Clinical trial results:
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.

Summary

EudraCT number	2016-002688-32
Trial protocol	DE LV HU GB PL BG ES BE RO
Global end of trial date	20 April 2018

Results information

Result version number	v1 (current)
This version publication date	02 November 2018
First version publication date	02 November 2018

Trial information

Trial identification

Sponsor protocol code	1602T0832

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02949011
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shionogi Ltd. [Sponsor for Europe, Australia, New Zealand and South Africa)
Sponsor organisation address	5th floor, 33 Kingsway, London, United Kingdom, WC2B 6UF
Public contact	Shionogi Ltd., Shionogi Ltd., +44 0203 053 4200, shionogiclintrials-admin@shionogi.co.jp
Scientific contact	shionogiclintrials-admin@shionogi.co.jp, Shionogi Ltd., +44 0203 053 4200, shionogiclintrials-admin@shionogi.co.jp
Sponsor organisation name	Shionogi & Co., Ltd. [Sponsor for Japan and other Asian countries]
Sponsor organisation address	3-1-8, Doshomachi 3-chome, Chuo-ku, Osaka, Japan, 541-0045
Public contact	Shionogi & Co. Ltd., Shionogi & Co. Ltd., +81 662097885, shionogiclintrials-admin@shionogi.co.jp
Scientific contact	Shionogi & Co. Ltd., Shionogi & Co. Ltd., +81 662097885, shionogiclintrials-admin@shionogi.co.jp
Sponsor organisation name	Shionogi Inc. [Sponsor for North America]
Sponsor organisation address	300 Campus Drive, Florham Park, NJ, United States, 07932
Public contact	Shionogi Inc., Shionogi Inc., +1 8008499707, shionogiclintrials-admin@shionogi.co.jp
Scientific contact	Shionogi Inc., Shionogi Inc., +1 8008499707, shionogiclintrials-admin@shionogi.co.jp

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 June 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 April 2018
Global end of trial reached?	Yes
Global end of trial date	20 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of a single, oral dose of S-033188 (baloxavir marboxil), compared with placebo by measuring the time to improvement of influenza symptoms in patients with influenza. Eligible patients were randomized in a 1:1:1 ratio to receive baloxavir marboxil or oseltamivir or placebo.

Protection of trial subjects:

The study was conducted in accordance with the protocol approved by the IRBs/IECs, all applicable regulatory requirements, the current Good Clinical Practice (GCP) guidelines, all applicable patient privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki (1996).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 January 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Romania: 15
Country: Number of subjects enrolled	New Zealand: 4
Country: Number of subjects enrolled	South Africa: 85
Country: Number of subjects enrolled	Philippines: 17
Country: Number of subjects enrolled	Korea, Republic of: 11
Country: Number of subjects enrolled	Taiwan: 10
Country: Number of subjects enrolled	Japan: 465
Country: Number of subjects enrolled	United States: 1302
Country: Number of subjects enrolled	Poland: 59
Country: Number of subjects enrolled	Spain: 11

Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Bulgaria: 117
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	Latvia: 40
Worldwide total number of subjects	2184
EEA total number of subjects	290

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)	0
Children (2-11 years)	0
Adolescents (12-17 years)	59
Adults (18-64 years)	1523
From 65 to 84 years	588
85 years and over	14

Subject disposition

Recruitment

Recruitment details:

A multicentre study conducted at 551 sites: included in Europe, USA, Japan, Asia Pacific and South Africa. Number of patients Consented: 2592 and Randomized: 2184 (730 in the baloxavir marboxil, 725 in the oseltamivir and 729 in the placebo groups respectively).

Pre-assignment

Screening details:

The study population composed of Male and female patients ≥ 12 years old with influenza A and/or B infection at high risk of developing influenza complications within 48 hours of symptom onset. Definition of high risk patients was adapted from the Centers for Disease Control and Prevention (CDC) criteria.

Pre-assignment period milestones

Number of subjects started	2592[1]
Number of subjects completed	2184

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Other: 22
Reason: Number of subjects	Lost to follow up: 1
Reason: Number of subjects	Failure to meet I/E Criteria: 319
Reason: Number of subjects	Consent withdrawn by subject: 66

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects reported to have 'started' the "pre-assignment" period is the number that signed the Informed Consent Form prior to randomization. The number reported to have 'completed' is the number of patients that were randomized and is therefore, lower. Thus, the world-wide number reported is equal to the number of randomised patients and not to the pre-assignment number.

Period 1

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

Blinding implementation details:

The study was conducted in a double-blind, double-dummy fashion by using placebo matching baloxavir marboxil and oseltamivir in appearance, labelling and packaging.

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment with baloxavir marboxil

Arm description:

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.

Arm type	Experimental

Investigational medicinal product name	Bloxavir marboxil 20 mg tablets
Investigational medicinal product code	S-033188
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

A single dose of baloxavir marboxil on Day 1 + oseltamivir placebo BID on Days 1 to 5.

Arm title	Treatment with placebo

Arm description:

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.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	Placebo
Other name	
Pharmaceutical forms	Capsule, hard, Tablet
Routes of administration	Oral use

Dosage and administration details:

A single dose of baloxavir marboxil placebo on Day 1 + oseltamivir placebo BID on Days 1 to 5.

Arm title	Treatment with oseltamivir

Arm description:

Patients randomized to oseltamivir received 1 capsule of oseltamivir 75 mg BID for 5 days (Day 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.

Arm type	Active comparator
Investigational medicinal product name	Oseltamivir
Investigational medicinal product code	Oseltamivir
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

A single dose of baloxavir marboxil placebo on Day 1 + oseltamivir BID on Days 1 to 5.

Number of subjects in period 1	Treatment with baloxavir marboxil	Treatment with placebo	Treatment with oseltamivir
Started	730	729	725
Completed	697	695	683
Not completed	33	34	42
Consent withdrawn by subject	13	13	21
Adverse event, non-fatal	6	7	3
Other	2	4	6
Death	-	-	1
Failure to meet I/E Criteria	-	-	3
Lost to follow-up	7	5	5

Protocol deviation	5	3	3
Lack of efficacy	-	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Treatment with baloxavir marboxil

Reporting group description:

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.

Reporting group title	Treatment with placebo

Reporting group description:

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.

Reporting group title	Treatment with oseltamivir

Reporting group description:

Patients randomized to oseltamivir received 1 capsule of oseltamivir 75 mg BID for 5 days (Day 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.

Reporting group values	Treatment with baloxavir marboxil	Treatment with placebo	Treatment with oseltamivir
Number of subjects	730	729	725
Age categorical			
Overall,			
Units: Subjects			
Adolescents (12-17 years)	21	17	21
Adults (18-64 years)	500	509	514
From 65-84 years	207	199	182
85 years and over	2	4	8
Age continuous			
Units: years			
arithmetic mean	51.7	52.0	51.1
full range (min-max)	12 to 86	12 to 92	12 to 93
Gender categorical			
Units: Subjects			
Female	401	417	424
Male	329	312	301

Reporting group values	Total		
Number of subjects	2184		
Age categorical			
Overall,			
Units: Subjects			
Adolescents (12-17 years)	59		
Adults (18-64 years)	1523		
From 65-84 years	588		
85 years and over	14		

Age continuous Units: years arithmetic mean full range (min-max)	- 		
Gender categorical Units: Subjects			
Female	1242		
Male	942		

End points

End points reporting groups

Reporting group title	Treatment with baloxavir marboxil

Reporting group description:

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.

Reporting group title	Treatment with placebo

Reporting group description:

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.

Reporting group title	Treatment with oseltamivir

Reporting group description:

Patients randomized to oseltamivir received 1 capsule of oseltamivir 75 mg BID for 5 days (Day 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.

Primary: Time to Improvement of Influenza Symptoms Primary Analysis in the Intention to Treat Infection (ITTI) Population

End point title	Time to Improvement of Influenza Symptoms Primary Analysis in the Intention to Treat Infection (ITTI) Population

End point description:

End point type	Primary

End point timeframe:

The assessment of influenza symptoms was carried out from Day 1 to Day 14.

End point values	Treatment with baloxavir marboxil	Treatment with placebo	Treatment with oseltamivir	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	385	385	388	
Units: Hours				
median (confidence interval 95%)	73.2 (67.2 to 85.1)	102.3 (92.7 to 113.1)	81.0 (69.4 to 91.5)	

Statistical analyses

Statistical analysis title	baloxavir marboxil comparison with placebo
Comparison groups	Treatment with baloxavir marboxil v Treatment with placebo

Number of subjects included in analysis	770
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Peto-Prentice's generalized Wilcoxon
Parameter estimate	Median difference (net)
Point estimate	-29.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-42.8
upper limit	-14.6

Statistical analysis title	baloxavir marboxil comparison with oseltamivir
Comparison groups	Treatment with oseltamivir v Treatment with baloxavir marboxil
Number of subjects included in analysis	773
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8347
Method	Peto-Prentice's generalized Wilcoxon
Parameter estimate	Median difference (net)
Point estimate	-7.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.7
upper limit	7.9

Primary: Time to Improvement of Influenza Symptoms Sensitivity Analysis in the ITTI Population

End point title	Time to Improvement of Influenza Symptoms Sensitivity Analysis in the ITTI Population

End point description:

End point type	Primary

End point timeframe:

The assessment of influenza symptoms was carried out from Day 1 to Day 14.

End point values	Treatment with baloxavir marboxil	Treatment with placebo	Treatment with oseltamivir	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	385	385	388	
Units: Hours				
median (confidence interval 95%)	73.2 (67.2 to 85.1)	102.3 (92.7 to 113.1)	81.0 (69.4 to 91.5)	

Statistical analyses

Statistical analysis title	baloxavir marboxil comparison with placebo
Comparison groups	Treatment with baloxavir marboxil v Treatment with placebo
Number of subjects included in analysis	770
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0008
Method	Stratified log-rank test
Parameter estimate	Median difference (net)
Point estimate	-29.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-42.8
upper limit	-14.6

Statistical analysis title	baloxavir marboxil comparison with oseltamivir
Comparison groups	Treatment with baloxavir marboxil v Treatment with oseltamivir
Number of subjects included in analysis	773
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8449
Method	Stratified log-rank test
Parameter estimate	Median difference (net)
Point estimate	-7.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.7
upper limit	7.9

Primary: Time to Improvement of Influenza Symptoms by Influenza Vaccination Status in the ITTI Population who had received an Influenza Vaccine

End point title	Time to Improvement of Influenza Symptoms by Influenza Vaccination Status in the ITTI Population who had received an

	Influenza Vaccine

End point description:

End point type	Primary

End point timeframe:

The assessment of influenza symptoms was carried out from Day 1 to Day 14.

End point values	Treatment with baloxavir marboxil	Treatment with placebo	Treatment with oseltamivir	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	91	99	104	
Units: Hours				
median (confidence interval 95%)	65.4 (52.6 to 85.1)	92.7 (76.1 to 110.6)	90.0 (70.4 to 103.7)	

Statistical analyses

Statistical analysis title	baloxavir marboxil comparison with placebo
Comparison groups	Treatment with baloxavir marboxil v Treatment with placebo
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1042
Method	Wilcoxon generalized test
Parameter estimate	Median difference (net)
Point estimate	-27.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-49.9
upper limit	-0.2

Statistical analysis title	baloxavir marboxil comparison with oseltamivir
Comparison groups	Treatment with oseltamivir v Treatment with baloxavir marboxil
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4069
Method	Wilcoxon generalized test
Parameter estimate	Median difference (net)
Point estimate	-24.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-43
upper limit	2.6

Primary: Time to Improvement of Influenza Symptoms by Influenza Vaccination Status in the ITTI Population who had Not received an Influenza Vaccine

End point title	Time to Improvement of Influenza Symptoms by Influenza Vaccination Status in the ITTI Population who had Not received an Influenza Vaccine

End point description:

End point type	Primary

End point timeframe:

The assessment of influenza symptoms was carried out from Day 1 to Day 14.

End point values	Treatment with baloxavir marboxil	Treatment with placebo	Treatment with oseltamivir	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	294	286	284	
Units: Hours				
median (confidence interval 95%)	76.9 (68.4 to 90.2)	103.1 (93.2 to 117.3)	77.0 (66.8 to 94.8)	

Statistical analyses

Statistical analysis title	baloxavir marboxil comparison with placebo
Comparison groups	Treatment with baloxavir marboxil v Treatment with placebo
Number of subjects included in analysis	580
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	Wilcoxon generalized test
Parameter estimate	Median difference (net)
Point estimate	-26.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-45.8
upper limit	-11.5

Statistical analysis title	baloxavir marboxil comparison with oseltamivir
Comparison groups	Treatment with baloxavir marboxil v Treatment with oseltamivir
Number of subjects included in analysis	578
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8998
Method	Wilcoxon generalized test
Parameter estimate	Median difference (net)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.5
upper limit	18.2

Primary: Time to Improvement of Influenza Symptoms by Influenza Virus Subtype A/H3 in the ITTI Population

End point title	Time to Improvement of Influenza Symptoms by Influenza Virus Subtype A/H3 in the ITTI Population
End point description:	
End point type	Primary
End point timeframe:	
The assessment of influenza symptoms was carried out from Day 1 to Day 14.	

End point values	Treatment with baloxavir marboxil	Treatment with placebo	Treatment with oseltamivir	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	180	185	190	
Units: Hours				
median (confidence interval 95%)	75.4 (62.4 to 91.6)	100.4 (88.4 to 113.4)	68.2 (53.9 to 81.0)	

Statistical analyses

Statistical analysis title	baloxavir marboxil comparison with placebo
Comparison groups	Treatment with baloxavir marboxil v Treatment with placebo

Number of subjects included in analysis	365
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0141
Method	Peto-Prentice's generalized Wilcoxon

Statistical analysis title	baloxavir marboxil comparison with oseltamivir
Comparison groups	Treatment with baloxavir marboxil v Treatment with oseltamivir
Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1433
Method	Peto-Prentice's generalized Wilcoxon

Primary: Time to Improvement of Influenza Symptoms by Influenza Virus Subtype B in the ITTI Population

End point title	Time to Improvement of Influenza Symptoms by Influenza Virus Subtype B in the ITTI Population

End point description:

End point type	Primary

End point timeframe:

The assessment of influenza symptoms was carried out from Day 1 to Day 14.

End point values	Treatment with baloxavir marboxil	Treatment with placebo	Treatment with oseltamivir	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	166	167	148	
Units: Hours				
median (confidence interval 95%)	74.6 (67.4 to 90.2)	100.6 (82.8 to 115.8)	101.6 (90.5 to 114.9)	

Statistical analyses

Statistical analysis title	baloxavir marboxil comparison with placebo
Comparison groups	Treatment with baloxavir marboxil v Treatment with placebo

Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0138
Method	Peto-Prentice's generalized Wilcoxon

Statistical analysis title	baloxavir marboxil comparison with oseltamivir
Comparison groups	Treatment with baloxavir marboxil v Treatment with oseltamivir
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0251
Method	Peto-Prentice's generalized Wilcoxon

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

Adverse events were classified by System Organ Class (SOC) and Preferred Term (PT) using Medical Dictionary for Regulatory Activities (MedDRA). Adverse events reported after the initial dose of study drug were used for safety analyses. All AEs, including those occurring prior to the initiation of the study treatment, were listed.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Baloxavir marboxil
Reporting group description: -	
Reporting group title	Treatment with Placebo
Reporting group description: -	
Reporting group title	Treatment with Oseltamivir
Reporting group description: -	

Serious adverse events	Baloxavir marboxil	Treatment with Placebo	Treatment with Oseltamivir
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 730 (0.68%)	9 / 727 (1.24%)	8 / 721 (1.11%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	1
Investigations			
Liver function test increased			
subjects affected / exposed	0 / 730 (0.00%)	0 / 727 (0.00%)	1 / 721 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test abnormal			
subjects affected / exposed	0 / 730 (0.00%)	0 / 727 (0.00%)	1 / 721 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			

subjects affected / exposed	0 / 730 (0.00%)	1 / 727 (0.14%)	1 / 721 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 730 (0.00%)	0 / 727 (0.00%)	1 / 721 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	0 / 730 (0.00%)	1 / 727 (0.14%)	0 / 721 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 730 (0.00%)	1 / 727 (0.14%)	0 / 721 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arachnoid cyst			
subjects affected / exposed	0 / 730 (0.00%)	0 / 727 (0.00%)	1 / 721 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 730 (0.00%)	0 / 727 (0.00%)	1 / 721 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 730 (0.00%)	1 / 727 (0.14%)	0 / 721 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			

subjects affected / exposed	1 / 730 (0.14%)	0 / 727 (0.00%)	1 / 721 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 730 (0.00%)	0 / 727 (0.00%)	1 / 721 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 730 (0.00%)	0 / 727 (0.00%)	1 / 721 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 730 (0.00%)	0 / 727 (0.00%)	1 / 721 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	2 / 730 (0.27%)	0 / 727 (0.00%)	0 / 721 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct stone			
subjects affected / exposed	1 / 730 (0.14%)	0 / 727 (0.00%)	0 / 721 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 730 (0.00%)	1 / 727 (0.14%)	0 / 721 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 730 (0.14%)	0 / 727 (0.00%)	0 / 721 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Urinary retention			
subjects affected / exposed	0 / 730 (0.00%)	1 / 727 (0.14%)	0 / 721 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	0 / 730 (0.00%)	1 / 727 (0.14%)	0 / 721 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	0 / 730 (0.00%)	0 / 727 (0.00%)	1 / 721 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia influenzal			
subjects affected / exposed	1 / 730 (0.14%)	0 / 727 (0.00%)	0 / 721 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 730 (0.14%)	1 / 727 (0.14%)	1 / 721 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Vulval abscess			
subjects affected / exposed	0 / 730 (0.00%)	0 / 727 (0.00%)	1 / 721 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	0 / 730 (0.00%)	0 / 727 (0.00%)	1 / 721 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 730 (0.00%)	0 / 727 (0.00%)	1 / 721 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

Hyperglycaemia			
subjects affected / exposed	0 / 730 (0.00%)	1 / 727 (0.14%)	0 / 721 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 730 (0.00%)	0 / 727 (0.00%)	1 / 721 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Baloxavir marboxil	Treatment with Placebo	Treatment with Oseltamivir
Total subjects affected by non-serious adverse events			
subjects affected / exposed	183 / 730 (25.07%)	216 / 727 (29.71%)	202 / 721 (28.02%)
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	20 / 730 (2.74%)	21 / 727 (2.89%)	23 / 721 (3.19%)
occurrences (all)	20	24	27
Nausea			
subjects affected / exposed	20 / 730 (2.74%)	28 / 727 (3.85%)	34 / 721 (4.72%)
occurrences (all)	20	29	36
Infections and infestations			
Bronchitis			
subjects affected / exposed	21 / 730 (2.88%)	33 / 727 (4.54%)	30 / 721 (4.16%)
occurrences (all)	21	33	30
Sinusitis			
subjects affected / exposed	14 / 730 (1.92%)	21 / 727 (2.89%)	22 / 721 (3.05%)
occurrences (all)	14	21	22

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