Clinical trial results:
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

Summary

EudraCT number	2020-000696-20
Trial protocol	Outside EU/EEA
Global end of trial date	25 March 2019

Results information

Result version number	v1 (current)
This version publication date	12 July 2020
First version publication date	12 July 2020

Trial information

Trial identification

Sponsor protocol code	1719T0834

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,
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	09 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 March 2019
Global end of trial reached?	Yes
Global end of trial date	25 March 2019
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 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 of influenza-infected patients

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 November 2018
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: 749
Worldwide total number of subjects	749
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)	6
Children (2-11 years)	136
Adolescents (12-17 years)	33
Adults (18-64 years)	551
From 65 to 84 years	21
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

752 subjects were randomized in this study but only 749 (374 in the baloxavir marboxil group and 375 in the placebo group) were included in the safety and efficacy analyses. 2 subjects were not dosed and 1 subject was discontinued due to non-compliance.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Baloxavir Marboxil

Arm description:

Participants will receive a single oral dose of baloxavir marboxil on Day 1 (based on body weight)

Arm type	Experimental
Investigational medicinal product name	S-033188
Investigational medicinal product code	
Other name	Baloxavir Marboxil
Pharmaceutical forms	Granules, Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

S-033188 is available as 20-mg tablets or 2% granules (containing 20 mg of baloxavir marboxil per 1 g of granules). Subjects ≥12 years of age at screening were administered 40 mg if their body weight was < 80 kg or 80 mg if their body weight was ≥ 80 kg. Subjects < 12 years of age at screening were administered 1 mg/kg (weight < 10 kg) or 10 mg (Weight 10 to < 20 kg) or 20 mg (weight 20 to < 40 kg) or 40 mg (Weight ≥ 40 kg)

Arm title	Placebo

Arm description:

Participants will receive a single oral dose of matching placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules, Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo was available as tablets or granules. Subjects ≥12 years of age at screening were administered 2 placebo tablets if their body weight was < 80 kg or 4 placebo tablets if their body weight was ≥ 80 kg. Subjects < 12 years of age at screening were administered granules (50 mg/kg if weight < 10 kg) or 1 placebo granule packet (Weight 10 to < 20 kg) or 1 placebo tablet (weight 20 to < 40 kg) or 2 placebo tablets (Weight ≥ 40 kg).

Number of subjects in period 1	Baloxavir Marboxil	Placebo
Started	374	375
Completed	373	375
Not completed	1	0
Consent withdrawn by subject	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Baloxavir Marboxil
Reporting group description:	
Participants will receive a single oral dose of baloxavir marboxil on Day 1 (based on body weight)	
Reporting group title	Placebo
Reporting group description:	
Participants will receive a single oral dose of matching placebo	

Reporting group values	Baloxavir Marboxil	Placebo	Total
Number of subjects	374	375	749
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)	1	5	6
Children (2-11 years)	70	66	136
Adolescents (12-17 years)	12	21	33
Adults (18-64 years)	283	268	551
From 65-84 years	7	14	21
85 years and over	1	1	2
Age Continuous Units: years			
arithmetic mean	33.5	33.6	
standard deviation	± 15.8	± 17.0	-
Gender Categorical Units: Subjects			
Female	297	290	587
Male	77	85	162

End points

End points reporting groups	
Reporting group title	Baloxavir Marboxil
Reporting group description:	
Participants will receive a single oral dose of baloxavir marboxil on Day 1 (based on body weight)	
Reporting group title	Placebo
Reporting group description:	
Participants will receive a single oral dose of matching placebo	

Primary: Proportion of subjects who are infected with influenza virus (RT-PCR positive), and present with fever and at least one respiratory symptom

End point title	Proportion of subjects who are infected with influenza virus (RT-PCR positive), and present with fever and at least one respiratory symptom
End point description:	
Influenza virus infection was confirmed through Reverse transcription polymerase chain reaction (RT-PCR positive). Fever was defined as subjects having a body temperature (axillary) of ≥37.5°C. Respiratory symptoms included having cough or nasal discharge/nasal congestion with a severity of 2: Moderate or 3: Severe as assessed in the subject diary.	
End point type	Primary
End point timeframe:	
Day 1 to Day 10	

End point values	Baloxavir Marboxil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	374	375		
Units: percentage of participants				
number (confidence interval 95%)	1.9 (0.8 to 3.8)	13.6 (10.3 to 17.5)		

