Clinical trial results:
An Open-label Study to Assess the Safety, Tolerability, Pharmacokinetics, and Efficacy of Baloxavir Marboxil 2% Granules after Administration of a Single Dose to Otherwise Healthy Pediatric Patients with Influenza

Summary

EudraCT number	2021-001026-22
Trial protocol	Outside EU/EEA
Global end of trial date	17 March 2020

Results information

Result version number	v1 (current)
This version publication date	28 March 2021
First version publication date	28 March 2021

Trial information

Trial identification

Sponsor protocol code	1813T0835

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shionogi & Co., Ltd.
Sponsor organisation address	12F, Hankyu Terminal Bldg., 1-4, Shibata 1-chome, Osaka, Japan, 530-0012
Public contact	Corporate Communications Department, Shionogi & Co., Ltd., shionogiclintrials-admin@shionogi.co.jp
Scientific contact	Corporate Communications Department, Shionogi & Co., Ltd., shionogiclintrials-admin@shionogi.co.jp

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002440-PIP01-18
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 March 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to assess the safety, tolerability, pharmacokinetics (PK), and efficacy of baloxavir marboxil 2% granules in otherwise healthy pediatric participants with influenza virus infection aged less than 12 years and weighing less than 20 kg at Screening.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form (ICF).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 January 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 45
Worldwide total number of subjects	45
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	13
Children (2-11 years)	32
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at 15 study centers in Japan.

Pre-assignment

Screening details:

Participants with a clinical diagnosis of influenza A and/or B virus infection were enrolled in each arm of the study based on weight. Participants in the <10 kg arm received a 1 mg/kg or 2 mg/kg dose based on age. Participants aged <3 months were to receive a dose of 1 mg/kg. No participants in the study were <3 months of age.

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Baloxavir Marboxil (Participants' weight <10 kg)

Arm description:

Participants who weighed <10 kilograms (kg) and were greater than or equal to (≥) 3 months of age received a single oral dose of 2 milligram per kilogram (mg/kg) baloxavir marboxil 2% granules on Day 1.

Arm type	Experimental
Investigational medicinal product name	Baloxavir marboxil
Investigational medicinal product code	
Other name	S-033188, RO7191686, Xofluza
Pharmaceutical forms	Granules in sachet
Routes of administration	Oral use

Dosage and administration details:

A single oral dose of 1 mg/kg or 2 mg/kg of baloxavir marboxil 2% granules was to be administered on Day 1 based on participants' age and body weight at Screening. All partipants in this arm received 2 mg/kg of baloxavir marboxil 2% granules.

Arm title	Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg)

Arm description:

Participants who weighed between 10 to <20 kg received 20 mg of baloxavir marboxil 2% granules as a single oral dose on Day 1 irrespective of their age.

Arm type	Experimental
Investigational medicinal product name	Baloxavir marboxil
Investigational medicinal product code	
Other name	S-033188, RO7191686, Xofluza
Pharmaceutical forms	Granules in sachet
Routes of administration	Oral use

Dosage and administration details:

A single oral dose of 20 mg of baloxavir marboxil 2% granules was administered on Day 1 based on participants' age and body weight at Screening.

Number of subjects in period 1	Baloxavir Marboxil (Participants' weight <10 kg)	Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg)
Started	9	36
Completed	9	36

Reporting groups	
Reporting group title	Baloxavir Marboxil (Participants' weight <10 kg)
Reporting group description:	
Participants who weighed <10 kilograms (kg) and were greater than or equal to (≥) 3 months of age received a single oral dose of 2 milligram per kilogram (mg/kg) baloxavir marboxil 2% granules on Day 1.	
Reporting group title	Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg)
Reporting group description:	
Participants who weighed between 10 to <20 kg received 20 mg of baloxavir marboxil 2% granules as a single oral dose on Day 1 irrespective of their age.	

Reporting group values	Baloxavir Marboxil (Participants' weight <10 kg)	Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg)	Total
Number of subjects	9	36	45
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	9	4	13
Children (2-11 years)	0	32	32
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	0.4	3.4	
standard deviation	± 0.5	± 1.5	-
Gender Categorical Units: Subjects			
Female	3	17	20
Male	6	19	25

End points

End points reporting groups

Reporting group title	Baloxavir Marboxil (Participants' weight <10 kg)

Reporting group description:

Participants who weighed <10 kilograms (kg) and were greater than or equal to (≥) 3 months of age received a single oral dose of 2 milligram per kilogram (mg/kg) baloxavir marboxil 2% granules on Day 1.

Reporting group title	Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg)

Reporting group description:

Participants who weighed between 10 to <20 kg received 20 mg of baloxavir marboxil 2% granules as a single oral dose on Day 1 irrespective of their age.

Subject analysis set title	Baloxavir marboxil 2 mg/kg dose
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PK concentration population consisted of all participants who received at least one dose of the study drug and had at least one evaluable PK assay result.

Subject analysis set title	Baloxavir marboxil 20 mg dose
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PK concentration population consisted of all participants who received at least one dose of the study drug and had at least one evaluable PK assay result.

Primary: Time to Alleviation of Influenza Illness

End point title	Time to Alleviation of Influenza Illness[1]

End point description:

Time to alleviation of influenza illness was defined as time taken from the start of treatment to the point at which all of the following criteria were met, and these clinical conditions persisted for at least 21.5 hours (90% of 24 hours): i) In the participant diary, cough and nasal discharge/nasal congestion were both rated as 0=absent or 1=mild; ii) Axillary temperature was < 37.5 degree Celsius [°C]. Intent-to-treat infected (ITTI) population included all participants who received study drug with a confirmed diagnosis of influenza virus infection on Day 1 and complied with Good Clinical Practice (GCP).

End point type	Primary

End point timeframe:

Day 1 up to Day 14

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for this endpoint.

End point values	Baloxavir Marboxil (Participants' weight <10 kg)	Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	35		
Units: hours				
median (confidence interval 95%)	26.4 (12.1 to 51.6)	42.1 (28.6 to 54.8)		

Statistical analyses

End point values	Baloxavir Marboxil (Participants' weight <10 kg)	Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	35		
Units: log[vp/mL]				
arithmetic mean (standard deviation)				
Day 1 (n=8, 35)	6.50 (± 0.80)	6.39 (± 0.94)		
Day 2 (n=8, 35)	4.57 (± 0.93)	5.26 (± 0.98)		
Day 3 (n=6, 18)	3.52 (± 0.76)	4.25 (± 1.22)		
Day 4 (n=3, 24)	2.57 (± 0.37)	4.15 (± 1.24)		
Day 6 (n=8, 35)	5.04 (± 1.55)	4.52 (± 1.37)		
Day 9 (n=8, 35)	2.75 (± 0.79)	3.66 (± 1.41)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Influenza Virus Titer

End point title	Change From Baseline in Influenza Virus Titer

End point description:

Influenza virus titer is the quantity of influenza virus in a given volume within the samples obtained from nasopharyngeal swabs. A lower value indicates a lower viral load. The change from Baseline in influenza virus titer at each time point was reported in log-transformed units i.e. log of the 50% tissue culture infective dose per mL (log[TCID/mL]). Participants with positive virus titer at baseline in the ITTI population were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline and Days 2, 3, 4 (one visit on either Day 3 or Day 4 was mandatory), 6 and 9

End point values	Baloxavir Marboxil (Participants' weight <10 kg)	Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	34		
Units: log[TCID/mL]				
arithmetic mean (standard deviation)				
Change from Baseline at Day 2 (n=8, 34)	-3.98 (± 1.05)	-4.51 (± 1.72)		
Change from Baseline at Day 3 (n=6, 18)	-3.83 (± 1.14)	-3.98 (± 1.91)		
Change from Baseline at Day 4 (n=3, 23)	-4.27 (± 0.64)	-4.11 (± 2.30)		
Change from Baseline at Day 6 (n=8, 34)	-2.69 (± 1.03)	-3.51 (± 2.46)		
Change from Baseline at Day 9 (n=8, 34)	-3.98 (± 1.05)	-4.29 (± 1.80)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Amount of Virus RNA Determined by RT-PCR

End point title	Change From Baseline in the Amount of Virus RNA Determined by RT-PCR

End point description:

The change from Baseline in the amount of virus RNA at each time point was reported in log-transformed units i.e. log of viral particles per mL (log[vp/mL]). Participants in the ITTI population were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline and Days 2, 3, 4 (one visit on either Day 3 or Day 4 was mandatory), 6 and 9

End point values	Baloxavir Marboxil (Participants' weight <10 kg)	Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	35		
Units: log[vp/mL]				
arithmetic mean (standard deviation)				
Change from Baseline at Day 2 (n=8, 35)	-1.93 (± 0.56)	-1.13 (± 1.18)		
Change from Baseline at Day 3 (n=6, 18)	-3.12 (± 0.50)	-1.96 (± 1.42)		
Change from Baseline at Day 4 (n=3, 24)	-3.45 (± 0.87)	-2.19 (± 1.54)		
Change from Baseline at Day 6 (n=8, 35)	-1.46 (± 1.52)	-1.87 (± 1.63)		
Change from Baseline at Day 9 (n=8, 35)	-3.75 (± 1.24)	-2.73 (± 1.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Positive For Influenza Virus Titer

End point title	Percentage of Participants Positive For Influenza Virus Titer

End point description:

Influenza virus titer is the quantity of influenza virus in a given volume within the samples obtained

from nasopharyngeal swabs. A lower value indicates lower viral load. Positive influenza virus titer was defined as virus titer not less than the lower limit of quantification among those assessed for virus titer on Days 2, 3, 4, 6, and 9. Participants positive for influenza virus titer at Baseline in the ITTI population were included in the analyses.

End point type	Secondary

End point timeframe:

Days 2, 3, 4 (one visit on either Day 3 or Day 4 was mandatory), 6, and 9

End point values	Baloxavir Marboxil (Participants' weight <10 kg)	Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	34		
Units: percentage of participants				
number (confidence interval 95%)				
Day 2 (n=8, 34)	0.0 (0.0 to 36.9)	29.4 (15.1 to 47.5)		
Day 3 (n=6, 18)	0.0 (0.0 to 45.9)	22.2 (6.4 to 47.6)		
Day 4 (n=3, 23)	0.0 (0.0 to 70.8)	34.8 (16.4 to 57.3)		
Day 6 (n=8, 34)	62.5 (24.5 to 91.5)	58.8 (40.7 to 75.4)		
Day 9 (n=8, 34)	12.5 (0.3 to 52.7)	32.4 (17.4 to 50.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Positive For Influenza Virus by RT-PCR

End point title	Percentage of Participants Positive For Influenza Virus by RT-PCR

End point description:

The percentage of participants positive for influenza virus by RT-PCR on Days 2, 3, 4, 6, and 9 and not less than the lower limit of detection among the participants with detectable amounts of virus RNA at Baseline was analysed.

End point type	Secondary

End point timeframe:

Days 2, 3, 4 (one visit on either Day 3 or Day 4 was mandatory), 6, and 9

End point values	Baloxavir Marboxil (Participants' weight <10 kg)	Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	35		
Units: percentage of participants				
number (confidence interval 95%)				
Day 2 (n=8, 35)	100.0 (63.1 to 100.0)	100.0 (90.0 to 100.0)		
Day 3 (n=6, 18)	100.0 (54.1 to 100.0)	94.4 (72.7 to 99.9)		
Day 4 (n=3, 24)	100.0 (29.2 to 100.0)	95.8 (78.9 to 99.9)		
Day 6 (n=8, 35)	100.0 (63.1 to 100.0)	97.1 (85.1 to 99.9)		
Day 9 (n=8, 35)	75.0 (34.9 to 96.8)	77.1 (59.9 to 89.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve (AUC) in Virus Titer

End point title	Area Under the Curve (AUC) in Virus Titer

End point description:

The AUC in virus titer was calculated using the trapezoidal method. Participants in the ITTI population were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline up to Day 9

End point values	Baloxavir Marboxil (Participants' weight <10 kg)	Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	34		
Units: log[TCID/mL]*hours				
arithmetic mean (standard deviation)	-659.1 (± 190.5)	-711.4 (± 357.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve (AUC) in the Amount of Virus RNA Determined by RT-PCR

End point title	Area Under the Curve (AUC) in the Amount of Virus RNA Determined by RT-PCR

End point description:

The AUC in the amount of virus RNA determined by RT-PCR was calculated using the trapezoidal method. Participants in the ITTI population were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline up to Day 9

End point values	Baloxavir Marboxil (Participants' weight <10 kg)	Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	35		
Units: log[vp/mL]*hours				
arithmetic mean (standard deviation)	-478.4 (± 165.0)	-357.9 (± 226.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Cessation of Viral Shedding by Virus Titer

End point title	Time to Cessation of Viral Shedding by Virus Titer

End point description:

Time to cessation of viral shedding by influenza virus titer was defined as the time from initiation of the study treatment until the virus titer was for the first time less than the lower limit of quantification. Participants in the ITTI population were included in the analysis. '0.9999' or '99999' means the limit of confidence interval was not calculated because there was no observation value corresponding the limit of confidence interval to ensure the 95% confidence coefficient.

End point type	Secondary

End point timeframe:

Day 1 up to Day 9

End point values	Baloxavir Marboxil (Participants' weight <10 kg)	Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	34		
Units: hours				
median (confidence interval 95%)	24 (0.9999 to 99999)	24 (0.9999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Cessation of Viral Shedding by RT-PCR

End point title	Time to Cessation of Viral Shedding by RT-PCR

End point description:

Time to cessation of viral shedding by RT-PCR was defined as the time from initiation of the study treatment until the amount of virus RNA was for the first time less than the lower limit of detection. Participants in the ITTI population were included in the analysis. '0.9999' or '99999' means the limit of confidence interval was not calculated because there was no observation value corresponding the limit of confidence interval to ensure the 95% confidence coefficient.

End point type	Secondary

End point timeframe:

Day 1 up to Day 9

End point values	Baloxavir Marboxil (Participants' weight <10 kg)	Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	35		
Units: hours				
median (confidence interval 95%)	300.0 (216.0 to 384.0)	240.0 (216.0 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Resolution of Fever

End point title	Time to Resolution of Fever

End point description:

Time to resolution of fever was defined as the time from the initiation of the study treatment until first experience of fever resolution. Resolution of fever was defined as the time point when the participant's self-measured axillary temperature had become less than 37.5ºC and remained below 37.5ºC for at least 12 hours. Participants in the ITTI population were included in the analysis.

End point type	Secondary

End point timeframe:

Day 1 up to Day 14

End point values	Baloxavir Marboxil (Participants' weight <10 kg)	Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	35		
Units: hours				
median (confidence interval 95%)	22.3 (12.1 to 32.8)	22.0 (20.2 to 29.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Reported Normal Body Temperature

End point title	Percentage of Participants Who Reported Normal Body Temperature

End point description:

Percentage of participants whose axillary temperature was below 37.5ºC in the ITTI population at each time point were analysed.

End point type	Secondary

End point timeframe:

Postdose: 12 hours (h), 24 h, 36 h, 48 h, 72 h, 76 h, 120 h, 144 h, 168 h, 192 h and 216 h (up to Day 10)

End point values	Baloxavir Marboxil (Participants' weight <10 kg)	Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	35		
Units: percentage of participants				
number (confidence interval 95%)				
12 h postdose (n=8, 35)	50.0 (15.7 to 84.3)	22.9 (10.4 to 40.1)		
24 h postdose (n=8, 35)	87.5 (47.3 to 99.7)	65.7 (47.8 to 80.9)		
36 h postdose (n=8, 34)	87.5 (47.3 to 99.7)	85.3 (68.9 to 95.0)		
48 h postdose (n=8, 35)	100.0 (63.1 to 100.0)	100.0 (90.0 to 100.0)		
72 h postdose (n=8, 35)	100.0 (63.1 to 100.0)	100.0 (90.0 to 100.0)		
96 h postdose (n=8, 35)	87.5 (47.3 to 99.7)	91.4 (76.9 to 98.2)		

120 h postdose (n=8, 34)	87.5 (47.3 to 99.7)	94.1 (80.3 to 99.3)		
144 h postdose (n=8, 35)	62.5 (24.5 to 91.5)	97.1 (85.1 to 99.9)		
168 h postdose (n=8, 33)	87.5 (47.3 to 99.7)	97.0 (84.2 to 99.9)		
192 h postdose (n=8, 34)	75.0 (34.9 to 96.8)	97.1 (84.7 to 99.9)		
216 h postdose (n=8, 35)	87.5 (47.3 to 99.7)	100.0 (90.0 to 100.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Body Temperature at Each Timepoint

End point title	Body Temperature at Each Timepoint

End point description:

Body temperature observed at each time point including Baseline was evaluated. Participants in the ITTI population were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline (0h, Day 1) and postdose 12 h, 24 h, 36 h, 48 h, 72 h, 96 h, 120 h, 144 h, 168 h, 192 h, and 216 h (up to Day 10)

End point values	Baloxavir Marboxil (Participants' weight <10 kg)	Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	35		
Units: degree Celsius (°C)				
arithmetic mean (standard deviation)				
Baseline (n=8, 35)	39.06 (± 0.77)	38.59 (± 0.60)		
12 h postdose (n=8, 35)	37.78 (± 1.20)	38.16 (± 1.03)		
24 h postdose (n=8, 35)	36.99 (± 0.55)	37.32 (± 0.93)		
36 h postdose (n=8, 34)	36.86 (± 0.79)	36.85 (± 0.72)		
48 h postdose (n=8, 35)	36.61 (± 0.22)	36.51 (± 0.42)		
72 h postdose (n=8, 35)	36.64 (± 0.41)	36.40 (± 0.52)		
96 h postdose (n=8, 35)	36.84 (± 0.53)	36.63 (± 0.66)		
120 h postdose (n=8, 34)	36.98 (± 0.85)	36.56 (± 0.45)		
144 h postdose (n=8, 35)	36.99 (± 0.70)	36.49 (± 0.42)		
168 h postdose (n=8, 33)	36.96 (± 0.81)	36.47 (± 0.46)		
192 h postdose (n=8, 34)	36.98 (± 0.43)	36.57 (± 0.38)		
216 h postdose (n=8, 35)	36.86 (± 0.49)	36.49 (± 0.33)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Alleviation of Cough Symptoms

End point title	Time to Alleviation of Cough Symptoms

End point description:

Time to alleviation of cough symptoms was defined as the time from initiation of the study treatment until the alleviation of cough symptoms. The alleviation of a symptom was defined as the time point when a symptom was assessed as 0=absent or 1=mild, for at least 21.5 hours (90% of 24 hours). Participants in the ITTI population, whose symptom scores at baseline were moderate or severe, were included in the analysis. '0.9999' or '99999' means the limit of confidence interval was not calculated because there was no observation value corresponding the limit of confidence interval to ensure the 95% confidence coefficient.

End point type	Secondary

End point timeframe:

Day 1 up to Day 14

End point values	Baloxavir Marboxil (Participants' weight <10 kg)	Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	10		
Units: hours				
median (confidence interval 95%)	30.8 (0.9999 to 99999)	3.8 (0.3 to 6.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Alleviation of Nasal Discharge/Nasal Congestion Symptoms

End point title	Time to Alleviation of Nasal Discharge/Nasal Congestion Symptoms

End point description:

Time to alleviation of nasal discharge/ nasal congestion symptoms was defined as the time from initiation of the study treatment until the alleviation of nasal discharge/nasal congestion symptoms. The alleviation of a symptom was defined as the time point when a symptom was assessed as 0=absent or 1=mild, for at least 21.5 hours (90% of 24 hours). Participants in the ITTI population, whose symptom scores at baseline were moderate or severe, were included in the analysis.

End point type	Secondary

End point timeframe:

Day 1 up to Day 14

End point values	Baloxavir Marboxil (Participants' weight <10 kg)	Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	16		
Units: hours				
median (confidence interval 95%)	30.8 (2.0 to 246.0)	30.3 (3.7 to 68.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Resumption of Normal Activity

End point title	Time to Resumption of Normal Activity

End point description:

Time to resumption of normal activity was defined as the time from initiation of the study treatment until the time when the participant's guardian assessed the participant's daily activities as 10. The participant's ability to perform daily activities was assessed by the participant's guardian on a scale of 0 (Unable to perform daily activities at all) to 10 (Able to perform all daily activities as usual). Participants in the ITTI population whose usual activity at Baseline was not 10 were included in the analyses.

End point type	Secondary

End point timeframe:

Day 1 up to Day 14

End point values	Baloxavir Marboxil (Participants' weight <10 kg)	Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	35		
Units: hours				
median (confidence interval 95%)	78.9 (48.8 to 194.0)	81.4 (55.3 to 105.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Influenza-related Complications

End point title	Percentage of Participants With Influenza-related Complications

End point description:

The percentage of participants who developed influenza-related complications such as death, hospitalization, radiologically confirmed pneumonia, bronchitis, sinusitis, and otitis media after initiation of the study treatment was analysed. Participants in the ITTI population were included in the analysis.

End point type	Secondary
End point timeframe: Day 1 up to Day 22	

End point values	Baloxavir Marboxil (Participants' weight <10 kg)	Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	35		
Units: percentage of participants				
number (confidence interval 95%)				
Any Influenza-related Complication	0 (0.0 to 36.9)	8.6 (1.8 to 23.1)		
Death	0 (0.0 to 36.9)	0 (0.0 to 1		

number (confidence interval 95%)				
Any pediatric influenza- related complication	0 (0.0 to 36.9)	0 (0.0 to 10.0)		
Influenza associated encephalitis / encephalopathy	0 (0.0 to 36.9)	0 (0.0 to 10.0)		
Febrile seizure	0 (0.0 to 36.9)	0 (0.0 to 10.0)		
Myositis	0 (0.0 to 36.9)	0 (0.0 to 10.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of S-033447

End point title	Plasma Concentration of S-033447

End point description:

S-033447 or baloxavir is the active metabolite of baloxavir marboxil. The observed plasma concentration of baloxavir at 24 hours postdose (C24) was analysed. The PK concentration population consisted of all participants who received at least one dose of the study drug and had at least one evaluable PK assay result.

End point type	Secondary

End point timeframe:

0.5 to 2 hours postdose at Day 1, Day 2, at one time point during the period from Day 6 to 22, and at Day 3 and/or Day 4 as needed

End point values	Baloxavir marboxil 2 mg/kg dose	Baloxavir marboxil 20 mg dose		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	26		
Units: nanogram/mL (ng/mL)				
geometric mean (geometric coefficient of variation)	100 (± 43.4)	87.7 (± 44.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Adverse Events (AEs)

End point title	Percentage of Participants With Adverse Events (AEs)

End point description:

An adverse event (AE) was defined as any untoward medical occurrence in a participant who was administered a pharmaceutical product (including an investigational drug) during the course of a clinical investigation. An AE could therefore be any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease that was temporally associated with the use of the investigational product, regardless of whether it was considered to be related to the investigational product or not. The safety population consisted of all participants who received at least one dose of the study drug and complied with GCP.

End point type	Secondary

End point timeframe:

Day 1 up to Day 22

End point values	Baloxavir Marboxil (Participants' weight <10 kg)	Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	36		
Units: percentage of participants				
number (confidence interval 95%)	55.6 (21.2 to 86.3)	52.8 (35.5 to 69.6)		

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

From the time of informed consent up to Day 22

Adverse event reporting additional description:

The safety population consisted of all participants who received at least one dose of the study drug and complied with GCP.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Baloxavir Marboxil (Participants' weight <10 kg)

Reporting group description:

Participants who weighed <10 kg and were greater than or equal to (≥) 3 months of age received a single oral dose of 2 mg/kg baloxavir marboxil 2% granules on Day 1.

Reporting group title	Baloxavir Marboxil (Participants' weight ≥ 10 kg to < 20 kg)

Reporting group description:

Participants who weighed between 10 to < 20 kg received 20 mg of baloxavir marboxil 2% granules as a single oral dose on Day 1 irrespective of their age.

Serious adverse events	Baloxavir Marboxil (Participants' weight <10 kg)	Baloxavir Marboxil (Participants' weight ≥ 10 kg to < 20 kg)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	0 / 36 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Baloxavir Marboxil (Participants' weight <10 kg)	Baloxavir Marboxil (Participants' weight ≥ 10 kg to < 20 kg)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 9 (55.56%)	13 / 36 (36.11%)	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 9 (0.00%)	5 / 36 (13.89%)	
occurrences (all)	0	5	
Respiratory, thoracic and mediastinal disorders			

Rhinorrhoea			
subjects affected / exposed	1 / 9 (11.11%)	0 / 36 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract inflammation			
subjects affected / exposed	1 / 9 (11.11%)	0 / 36 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Skin fissures			
subjects affected / exposed	1 / 9 (11.11%)	0 / 36 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 9 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Influenza			
subjects affected / exposed	1 / 9 (11.11%)	0 / 36 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	2 / 9 (22.22%)	6 / 36 (16.67%)	
occurrences (all)	2	6	
Enterocolitis viral			
subjects affected / exposed	1 / 9 (11.11%)	1 / 36 (2.78%)	
occurrences (all)	1	1	
Rotavirus infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 36 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 9 (11.11%)	2 / 36 (5.56%)	
occurrences (all)	1	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 April 2019	The original study protocol was amended as follows: 1) The planned duration of the study was increased by one year; 2) Shionogi & Co., Ltd. Was added to the Study Monitoring section.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported