2. SYNOPSIS

Sponsor: Shionogi & Co., Ltd.	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of Finished Product: Xofluza	**Volume:**	:
Name of Active Ingredient: Baloxavir marboxil (S-033188 or RO7191686)	**Page:**	

Study Title:
A phase 3 randomized, double-blind, placebo-controlled study to confirm the efficacy of a single dose of baloxavir marboxil in the prevention of influenza virus infection

Investigators and Study Centers: This was a multicenter study conducted at 52 sites in Japan.

Publication (reference): Not applicable

Studied Period:
5 months between 09 Nov 2018 (first subject signed informed consent form) and 25 Mar 2019 (last patient completed)

Phase of Development: 3

Objectives:

The primary objective of this study was:

- To evaluate the efficacy of a single oral dose of baloxavir marboxil compared with placebo in the prevention of influenza virus infection in subjects who were household members (hereinafter referred to as "subjects") of influenza-infected patients (hereinafter referred to as "index patients"). The primary efficacy endpoint was the proportion of subjects who were infected with influenza virus (reverse transcription polymerase chain reaction [RT-PCR] positive), and presented with fever and at least one respiratory symptom in the period from Day 1 to Day 10.

The secondary objectives of this study were:

- To evaluate the efficacy of a single oral dose of baloxavir marboxil compared with placebo in the prevention of influenza virus infection by measuring the secondary endpoints in subjects.
- To determine the pharmacokinetics (PK) of the active form of baloxavir marboxil, ie, baloxavir in subjects treated with baloxavir marboxil for prophylaxis.
- To evaluate the safety of a single oral dose of baloxavir marboxil for prophylaxis.

Methodology: This was a randomized, double-blind, multicenter, parallel-group, placebo-controlled comparative study to evaluate the efficacy and safety of a single oral dose of baloxavir marboxil in the prevention of influenza virus infection in approximately 750 subjects who were household members of influenza-infected index patients.

Investigators confirmed the eligibility of index patients and subjects for participation in this study, before study drug administration on Day 1. Eligible subjects were then randomly assigned with the stochastic minimization method in a 1:1 ratio to receive baloxavir marboxil or placebo. The dose of baloxavir marboxil was determined according to subject age and body weight at Screening. The study drug was orally administered at the study site on Day 1. Subjects visited the study site a maximum of 5 times during the 15-day period for 11 days of efficacy evaluation and 15 days of safety evaluation.

The subject or a guardian measured/assessed body temperature and the severity of influenza symptoms (cough, sore throat, headache, nasal discharge/nasal congestion, feverishness or chills, muscle or joint pain, and fatigue) and recorded the results in the subject diary from pre-dose on Day 1 until Day 10, twice daily (morning and evening). For the virology test, nasopharyngeal swabs from the index patients were collected at Screening (Day 1), and the swabs from the subjects were collected pre-dose on Day 1, Day 5, at a subject's visit between Day 1 (post-dose) and Day 10 (if applicable), and Day 11 (at the time point of withdrawal if withdrawn prior to Day 11).

Number of Patients (Planned and Analyzed):

Planned: 750 subjects (375 subjects/group)

Randomized: 752 subjects (375 subjects in the baloxavir marboxil group and 377 subjects in the placebo group)

Analyzed for efficacy:

- Modified intention-to-treat (mITT) population: 749 subjects (374 subjects in the baloxavir marboxil group and 375 subjects in the placebo group)
- Per protocol set (PPS): 741 subjects (370 subjects in the baloxavir marboxil group and 371 subjects in the placebo group)

Analyzed for safety: 749 subjects (374 subjects in the baloxavir marboxil group and 375 subjects in the placebo group)

Analyzed for PK concentration: 370 subjects in the baloxavir marboxil group

Analyzed for PK parameters: 369 subjects in the baloxavir marboxil group

Diagnosis and Main Criteria for Inclusion:

Inclusion criteria for index patients

Patients who fulfilled all of the following criteria were included in the study as index patients:

1. For adult patients, written informed consent had to be obtained from the patients, who participated voluntarily in the study, prior to Screening. For patients under legal age, written informed consent had to be obtained from the parent/legal representative of the patients; written informed assent also had to be provided in the case of patients aged ≥ 12 years, and should be provided in the case of patients aged < 12 years when feasible.
2. The first patient in a household with influenza virus infection in the 2018-2019 influenza season (November 2018 to April 2019).
3. Patients diagnosed as having influenza with a positive rapid influenza diagnostic test by nasopharyngeal (if difficult, nasal or throat) swabs.
4. Patients with onset of symptoms within 48 hours at the time of informed consent. The onset of symptoms was defined as the time when body temperature first rose

to 37.5°C or higher.

5. Patients who were to receive any treatment with anti-influenza drugs after informed consent was obtained.
6. Patients with a body weight of at least 10 kg at Screening.

Inclusion criteria for subjects

Subjects who fulfilled all of the following criteria were included in the study:

1. For adult subjects, written informed consent had to be obtained from the subjects, who participated voluntarily in the study, prior to Screening. For subjects under legal age, written informed consent had to be obtained from the parent/legal representative of the subjects; written informed assent also had to be provided in the case of subjects aged ≥ 12 years, and should be provided in the case of subjects aged < 12 years when feasible.
2. Subjects who had lived with the index patient for 48 hours or more prior to the time of informed consent.
3. Subjects who met all of the following criteria and were judged not to have influenza virus infection by the investigator or subinvestigator.
   - Subjects who had a body temperature (axillary) < 37.0°C at Screening
   - Subjects who had no influenza-like symptoms (cough, sore throat, headache, nasal discharge/nasal congestion, feverishness or chills, muscle or joint pain, and fatigue) at Screening
4. Subjects 12 years of age or older, or subjects under 12 years of age whose guardian was capable of evaluating influenza symptoms by using a subject diary.
5. Subjects who were able to provide informed consent within 48 hours from the onset of symptoms in index patients and within 24 hours from the time of informed consent in index patients.
6. Women of childbearing potential who agreed to use a highly effective method of contraception for 3 months after study drug administration.

Exclusion criteria for subjects

Subjects who met any of the following criteria were excluded from the study.

1. Subjects who had been diagnosed with influenza during the 2018-2019 influenza season (November 2018 to April 2019).
2. Subjects who were unable to live with the index patient from Screening until Day 10.
3. Subjects who lived with a household member who had any influenza-like symptom(s) (body temperature of > 37.5°C, cough, sore throat, headache, nasal discharge/nasal congestion, feverishness or chills, muscle or joint pain, or fatigue) other than the index patient on the day of Screening.
4. Subjects living with household members other than the index patient who were diagnosed with or strongly suspected to have influenza during the 2018-2019 influenza season (November 2018 to April 2019).
5. Subjects who had any underlying diseases requiring systemic (oral or injectible), or nasal treatment of antipyretics/analgesics, corticosteroids, or immunosuppressive agents.
6. Subjects who were immunocompromised (including subjects receiving systemic

immunosuppressant agents or subjects with human immunodeficiency virus infection).

7. Subjects who had received baloxavir marboxil (Xofluza®), peramivir (Rapiacta®), laninamivir (Inavir®), oseltamivir (Tamiflu®), zanamivir (Relenza®) or amantadine (Symmetrel®) within 30 days prior to Screening (including prophylaxis).
8. Subjects with a known allergy and/or history of significant intolerance against baloxavir marboxil.
9. Subjects with severe (Grade 3 or higher of Common Terminology Criteria for Adverse Events [CTCAE] ver. 5 [7]) underlying diseases.
10. Subjects who had been exposed to an investigational drug within 30 days or 5 half-lives of the drug prior to Screening.
11. Women who were pregnant or lactating.
12. Subjects with any condition or circumstance that, in the opinion of the investigator or subinvestigator, would compromise the safety of the subject or the quality of the study data.

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

- Baloxavir marboxil 20-mg tablets (lot number: [redacted])
- Baloxavir marboxil 2% granules (lot number: [redacted])

Baloxavir marboxil 20-mg tablets or 2% granules were orally administered to subjects as a single dose on Day 1 at a dose which depends on the subject's age and body weight at Screening.

Subjects ≥ 12 years of age at Screening:

Subject's body weight at Screening	Dose	Baloxavir marboxil group
Weight < 80 kg	40 mg	2 baloxavir marboxil 20-mg tablets
Weight ≥ 80 kg	80 mg	4 baloxavir marboxil 20-mg tablets

Subjects < 12 years of age at Screening:

Subject's body weight at Screening	Dose	Baloxavir marboxil group
Weight < 10 kg	1 mg/kg	Baloxavir marboxil 2% granules 1 mg/kg (50 mg/kg[a])
Weight 10 to < 20 kg	10 mg	Baloxavir marboxil 2% granules 10 mg (0.5 g[a] [1 packet])
Weight 20 to < 40 kg	20 mg	1 baloxavir marboxil 20-mg tablet
Weight ≥ 40 kg	40 mg	2 baloxavir marboxil 20-mg tablets

a: Amount of drug granules

Duration of Treatment: 1 day

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

- Placebo tablets (lot number: [redacted])
- Placebo granules (lot number: [redacted])

Placebo tablets or granules were orally administered to subjects as a single dose on Day 1 at a dose which depends on the subject's age and body weight at Screening.

Subjects ≥ 12 years of age at Screening:

Subject's body weight at Screening	Dose	Placebo group
Weight < 80 kg	40 mg	2 placebo tablets
Weight ≥ 80 kg	80 mg	4 placebo tablets

Subjects < 12 years of age at Screening:

Subject's body weight at Screening	Dose	Placebo group
Weight < 10 kg	1 mg/kg	Placebo granules (50 mg/kg[a])
Weight 10 to < 20 kg	10 mg	1 placebo granules packet (0.5 g[a])
Weight 20 to < 40 kg	20 mg	1 placebo tablet
Weight ≥ 40 kg	40 mg	2 placebo tablets

a: Amount of placebo granules

Criteria for Evaluation:

Efficacy Assessment:

Primary Endpoint:

"Proportion of subjects who are infected with influenza virus (RT-PCR positive), and present with fever and at least one respiratory symptom in the period from Day 1 to Day 10" was the primary efficacy endpoint. Influenza-infected (RT-PCR positive) subjects with fever and at least one respiratory symptom were defined as subjects having a body temperature (axillary) of ≥ 37.5°C, having symptom of "cough" and/or "nasal discharge/nasal congestion" with a severity of "2, Moderate" or "3, Severe" assessed in the subject diary, and influenza virus positivity assessed by RT-PCR.

The secondary efficacy endpoints included the following variables:

- Time from study treatment to the time when fever, at least one respiratory symptom (cough or nasal discharge/nasal congestion), and influenza virus infection (RT-PCR positive) were observed.
  Defined as the later time point of the following (1) and (2):

(1) Timepoint when body temperature (axillary) rose first to ≥ 37.5°C
(2) Timepoint when symptom of "cough" and/or "nasal discharge/nasal congestion" was first assessed as "2, Moderate" or "3, Severe" in the subject diary

- Proportion of subjects who were infected with influenza virus (RT-PCR positive), and presented with fever or at least one influenza symptom (respiratory symptom or systemic symptom) in the period from Day 1 to Day 10
  Defined as the proportion of subjects having body temperature (axillary) ≥ 37.5°C or having at least one symptom of influenza with a severity of "2, Moderate" or "3, Severe" assessed in the subject diary, and influenza virus positive assessed by RT-PCR.
- Time from study treatment to the time when fever or at least one influenza symptom (respiratory symptom or systemic symptom), and influenza virus infection (RT-PCR positive) were observed
  Defined as the timepoint of the following (1) and (2), whichever was earlier:

(1) Timepoint when body temperature (axillary) rose first to ≥ 37.5°C
(2) Timepoint when an influenza symptom was first assessed as "2, Moderate" or "3, Severe" in the subject diary

- Proportion of asymptomatic influenza-infected (RT-PCR positive) subjects in the period from Day 1 to Day 10
  Defined as the proportion of subjects having body temperature (axillary) < 37.5°C, influenza symptoms all assessed as "0, Absent" or "1, Mild", and influenza virus positive assessed by RT-PCR.
- Proportion of subjects with influenza virus infection (RT-PCR positive) in the period from Day 1 to Day 10
  Defined as the proportion of subjects having influenza virus positive assessed by RT-PCR regardless of body temperature or influenza symptoms.

Other Assessment:

- Ratio of serum antibody titers against influenza virus on Day 15 to that on Day 1
- Proportion of subjects who are not infected with influenza virus (RT-PCR negative), and present with fever and at least one respiratory symptom in the period from Day 1 to Day 10

Safety Assessment:

Adverse events (AEs), treatment-related AEs, serious adverse events (SAEs), and clinical laboratory tests

Pharmacokinetics Assessment:

Plasma baloxavir concentrations

Statistical Methods:

The mITT population was the primary efficacy analysis population in this study. The PPS was used for supplementary analyses of the primary analyses of efficacy. All statistical tests were performed at a two-sided significance level of 0.05 unless stated otherwise.

Primary efficacy analysis of primary endpoint

In the mITT population, the risk ratio of the baloxavir marboxil group versus the placebo group, its 95% confidence interval (CI) and P value were calculated using the modified Poisson regression approach (ie, Poisson regression with sandwich estimator as a robust error variance) of a binary response (whether all of the following were confirmed for a subject or not; occurrence of fever, at least one respiratory symptom, and influenza virus infection) on a study treatment for the subject with randomization factors (time from onset of influenza in the index patient to informed consent of the subject, treatment for influenza virus infection in the index patient, age of the subject) as covariates. A P value was calculated for the null hypothesis that the true risk ratio was 1. In this primary analysis, the proportion of influenza-infected (RT-PCR positive) subjects with fever and at least one respiratory symptom, which was the primary endpoint, in the baloxavir marboxil group was compared with that in the placebo group.

Efficacy analyses of secondary endpoints

In the mITT population, an influenza infection proportion curve based on the length of time from the study treatment to the first time point when fever, at least one respiratory symptom (cough and/or nasal discharge/nasal congestion), and influenza virus infection were all confirmed was plotted for each treatment group using the Kaplan-Meier method. Restricted mean survival time (RMST) up to Day 10 was

estimated for each treatment group. In addition, the difference in RMST between the treatment groups was estimated.

For each of other secondary efficacy endpoints given as a proportion of subjects, similar analysis for the primary efficacy endpoint was performed and the proportion was compared between the treatment groups.

For each of the remaining other secondary efficacy endpoints presented as time to influenza infection, the influenza infection proportion curve was plotted and the treatment group difference in RMST up to Day 10 was estimated as described above.

Safety analyses

In the safety population, the numbers of events and subjects with AEs were counted for each treatment group. The proportion of subjects with AEs was calculated for each treatment group. Treatment-related AEs were summarized in the same way as AEs for the overall summary. The numbers and proportions of subjects with AEs/treatment-related AEs were counted by system organ class (SOC) and preferred term (PT) for each treatment group.

For quantitative data, observed measurements and changes from baseline were summarized at each planned time point for each treatment group using descriptive statistics. For qualitative data, the number of subjects in each treatment group was counted for each pair of categories at baseline and at each planned time point and presented as shift tables.

Pharmacokinetics

Individual plasma baloxavir concentrations were plotted against actual sampling time by dose to confirm the PK. Individual plasma baloxavir concentrations were listed and summarized by dose and nominal sampling time window with the number of non-missing observations (N), arithmetic mean (Mean), standard deviation (SD) and coefficient of variation (CV%, calculated by SD/Mean × 100), geometric mean (Geometric Mean) and coefficient of variation for geometric mean (CV% Geometric Mean), and median, minimum (Min) and maximum (Max) values. The CV% Geometric Mean was calculated according to a formula CV% Geometric Mean $[\exp(sd^2)\ \ 1]^{1/2} \times 100$, where sd was the standard deviation for natural log (ln)-transformed data. Actual sampling time (or scheduled sampling time) was used for PK analyses.

Based on population PK parameters in adults and pediatrics, the maximum plasma concentration (C_{max}), area under the plasma concentration-time curve extrapolated from time zero to infinity ($AUC_{0\ inf}$), and plasma baloxavir concentration 24 hours (acceptable time window: 20 to 28 hours) post-dose (C_{24}) in each subject were estimated by the Bayesian method, and were summarized with N, Mean, SD, and CV%, Geometric Mean and CV% Geometric Mean, and median, Min, and Max values.

Summary of Results

Efficacy:

Primary Endpoint

- The proportion of subjects who were infected with influenza virus (RT-PCR positive) and presented with fever and at least one respiratory symptom from Day 1 to Day 10 in the mITT population was significantly lower in the

baloxavir marboxil group (1.9% [7/374 subjects]) compared with the placebo group (13.6% [51/375 subjects]); adjusted risk ratio: 0.14 [95% CI: 0.06, 0.30], $p < 0.0001$. The result in the PPS was similar to the result in the mITT popularion.

- In the subgroup of subjects who had negative RT-PCR at baseline and whose index patients had positive RT-PCR, a similar result was observed to that in the overall mITT population (1.5% [5/344 subjects] in the baloxavir marboxil group and 11.6% [39/337 subjects] in the placebo group; adjusted risk ratio: 0.13 [95% CI: 0.05, 0.31], $p < 0.0001$).
- No subjects were infected with influenza subtype B virus. The results in the other subgroups including by influenza virus subtype of index patient (A/H1N1pdm, A/H3NX), by age of subject (< 12 years or ≥ 12 years), and by high risk factor of subject (presence or absence) were similar to the result in the overall mITT population; the proportions of subjects who were infected with influenza virus (RT-PCR positive) and presented with fever and at least one respiratory symptom from Day 1 to Day 10 were lower in the baloxavir marboxil group compared with the placebo group.

Secondary Endpoints

- The RMST from study treatment to the time when fever, at least one respiratory symptom, and influenza virus infection (RT-PCR positive) were observed up to Day 10 in the mITT population was 10.0 days (95% CI: 9.9, 10.0) in the baloxavir marboxil group and 9.1 days (95% CI: 8.9, 9.4) in the placebo group. The difference in RMST between the treatment groups was 0.8 days (95% CI: 0.6, 1.0, $p < 0.0001$).
- The proportion of subjects who were infected with influenza virus (RT-PCR positive) and presented with fever or at least one influenza symptom from Day 1 to Day 10 in the mITT population was lower in the baloxavir marboxil group (5.3% [20/374 subjects]) compared with the placebo group (22.4% [84/375 subjects]); adjusted risk ratio: 0.24 (95% CI: 0.15, 0.38), $p < 0.0001$.
- The RMST from study treatment to the time when fever or at least one influenza symptom and influenza virus infection (RT-PCR positive) were observed up to Day 10 in the mITT population was 9.8 days (95% CI: 9.7, 9.9) in the baloxavir marboxil group and 8.5 days (95% CI: 8.2, 8.8) in the placebo group. The difference in RMST between the treatment groups was 1.3 days (95% CI: 1.0, 1.6, $p < 0.0001$).
- The proportion of asymptomatic influenza-infected (RT-PCR positive) subjects from Day 1 to Day 10 in the mITT population was similar between the treatment groups; 7.8% (29/374 subjects) in the baloxavir marboxil group and 7.7% (29/375 subjects) in the placebo group (adjusted risk ratio: 1.00 [95% CI: 0.61, 1.64], p 0.9917).
- The proportion of subjects with influenza virus infection (RT-PCR positive) regardless of symptoms from Day 1 to Day 10 in the mITT population was lower in the baloxavir marboxil group (13.1% [49/374 subjects]) compared with the placebo group (30.4% [114/375 subjects]); adjusted risk ratio: 0.43 (95% CI: 0.32, 0.58]), $p < 0.0001$.

Safety:

- The incidence of AEs was 22.2% (83/374 subjects, 102 events) in the baloxavir marboxil group and 20.5% (77/375 subjects, 99 events) in the placebo group. The incidence of treatment-related AEs was 1.9% (7/374 subjects, 7 events) in the baloxavir marboxil group and 1.6% (6/375 subjects, 7 events) in the placebo group. The incidences of AEs and treatment-related AEs were similar between the treatment groups.
- No deaths were reported. Only 1 SAE (psychotic disorder in the placebo group) was reported in this study. The event was also the only AE leading to withdrawal from the study. The event was considered not related to the study drug.
- The AEs occurring at an incidence of ≥ 2% in any of the treatment groups were nasopharyngitis (6.4% in the baloxavir marboxil group and 6.7% in the placebo group) and headache (2.1% in the baloxavir marboxil group and 1.6% in the placebo group). The incidences of these events were similar between the treatment groups.
- All AEs were Grade 1 or Grade 2 in severity except for 1 Grade 3 psychotic disorder in 1 (0.3%) subject in the placebo group. The majority of the AEs resolved or were resolving.
- No clinically relevant differences were found in the changes from baseline in laboratory values between the treatment groups. Although the incidence of AEs of blood urine present was ≥ 1% higher in the baloxavir marboxil group compared with the placebo group, no apparent differences were observed in the changes from baseline in urine occult blood between the baloxavir marboxil and placebo groups.

Pharmacokinetics:

- No clear difference was observed in the plasma baloxavir concentrations between subjects administered 80 mg (body weight ≥ 80 kg) and subjects administered 40 mg (body weight < 80 kg) in subjects with ≥ 12 years of age.
- No clear difference was observed in the plasma baloxavir concentrations between influenza-infected subjects with fever and at least one respiratory symptom and the other subjects in subjects with ≥ 12 years of age.
- No clear difference was observed in the plasma baloxavir concentrations among subjects administered 10 mg (body weight 10 to < 20 kg), subjects administered 20 mg (body weight 20 to < 40 kg), and subjects administered 40 mg (body weight ≥ 40 kg) in subjects with < 12 years of age.
- No clear difference was observed in the plasma baloxavir concentrations between influenza-infected subjects with fever and at least one respiratory symptom and the other subjects in subjects with < 12 years of age.

CONCLUSIONS

Efficacy Conclusions:

The efficacy of baloxavir marboxil was demonstrated compared with placebo in the prevention of influenza virus infection in subjects who were household members of influenza-infected patients.

Safety Conclusions:

No clinically significant safety concerns were identified; therefore, a single oral dose

of baloxavir marboxil for the prevention of influenza virus infection was well tolerated with no excess of AEs compared with placebo. The safety profile of baloxavir marboxil observed in this study was similar to that noted in previous studies for treatment of influenza virus infection.
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