Statistical analyses

Statistical analysis title	Baloxavir versus Placebo
Comparison groups	Placebo v Baloxavir Marboxil
Number of subjects included in analysis	749
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	modified Poisson regression approach
Parameter estimate	Risk ratio (RR)
Point estimate	0.14

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	0.3

Secondary: Time from study treatment to the time when fever, at least one respiratory symptom, and influenza virus infection (RT-PCR) were observed

End point title	Time from study treatment to the time when fever, at least one respiratory symptom, and influenza virus infection (RT-PCR) were observed

End point description:

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 by treatment group, using the Kaplan-Meier method. Restricted mean survival time (RMST) up to Day 10 in each treatment group was estimated by integrating the Kaplan-Meier survival curve. If a subject had no positive test result for influenza virus or has no fever or any respiratory symptom (cough or nasal discharge/nasal congestion) at any time after the study treatment, the subject was handled as a censored case at the last observation time point.

End point type	Secondary

End point timeframe:

Day 1 (baseline) to study end (approximately 15 days)

End point values	Baloxavir Marboxil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	374	375		
Units: Day				
number (confidence interval 95%)	10.0 (9.9 to 10.0)	9.1 (8.9 to 9.4)		

Statistical analyses

Statistical analysis title	Difference in RMST up to day 10 (day)
Comparison groups	Baloxavir Marboxil v Placebo
Number of subjects included in analysis	749
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	RMST
Point estimate	0.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1

Secondary: Proportion of subjects who are infected with influenza virus (RT-PCR positive), and present with fever or at least one influenza symptom

End point title	Proportion of subjects who are infected with influenza virus (RT-PCR positive), and present with fever or at least one influenza symptom

End point description:

Influenza symptoms could be a respiratory symptom (cough or nasal discharge/nasal congestion) or a systemic symptom (headache, feverishness or chills, muscle or joint pain, fatigue).

End point type	Secondary

End point timeframe:

Day 1 (baseline) to Day 10

End point values	Baloxavir Marboxil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	374	375		
Units: percentage of participants				
number (confidence interval 95%)	5.3 (3.3 to 8.1)	22.4 (18.3 to 27.0)		

Statistical analyses

Statistical analysis title	Baloxavir Marboxil vs. Placebo
Comparison groups	Baloxavir Marboxil v Placebo
Number of subjects included in analysis	749
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	modified Poisson regression approach
Parameter estimate	Risk ratio (RR)
Point estimate	0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	0.38

Secondary: Time from study treatment to the time when fever or at least one influenza symptom, and influenza virus infection (RT-PCR) are observed.

End point title	Time from study treatment to the time when fever or at least one influenza symptom, and influenza virus infection (RT-PCR) are observed.

End point description:

Restricted mean survival time (RMST) up to Day 10 in each treatment group was estimated by integrating the Kaplan-Meier survival curve.

End point type	Secondary

End point timeframe:

Day 1 (baseline) to study end (approximately 15 days)

End point values	Baloxavir Marboxil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	374	375		
Units: Days				
number (confidence interval 95%)	9.8 (9.7 to 9.9)	8.5 (8.2 to 8.8)		

Statistical analyses

Statistical analysis title	Difference in RMST up to Day 10
Comparison groups	Baloxavir Marboxil v Placebo
Number of subjects included in analysis	749
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	RMST
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	1.6

Secondary: Proportion of asymptomatic influenza-infected (RT-PCR positive) subjects

End point title	Proportion of asymptomatic influenza-infected (RT-PCR positive) subjects

End point description:

End point type	Secondary

End point timeframe:

Day 1 (baseline) to Day 10

End point values	Baloxavir Marboxil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	374	375		
Units: percentage of participants				
number (confidence interval 95%)	7.8 (5.3 to 10.9)	7.7 (5.2 to 10.9)		

Statistical analyses

Statistical analysis title	Baloxavir Marboxil vs. Placebo
Comparison groups	Baloxavir Marboxil v Placebo
Number of subjects included in analysis	749
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9917
Method	modified Poisson regression approach
Parameter estimate	Risk ratio (RR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.64

Secondary: Proportion of subjects with influenza virus infection (RT-PCR positive)

End point title	Proportion of subjects with influenza virus infection (RT-PCR positive)
End point description:	
The proportion of subjects with influenza virus infection (RT-PCR positive) regardless of symptoms	
End point type	Secondary
End point timeframe:	
Day 1 (baseline) to Day 10	

End point values	Baloxavir Marboxil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	374	375		
Units: percentage of participants				
number (confidence interval 95%)	13.1 (9.9 to 16.9)	30.4 (25.8 to 35.3)		

Statistical analyses

Statistical analysis title	Baloxavir Marboxil vs. Placebo
Comparison groups	Baloxavir Marboxil v Placebo
Number of subjects included in analysis	749
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	modified Poisson regression approach
Parameter estimate	Risk ratio (RR)
Point estimate	0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	0.58

Secondary: Proportion of subjects with Adverse Events (AEs)	
End point title	Proportion of subjects with Adverse Events (AEs)
End point description:	
End point type	Secondary
End point timeframe:	
Day 1 (baseline) to study end (approximately 15 days)	

End point values	Baloxavir Marboxil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	374	375		
Units: percentage of participants				
number (confidence interval 95%)				
Adverse Events	22.2 (18.1 to 26.7)	20.5 (16.6 to 25.0)		
Deaths	0 (0 to 1.0)	0 (0 to 1.0)		
Other Serious Adverse Events	0 (0 to 1.0)	0.3 (0.0 to 1.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum plasma concentration (Cmax) of S-033447

End point title	Maximum plasma concentration (Cmax) of S-033447[1]

End point description:

I = Influenza-infected subjects with fever and at least one respiratory symptom; and O = The other subjects.

End point type	Secondary

End point timeframe:

Day 1 (baseline) to study end (approximately 15 days)

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: S-033447 concentrations were only measured in the Baloxavir Marboxil arm.

End point values	Baloxavir Marboxil			
Subject group type	Reporting group			
Number of subjects analysed	369			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
≥ 12 years I (n=4)	95.3 (± 54.1)			
≥ 12 years O (n=297)	91.0 (± 32.4)			
< 12 years I (n=3)	85.2 (± 10.5)			
< 12 years O (n=65)	93.5 (± 17.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the plasma concentration-time curve extrapolated from time zero to infinity (AUC0-inf) of S-033447

End point title	Area under the plasma concentration-time curve extrapolated from time zero to infinity (AUC0-inf) of S-033447[2]

End point description:

I = Influenza-infected subjects with fever and at least one respiratory symptom; and O = The other subjects.

End point type	Secondary

End point timeframe:

Day 1 (baseline) to study end (approximately 15 days)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: S-033447 concentrations were only measured in the Baloxavir Marboxil arm.

End point values	Baloxavir Marboxil			
Subject group type	Reporting group			
Number of subjects analysed	369			
Units: ng.hr/mL				
geometric mean (geometric coefficient of variation)				
≥ 12 years I (n=4)	6895 (± 63.1)			
≥ 12 years O (n=297)	6178 (± 30.8)			
< 12 years I (n=3)	4001 (± 12.3)			
< 12 years O (n=65)	4218 (± 25.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentration 24 hours post-dose (C24) of S-033447

End point title	Plasma concentration 24 hours post-dose (C24) of S-033447[3]

End point description:

I = Influenza-infected subjects with fever and at least one respiratory symptom; and O = The other subjects.

End point type	Secondary

End point timeframe:

Day 1 (baseline) to 24 hours post-dose

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: S-033447 concentrations were only measured in the Baloxavir Marboxil arm.

End point values	Baloxavir Marboxil			
Subject group type	Reporting group			
Number of subjects analysed	369			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
≥ 12 years I (n=4)	51.8 (± 25.7)			
≥ 12 years O (n=297)	52.7 (± 25.1)			
< 12 years I (n=3)	48.9 (± 11.1)			
< 12 years O (n=65)	51.9 (± 20.3)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Day 1 (baseline) to study end (approximately 15 days)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	Baloxavir Marboxil
Reporting group description: Participants will receive a single oral dose of baloxavir marboxil on Day 1 (based on body weight)	
Reporting group title	Placebo
Reporting group description: Participants will receive a single oral dose of matching placebo	

Serious adverse events	Baloxavir Marboxil	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 374 (0.00%)	1 / 375 (0.27%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Psychiatric disorders			
Psychotic disorders			
subjects affected / exposed	0 / 374 (0.00%)	1 / 375 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Baloxavir Marboxil	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 374 (6.42%)	25 / 375 (6.67%)	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	24 / 374 (6.42%)	25 / 375 (6.67%)	
occurrences (all)	24	25	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported