median time to cessation of viral shedding determined by virus titer was shorter for the baloxavir marboxil group than that observed in the ITTI population. The difference in the time to cessation of viral shedding determined by virus titer between the baloxavir marboxil group and the placebo group and between the baloxavir marboxil group and the oseltamivir group was statistically significant in favor of baloxavir marboxil ($p < 0.0001$ for both comparisons).

In the patients infected with type B virus, the difference in the time to cessation of viral shedding determined by virus titer between the baloxavir marboxil group and the placebo group was statistically significant, as was the comparison between the baloxavir marboxil group and the oseltamivir group ($p < 0.0001$ for both comparisons). The time to cessation of viral shedding was longer for those treated with baloxavir marboxil who were infected with influenza type B virus (median of 72.0 hours) than for those infected with influenza type A/H3 virus (median of 24.0 hours).

Time to Cessation of Viral Shedding by RT-PCR

The median time to cessation of viral shedding determined by RT-PCR was 216.0 hours (95% CI: 192.0, 240.0) in the baloxavir marboxil group compared with 240.0 hours (95% CI: 216.0, 312.0) in the placebo group. The difference in the time to cessation of viral shedding by RT-PCR between the baloxavir marboxil group and the placebo group was statistically significant (median difference of -24.0 hours; stratified generalized Wilcoxon test, $p = 0.0006$). The comparison between the baloxavir

marboxil group and the oseltamivir group was not statistically significant, as the median time to cessation of viral shedding was 216.0 hours in both groups.

In the patients infected with type A/H3 virus, results of time to cessation of viral shedding evaluated using RT-PCR were similar to that in the full ITTI population. The difference in the time to cessation of viral shedding evaluated using RT-PCR between the baloxavir marboxil group (216.0 hours) and the placebo group (264.0 hours) was statistically significant ($p = 0.0008$). The median time to cessation of viral shedding was the same in the baloxavir marboxil group and the oseltamivir group (216.0 hours) for those infected with influenza type A/H3 virus.

In the patients infected with type B virus, the time to cessation of viral shedding evaluated using RT-PCR in the baloxavir marboxil group was the same across all 3 treatment groups (240.0 hours).

Proportion of Patients with Positive Influenza Virus Titer at Each Time Point

The proportion of patients with positive influenza virus titer (log_{10} of $TCID_{50}$/mL) was analyzed using the stratified Mantel-Haenszel test. The stratification factors included region, composite symptom scores at baseline, and preexisting and worsened symptoms. The proportion of patients with positive influenza virus titer was significantly lower in the baloxavir marboxil group than in the placebo group from Days 2 through 6 ($p < 0.0001$ for Days 2 through 5, $p = 0.0046$ for Day 6) as follows: on Day 2, 58.6% in the baloxavir marboxil group compared with 86.9% in the placebo group; on Day 3, 31.7% in the baloxavir marboxil group compared with 72.7% in the placebo group; on Day 4, 18.5% in the baloxavir marboxil group compared with 50.0% in the placebo group; on Day 5, 16.0% in the baloxavir marboxil group compared with 30.7% in the placebo group; on Day 6, 4.3% in the baloxavir marboxil group compared with 16.0% in the placebo group. The proportion of patients with positive influenza virus titer was significantly lower in the baloxavir marboxil group than in the oseltamivir group from Days 2 through 4.

Proportion of Patients with Positive Influenza Virus RNA Determined by RT-PCR at Each Time Point

The proportion of patients with positive influenza virus RNA determined by RT-PCR (log_{10} virus particles/mL) was lower in the baloxavir marboxil group than in the placebo group on Days 2 through 6 and Day 9, but the difference was significant only on Day 9. The differences in the proportion of patients with positive influenza virus RNA were very similar between the baloxavir marboxil group and the oseltamivir group at each time point, with proportions in the baloxavir marboxil group being slightly lower on Days 3, 5, and 9; the differences were not statistically significant at any time point.

Change from Baseline in Virus Titer at Each Time Point

The mean change from baseline in the influenza virus titer was significantly greater in the baloxavir marboxil group than in the placebo group from Days 2 through 3 (the van Elteren test, p-value < 0.0001 for Day 2, $p < 0.0001$ for Day 3). The mean change from baseline in the influenza virus titer in the baloxavir marboxil group compared with the placebo group was not statistically significant for Day 6 ($p = 0.0543$). When compared with the oseltamivir group, the mean change from baseline in the influenza virus titer

was significantly greater in the baloxavir marboxil group than in the oseltamivir group from Days 2 through 3 ($p < 0.0001$ for Day 2, $p < 0.0024$ for Day 3).

Change from Baseline in Amount of Virus RNA at Each Time Point

The mean change from baseline in amount of virus RNA was significantly greater in the baloxavir marboxil group than in the placebo group from Days 2 through 5 (the van Elteren test, p-value < 0.0001 for Days 2 through 3, $p = 0.0028$ for Day 4, $p = 0.0247$ for Day 5). When compared with oseltamivir, the mean change from baseline in amount of virus RNA was significantly greater in the baloxavir marboxil group for Days 2 through 4 ($p < 0.0001$ for Day 2, $p = 0.0015$ for Day 3, $p = 0.0265$ for Day 4).

Area Under the Curve Adjusted by Baseline in Virus Titer

The mean AUC adjusted by baseline in the influenza virus titer was -727.7 $\log_{10}$ [$TCID_{50}$/mL]·hours in the baloxavir marboxil group compared with -660.5 $\log_{10}$ [$TCID_{50}$/mL]·hours in the placebo group. The baloxavir marboxil group showed significantly greater mean AUC adjusted by baseline in the influenza virus titer compared with that in the placebo group (the van Elteren test, p-value = 0.0340). When compared with the oseltamivir group (-695.5 $\log_{10}$ [$TCID_{50}$/mL]·hours), the difference was not statistically significant.

Area Under the Curve Adjusted by Baseline in Amount of Virus RNA

The mean AUC adjusted by baseline in amount of virus RNA was -490.0 $\log_{10}$ virus particles/mL·hours in the baloxavir marboxil group compared with -434.9 $\log_{10}$ virus particles/mL·hours in the placebo group. The baloxavir marboxil group showed a significantly greater AUC adjusted by baseline in amount of virus RNA compared with that in the placebo group (the van Elteren test, p-value = 0.0072). When compared with the oseltamivir group, no statistically significant difference was observed.

Proportion of Patients Whose Symptoms Improved by Time Point

The proportion of patients whose influenza symptoms (any qualifying symptoms present at baseline) improved was significantly higher in the baloxavir marboxil group than in the placebo group from 36 hours postdose through 168 hours postdose (the Mantel-Haenszel test, p-value = 0.0004 at 36 hours postdose; $p = 0.0072$ for 48 hours postdose; $p = 0.0002$ for 72 hours postdose; $p = 0.0012$ for 96 hours postdose; $p = 0.0274$ for 120 hours postdose; $p = 0.0081$ for 144 hours postdose; and $p = 0.0209$ for 168 hours postdose). For the comparison between the baloxavir marboxil group and the oseltamivir group, no notable difference was observed in the proportion of patients whose influenza symptoms improved during the study.

Time to Alleviation of Symptoms (Sensitivity Analysis)

The median time to alleviation of symptoms (any qualifying symptoms present at baseline) was 77.0 hours in the baloxavir marboxil group compared with 102.8 hours in the placebo group. A significant reduction in the time to alleviation of symptoms was observed for the baloxavir marboxil group compared with the placebo group (the stratified Peto-Prentice's generalized Wilcoxon test, p-value < 0.0001). For the comparison between the baloxavir marboxil group and the oseltamivir group, no significant difference was observed.

Time to Improvement of the Four Systemic Symptoms

The median time to improvement of the 4 systemic symptoms was 51.7 hours in the baloxavir marboxil group compared with 66.8 hours in the placebo group. A significant reduction in the time to improvement of the 4 systemic symptoms was observed in the baloxavir marboxil group compared with the placebo group (the stratified Peto-Prentice's generalized Wilcoxon test, p-value = 0.0013). In the comparison between the baloxavir marboxil group and the oseltamivir group, no significant difference was observed.

Time to Improvement of the Three Respiratory Symptoms

The median time to improvement of the 3 respiratory symptoms was 63.6 hours in the baloxavir marboxil group compared with 87.8 hours in the placebo group. A significant reduction in the time to improvement of the 3 respiratory symptoms was observed in the baloxavir marboxil group compared with the placebo group (the stratified Peto-Prentice's generalized Wilcoxon test, p-value = 0.0001). In the comparison between the baloxavir marboxil group and the oseltamivir group, no significant difference was observed. Overall, the time to improvement of the 3 respiratory symptoms was longer than that for improvement of the 4 systemic symptoms in all 3 treatment groups.

Time to Improvement of Individual Symptoms

In the analysis using the stratified Peto-Prentice's generalized Wilcoxon test, a reduction in the time to improvement for 6 of the 7 individual symptoms (all symptoms but fever) was observed for the baloxavir marboxil group compared with the placebo group. For 6 of the individual symptoms, ie, cough, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue, the median time to improvement of each symptom in the baloxavir marboxil group was 47.3, 33.4, 45.6, 28.3, 37.2, and 41.3 hours, respectively, and significant differences in the time to improvement of each symptom were found between the baloxavir marboxil group and the placebo group (p-value = 0.0009, 0.0390, 0.0017, 0.0070, 0.0232, and 0.0207, respectively). A reduction in the time to improvement of sore throat was also observed for the baloxavir marboxil group compared with the placebo group (40.2 hours versus 46.5 hours); however, the difference between the groups was not statistically significant. Among the individual symptoms, particularly rapid improvement of symptom was found for cough and nasal congestion in the baloxavir marboxil group compared with the placebo group. For the comparison between the baloxavir marboxil group and the oseltamivir group, no significant differences were observed in the time to improvement of the individual symptoms.

Time to Resolution of Fever

The proportion of patients who had fever was reduced more rapidly in the baloxavir marboxil group than in the placebo group following study drug administration. The median time to resolution of fever was 30.8 hours in the baloxavir marboxil group compared with 50.7 hours in the placebo group. A significant reduction in the time to resolution of fever was observed for the baloxavir marboxil group compared with the placebo group (the stratified Peto-Prentice's generalized Wilcoxon test, p-value < 0.0001). For the comparison between baloxavir marboxil group and the

oseltamivir group, the median time to resolution of fever was 30.8 hours in the baloxavir marboxil group compared with 34.3 hours in the oseltamivir group. No significant difference between these groups was observed in the time to resolution of fever.

Proportion of Patients Reporting Normal Temperature at Each Time Point

The proportion of patients reporting a normal temperature was significantly higher in the baloxavir marboxil group than in the placebo group from 24 hours postdose through 96 hours postdose (Mantel-Haenszel test, p-value = 0.0387 for 24 hours postdose; $p < 0.0001$ for 36 and 48 hours postdose; $p = 0.0001$ for 72 hours postdose; $p = 0.0064$ for 96 hours postdose). No significant differences between the baloxavir marboxil group and the oseltamivir group were observed throughout the assessment period in the proportion of patients reporting a normal temperature.

Body Temperature at Each Time Point

The least squares mean body temperature was significantly lower in the baloxavir marboxil group than in the placebo group from 12 through 72 hours postdose (ANCOVA, p-value = 0.0408 at 12 hours; $p = 0.0025$ at 24 hours; $p < 0.0001$ at 36 and 48 hours; and $p = 0.0025$ at 72 hours). For the comparison between the baloxavir marboxil group and the oseltamivir group, no significant differences were observed in the least squares mean body temperature at each time point.

Time to Return to Preinfluenza Health Status

The median time to return to preinfluenza status was 126.4 hours in the baloxavir marboxil group compared with 149.8 hours in the placebo group. Although there was no statistically significant difference between treatment groups, the baloxavir marboxil group showed a numerical reduction in the time to return to preinfluenza status compared with the placebo group. The difference in the median time to return to preinfluenza health status between the groups was −23.4 hours. For the comparison between the baloxavir marboxil group and the oseltamivir group, no significant difference was observed between treatment groups. The median value of time to return to preinfluenza status was comparable between the groups (126.4 versus 126.9 hours in the baloxavir marboxil and oseltamivir groups, respectively).

Requirement for Systemic Antibiotics for Infections Secondary to Influenza Infection

The proportion of patients requiring systemic antibiotics for infections secondary to influenza infection was lower in the baloxavir marboxil group (3.4%) compared with the placebo group (7.5%), and the difference between these 2 groups was statistically significant ($p = 0.0112$). The proportion of patients requiring systemic antibiotics for infections secondary to influenza was comparable between the baloxavir marboxil and oseltamivir groups (3.4% versus 3.9%, respectively); no significant difference was observed between the treatment groups.

Incidence of Influenza-related Complications

In the ITTI population, a significantly lower proportion of patients in the baloxavir marboxil group (2.8%, 11 of 388) compared with the placebo group (10.4%, 40 of 386) experienced influenza-related complications ($p < 0.0001$). The significant difference between the baloxavir marboxil group and the placebo group in the overall incidence of

influenza-related complications was likely driven by the significant differences between the groups in the proportion of patients with complications of sinusitis (0.3% versus 2.1%, respectively; p = 0.0205) and bronchitis (1.8% versus 6.0%, respectively; p = 0.0027). There were no significant differences between the baloxavir marboxil and placebo groups in the incidence of complications of death, hospitalization, otitis media, and pneumonia.

In the ITTI population, 11 of 388 patients (2.8%) in the baloxavir marboxil group and 18 of 389 patients (4.6%) in the oseltamivir group experienced influenza-related complications. No significant difference in the overall incidence of influenza-related complications was observed between these groups.

For the individual complications, bronchitis was the most frequent complication reported. The incidences of bronchitis were 1.8% in the baloxavir marboxil group, 6.0% in the placebo group, and 2.3% in the oseltamivir group. The incidences of bronchitis and sinusitis were lower in the baloxavir marboxil and oseltamivir groups compared with the placebo group; however, the incidences of the other complications (death, hospitalization, otitis media, and pneumonia) were similar across the treatment groups.

Based on the efficacy results regarding the primary endpoint and the secondary endpoints described above, a single dose of 40 or 80 mg of baloxavir marboxil administered depending on patient's weight was considered effective to treat influenza at high risk of influenza complications.

(3) Other Endpoints

Serum Influenza Antibody Titer

Regardless of the infected virus type/subtype, increases in influenza antibody titer were found on Day 22 in all the 3 treatment groups. The geometric mean ratios of influenza antibody titer on Day 22 to Day 1 were 4.3 to 4.9 for influenza A/H3 antibody in patients infected with virus A/H3, 7.2 to 9.9 for influenza B/Yamagata antibody in patients infected with virus B, and 1.6 to 2.0 for influenza B/Victoria antibody in patients infected with virus B.

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

In all 3 treatment groups, the EQ-5D-5L index improved over time. The mean improvement in the EQ-5L-5D index in the baloxavir marboxil group was numerically greater compared with that in the placebo group at 12 to 96 hours. The mean improvement in the EQ-5L-5D index was numerically greater in the oseltamivir group compared with the baloxavir marboxil group at most time points evaluated.

In all the 3 treatment groups, the EQ VAS score improved over time. The improvement in mean EQ VAS score in the baloxavir marboxil group was numerically greater compared with that in the placebo group from 24 to 180 hours. Mean changes from baseline in the EQ VAS score between the baloxavir marboxil group and the oseltamivir group were comparable.

Work Productivity Questionnaire

Both the mean percentage of absenteeism and the mean percentage of work

productivity loss due to influenza illness were numerically lower in the baloxavir marboxil group than in the placebo group (28.2% versus 36.8% and 48.7% versus 62.1%, respectively). No notable differences in the mean percentage of absenteeism or the mean percentage of work productivity loss were observed between the baloxavir marboxil group and the oseltamivir group. The mean time period requiring another person's assistance due to influenza illness was 1.3 days in the baloxavir marboxil group, 2.1 days in the placebo group, and 1.8 days in the oseltamivir group.

Intrahousehold Infection Rate

The intrahousehold infection rate of influenza postdose was evaluated only with the study participants in Japan. The intrahousehold infection rate of influenza between Days 1 and 3 was similar among the Japanese patients in the 3 treatment groups (ranging from 4.1% to 6.4%); no statistically significant differences were found between the baloxavir marboxil group and the placebo group or between the baloxavir marboxil group and the oseltamivir group.

Pharmacokinetics:

The following results were obtained from the PK analysis for patients with influenza at high risk of influenza complications.

- Plasma concentration profiles were similar between patients with body weight < 80 kg and ≥ 80 kg.
- The C_{24}, C_{96}, and Bayesian-estimated exposure indices (C_{max}, $AUC_{0\text{-}inf}$, C_{24}, C_{72}, and C_{96}) were 34% to 48% lower for non-Asian patients than Asian patients when the exposure indices were compared in each body weight category.
- The C_{24}, C_{96}, and Bayesian-estimated exposure indices (C_{max}, $AUC_{0\text{-}inf}$, C_{24}, C_{72}, and C_{96}) were 34% to 50% lower for patients in North America/Europe and 49% to 71% lower for patients in Southern Hemisphere than that in Asia, when the exposure indices were compared in each body weight category, although the number of patients in Southern Hemisphere was limited (regarding Bayesian-estimated exposure indices, n = 165 for Asia, n = 467 for North America/Europe, and n = 30 for Southern Hemisphere).
- None of the 5 individual high-risk categories representing ≥ 10% of the whole population (asthma or chronic lung disease, endocrine disorders, heart disease, adults ≥ 65 years of age, and morbid obesity) affected the PK of baloxavir marboxil.
- The C_{24}, C_{96}, and Bayesian-estimated exposure indices (C_{max}, $AUC_{0\text{-}inf}$, C_{24}, C_{72}, and C_{96}) were 24% to 43% higher for patients with metabolic disorders than patients without metabolic disorders.
- All of the PK parameters were similar regardless of the time of food intake.
- No relevant differences were observed for PK parameters among age categories.
- All of the PK parameters were similar between patients infected with influenza virus type A and type B.

The following results were obtained from the PK/PD analysis for patients with influenza at high risk of influenza complications.

- For overall virus type, the time to improvement of influenza symptoms and time

to alleviation of symptoms showed statistically significant relationships ($p < 0.05$) to C_{24} based on the linear model. However, no statistically significant relationships to C_{24} were shown when analyzed separately for virus type A and B.

- The changes from baseline in virus titer on Day 2 and 3 were evaluated by using the E_{max} model. The EC_{50} was 44.8 ng/mL (95%CI: −9.83, 99.5) (Day 2 data). The data was well described by the model although the 95% CIs of EC_{50} included 0.
- For time to improvement of influenza symptoms and time to alleviation of symptoms, no clear relationships to C_{24} category was observed. However, for type B, greater reduction was observed for baloxavir marboxil group compared with the oseltamivir group.
- For type A, a substantial viral reduction (as measured by change from baseline in virus titer on Day 2) was seen in the baloxavir marboxil group regardless of C_{24}. For type B, an apparent exposure (C_{24}) dependent viral reduction was observed as the reduction in the higher exposure groups (40 to < 60 and ≥ 60 ng/mL) were generally larger than in the other groups. Nonetheless, even the lower exposure group of 20 to < 40 ng/mL demonstrated a more than 1-log reduction in the median difference compared with the oseltamivir group.
- The Bayesian-estimated C_{max} and $AUC_{0\text{-}inf}$ for patients with frequent (≥ 2%) adverse events and for patients with severe adverse events were similar to those for patients without frequent adverse events or severe adverse events.

Safety:

Two deaths were reported during the study, including 1 treatment-emergent death due to an SAE of pneumonia (oseltamivir group) and 1 nontreatment-emergent death due to an SAE of acute myocardial infarction (baloxavir marboxil group). The incidence of SAEs (excluding death) was similar among the 3 treatment groups, occurring in 0.7% of patients (5 of 730) in the baloxavir marboxil group, 1.2% of patients (9 of 727) in the placebo group, and 1.1% of patients (8 of 721) in the oseltamivir group. The only SAE occurring in > 1 patient in any treatment group was cholelithiasis (2 patients in the baloxavir marboxil group only). The majority of the SAEs were considered not related to the study drug and resolved. Treatment-related SAEs were reported in no patients in the baloxavir marboxil group, 2 of 727 patients (0.3%, 2 events) in the placebo group, and 2 of 721 patients (0.3%, 2 events) in the oseltamivir group. Serious AEs (excluding death) considered by the investigator to be related to the study drug included hypotension (1 patient in the placebo group), nausea (1 patient in the placebo group), liver function test abnormal (1 patient in the oseltamivir group), and liver function test increased (1 patient in the oseltamivir group).

Adverse events leading to withdrawal of study drug were reported in a similar percentage of patients in each treatment group (0.7%, 5 of 730 patients in the baloxavir marboxil group; 0.7%, 5 of 727 patients in the placebo group, and 0.6%, 4 of 721 patients in the oseltamivir group). Adverse events leading to withdrawal of study drug occurring in > 1 patient in any treatment group were pneumonia (2 patients in the baloxavir marboxil group and 1 in the oseltamivir group), vomiting (2 patients in the

baloxavir marboxil group only), and bronchitis (2 patients in the placebo group only). The majority of the AEs leading to withdrawal of study drug were categorized as Grade 1 or 2. The AEs leading to withdrawal of study drug considered by the investigator to be related to study drug were vomiting and urticaria in the baloxavir marboxil group; nausea and headache in the placebo group; and epigastric discomfort, abdominal pain upper, dysgeusia, abdominal discomfort, and nausea in the oseltamivir group. All of the AEs leading to withdrawal were reported to have resolved by end of study or last follow-up, except for 1 event of vomiting (not resolved) in the baloxavir marboxil group (patient withdrew from study on Day 2 with no further follow-up) and 1 event of bronchitis and 1 event of asthma (both resolving) in the same patient in the placebo group (patient withdrew from study on Day 4 with no further follow-up).

Adverse events were reported in a lower percentage of patients in the baloxavir marboxil group (25.1%, 183 of 730 patients [282 events]) than in the placebo group (29.7%, 216 of 727 patients [342 events]) and the oseltamivir group (28.0%, 202 of 721 patients [332 events]). However, there were no statistically significant differences in the incidence of AEs between the baloxavir marboxil group and the placebo group (Fisher's exact test, p-value = 0.0525) or between the baloxavir marboxil group and the oseltamivir group (Fisher's exact test, p-value = 0.2121).

Treatment-related AEs were reported in a lower percentage of patients in the baloxavir marboxil group (5.6%, 41 of 730 patients [49 events]) than in the placebo group (8.3%, 60 of 727 patients [76 events]) and the oseltamivir group (7.9%, 57 of 721 patients [72 events]). However, there were no statistically significant differences in the incidence of treatment-related AEs between the baloxavir marboxil group and the placebo group (Fisher's exact test, p-value = 0.0503) or between the baloxavir marboxil group and the oseltamivir group (Fisher's exact test, p-value = 0.0940).

The most commonly (≥ 2% of patients in any treatment group) reported AEs were bronchitis, sinusitis, diarrhea, and nausea; however, the incidence of each of these AEs was lower in the baloxavir marboxil group than in the placebo group and the oseltamivir group. There was no AE reported in ≥ 5% of patients in any of the treatment groups. Adverse events occurred most commonly in the System Organ Classes of infections and infestations followed by gastrointestinal disorders in all of the treatment groups. For both of these System Organ Classes, the incidence of AEs was similar among the 3 treatment groups.

The majority of the AEs were categorized as Grade 1 or 2. The incidence of AEs categorized as Grade 3 was 1.5% (11 of 730 patients) in the baloxavir marboxil group, 1.8% (13 of 727 patients) in the placebo group, and 1.7% (12 of 721 patients) in the oseltamivir group. A total of 6 patients experienced 10 Grade 4 AEs, including 3 patients in the placebo group (loss of consciousness and atrioventricular block complete in 1 patient, chronic obstructive pulmonary disease in 1 patient, and blood potassium increased in 1 patient) and 3 patients in the oseltamivir group (arachnoid cyst in 1 patient; and septic shock, staphylococcal infection, cardiac failure, and acute respiratory distress syndrome in 1 patient, who also had a Grade 5 AE of pneumonia leading to death; and acute kidney injury in 1 patient). No patient in the baloxavir marboxil group experienced a Grade 4 or 5 AE during the study. The majority of the Grade 3 AEs and all of the Grade 4 or 5 AEs were considered unrelated to the study

treatment. The majority of the Grade 3 or 4 AEs resolved.

Overall, the majority of the AEs reported during the study resolved. The incidence of AEs that did not resolve was 2.9% (21 of 730 patients) in the baloxavir marboxil group, 1.8% (13 of 727 patients) in the placebo group, and 2.5% (18 of 721 patients) in the oseltamivir group. The most common (> 1 patient in any treatment group) AEs that did not resolve (excluding resolving) were bronchitis (2 patients each in the baloxavir marboxil and oseltamivir groups), hypertension (1 patient each in the baloxavir marboxil and placebo groups, and 2 patients in the oseltamivir group), cough (2 patients in the baloxavir marboxil group only), diarrhea (2 patients in the baloxavir marboxil group only), and gamma-glutamyltransferase increased (2 patients in the oseltamivir group only). All of the AEs that did not resolve were considered not related to the study drug, except for the following: diarrhea in 2 patients and vomiting in 1 patient in the baloxavir marboxil group; dysgeusia and parosmia in 1 patient and liver function test increased in 1 patient in the placebo group; and thrombocytosis in 1 patient in the oseltamivir group.

In this study, "AEs related to hepatic disorders" were defined as the PTs included in the SMQ "Drug related hepatic disorders (MedDRA Code: 20000006)." A total of 46 patients experienced 69 AEs related to liver function. Adverse events related to liver function were reported in 15 of 730 patients (2.1%) in the baloxavir marboxil group, 13 of 727 patients (1.8%) in the placebo group, and 18 of 721 patients (2.5%) in the oseltamivir group. The incidence of each of the AEs related to hepatic disorders was similar among the 3 treatment groups. The only AE related to hepatic disorders occurring in ≥ 1% of patients in any treatment group was ALT increased (ranging from 0.3% to 1.0% in each of the treatment groups). All of the AEs related to liver function were considered by the investigator to be Grade 1 or 2, and the majority of the events were considered unrelated to the study drug and resolved or were resolving. No cases meeting Hy's law criteria or drug-induced liver injury were reported.

For clinical laboratory tests, no clinically relevant differences were found in the changes from baseline among any of the treatment groups, with the exception of C-reactive protein. The mean C-reactive protein level was high and similar among the 3 treatment groups at baseline (mean value ranged from 1.759 to 1.991 across the treatment groups), and decreased in all 3 treatment groups to within the normal range by Day 22 (mean value ranged from 0.392 to 0.475 across the treatment groups). No clinically meaningful trends were noted in vital signs or ECGs.

CONCLUSIONS

Efficacy Conclusions:

In this study of patients ≥ 12 years of age with influenza A and/or B infection at high risk of developing influenza complications, a single oral dose of 40 or 80 mg of baloxavir marboxil (administered depending on patient's weight and within 48 hours of symptom onset) resulted in a significantly greater improvement in the median time to improvement of influenza symptoms compared with treatment with placebo. A sensitivity analysis applying a time to alleviation endpoint (a traditional endpoint that does not adjust for preexisting symptoms associated with underlying conditions that may not be alleviated following treatment) demonstrated consistency with the time to

improvement results. In addition, a significantly lower proportion of patients in the baloxavir marboxil group (2.8%) compared with the placebo group (10.4%) experienced influenza-related complications, and this difference was likely driven by the significant differences between the groups in the proportion of patients with complications of sinusitis and bronchitis. Rapid reduction in virus titer/amount of virus RNA resulted in a significantly shortened time to cessation of viral shedding, which may result in a shortened infectivity period. Beneficial effects of baloxavir marboxil on the time to resolution of fever compared with treatment with placebo were also observed.

Results for the baloxavir marboxil group were generally similar to the oseltamivir group for the improvement of clinical symptoms in the overall ITTI population and in the subgroup of patients infected with type A/H3 virus. However, in the subgroup of patients infected with type B virus, the median time to improvement of influenza symptoms was statistically significantly shorter in the baloxavir marboxil compared with the oseltamivir group. No significant difference in the overall incidence of influenza-related complications was observed between the baloxavir marboxil and oseltamivir groups. Additionally, the baloxavir marboxil group resulted in a significantly shortened time to cessation of viral shedding by virus titer and faster reduction in virus titer/amount of virus RNA compared with the oseltamivir group. The time to cessation of viral shedding by RT-PCR was similar between the baloxavir marboxil group and the oseltamivir groups; however, it should be noted that RT-PCR is not a culture based test and detects nonviable virus, in contrast to virus titer, which is a culture based assay.

Thus, treatment with a single dose of baloxavir marboxil at 40 or 80 mg given according to patient's weight is considered to be effective as a treatment for influenza in patients at high risk of influenza complications.

Safety Conclusions:

Overall, no safety concerns were identified for baloxavir marboxil compared with placebo or oseltamivir; therefore, baloxavir marboxil was considered generally safe when administered to patients with influenza at high risk of influenza complications as a single oral dose of either 40 or 80 mg administered depending on the patient's body weight.

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